UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

BRUNO PALAZZO NAZAR

TRANSTORNOS ALIMENTARES E O TRANSTORNO DO DÉFICIT DE ATENÇÃO / HIPERATIVIDADE

RIO DE JANEIRO
2017


Bruno Palazzo Nazar
Transtornos Alimentares e o Transtorno do Déficit de Atenção / Hiperatividade
UFRJ

Instituto de Psiquiatria
Universidade Federal do Rio de Janeiro
Programa de Pós-Graduação em Psiquiatria e Saúde Mental - PROPSAM

BRUNO PALAZZO NAZAR

TRANSTORNOS ALIMENTARES E O TRANSTORNO DE DÉFICIT DE ATENÇÃO / HIPERATIVIDADE

Volume Único

Tese de Doutorado submetida ao Programa de Pós-Graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para obtenção do grau de Doutor em Psiquiatria.

Orientador: **Prof. Paulo Eduardo Luiz de Mattos**

RIO DE JANEIRO
2017

CIP - Catalogação na Publicação

N335t

Nazar, Bruno Palazzo
Transtornos Alimentares e o Transtorno do Déficit de Atenção / Hiperatividade / Bruno Palazzo Nazar. -- Rio de Janeiro, 2017.
163 f.

Orientador: Paulo Eduardo Luiz de Mattos.
Tese (doutorado) - Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, Programa de Pós-Graduação em Psiquiatria e Saúde Mental, 2017.

1. Transtorno do Déficit de Atenção e Hiperatividade. 2. Transtornos Alimentares. 3. Impulsividade. 4. Comorbidade. 5. Diagnóstico. I. Mattos, Paulo Eduardo Luiz de, orient. II. Título.

Elaborado pelo Sistema de Geração Automática da UFRJ com os dados fornecidos pelo(a) autor(a).

TRANSTORNOS ALIMENTARES E O TRANSTORNO DO DÉFICIT DE ATENÇÃO / HIPERATIVIDADE

Bruno Palazzo Nazar

Orientador: **Prof. Paulo Eduardo Luiz de Mattos**

Tese de Doutorado submetida ao Programa de Pós-Graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para obtenção do grau de Doutor em Psiquiatria.

Aprovada por:

_____
Presidente - Paulo Eduardo Luiz de Mattos

_____
Silvia Regina de Freitas

_____
Julia Nunes Perez Fandiño

_____
Antonio Egidio Nardi

_____
Walmir Ferreira Coutinho

RIO DE JANEIRO
2017

DEDICATÓRIA

Dedico este trabalho à minha família.

Espero que Teresa, José e Anderson, possam olhar para minha jornada com inspiração e orgulho.

O apoio, a paciência e o amor de vocês fazem tudo ser possível.

AGRADECIMENTOS

Um agradecimento à **CAPES** e à **Universidade Federal do Rio de Janeiro** por terem me proporcionado o financiamento para a realização do meu Doutorado Sanduíche no Reino Unido.

Agradeço aos **alunos da Faculdade de Medicina da UFRJ** por terem participado dessa pesquisa e ao **IPUB – UFRJ** pela parceria de tantos anos.

Com muito carinho agradeço **aos residentes de psiquiatria do IPUB-UFRJ**, Amanda Pompeu, Paula Gibim Pacheco, David Sender e João Hiluy, dentre outros, que confiaram em minha orientação. Espero que eu tenha lhes transmitido uma vontade de saber que em outra época me foi passada.

À diretora do IPUB-UFRJ, **Professora Maria Tavares Cavalcanti**. Obrigado pelo apoio e pela intervenção quando expressei dúvidas sobre ir estudar na Inglaterra: "Você precisa ir. Isso vai mudar a sua vida!". É fato que mudou completamente.

Ao **Professor Antonio Egidio Nardi** que me questionou ao final da minha defesa de mestrado "Estou curioso para ver como esse aluno vai se superar no Doutorado". Obrigado pelo apoio e conselhos, foram escutados com atenção. Espero que as expectativas tenham sido superadas.

À equipe do Grupo de Estudos do Déficit de Atenção (**GEDA**), especialmente à Dra Camilla Pinna e às neuropsicólogas Cintia Mesquita, Beatriz Rabelo e Camila Bernardes que foram fundamentais para a realização deste trabalho e à equipe do Grupo de Obesidade e Transtornos Alimentares (**GOTA**) pela parceria e e apoio.

Agradeço **aos meus amigos** queridos que fazem dos momentos mais difíceis algo leve e com quem vale a pena dividir a vida e os momentos importantes. Um agradecimento especial aos meus amigos de tantos anos Dr. Gabriel de Mattos, Dr. Gustavo Stock, Dr. André Teixeira, Daniel Gunzburger, Edson Schueler e Ricardo Treu. E aos mais recentes Dra Alessandra Mendes, Dr Felipe Sudo, Monica Duchesne, Dinair Couto, além de tantos outros.

Eu agradeço todas as aulas e os momentos que vivi no **King's College London**, foi diferente de tudo o que eu poderia imaginar. Agradeço a possibilidade de conviver com os colegas da **Eating Disorders Unit**, Robert Turton, Charlotte Rhind, Gaia Albano, Jenni Leppanen, Louise Gregor, Heather Westwood, Savani Bartholdi e mais ainda a de viver em Londres.

Aos meus enteados amados **Pedro e Tiago Amorim**. Espero que eu esteja dando um bom exemplo.

Ao **Romildo do Rêgo Barros**, meu analista de tantos anos, pela infinita paciência de me ajudar a escutar meus sonhos e a encontrar um caminho que me seja próprio.

Um agradecimento muito especial ao **Professor Joseph Sergeant**. Uma mente inquieta que nunca me deixou descansar no mediano, nunca aceitou que nossos estudos acabassem em meias-verdades e com isso me fez avançar ainda mais. Obrigado pela disponibilidade para dar inúmeras supervisões além do Atlântico e pela satisfação cada vez que me via avançar.

Já dizia Henfil que "Enquanto acreditarmos em nossos sonhos, nada será por acaso". Eu tive o privilégio de trabalhar e receber a orientação da **Professora Janet Treasure**. Ela é uma pessoa incrivelmente generosa e que me desafiou imensamente. Em nossa despedida, ela me chamou em seu escritório e me presenteou com uma gravura de uma artista. Eram várias faces, uma englobando a outra. Perguntei o que o desenho simbolizava, ela me olhou e me respondeu:

"It's a generational thing, it's what's passed by".

O meu agradecimento mais especial segue para o meu querido orientador,

o **Professor Paulo Mattos.**

Desde a época da residência médica ele me confiou numa possibilidade que ia para além do que eu me achava capaz. É muito importante que alguém aposte em nós. Somos aquilo que sonhamos mas também somos naquilo que imaginam para nós. Também conhecemos uma árvore pelos seus frutos. Ninguém se faz sozinho.

Obrigado por toda a generosidade e mentoria. Eu olho com carinho para toda a estrada percorrida, assim como olho corajosamente para todos os desafios e possibilidades na estrada que se abre à frente. É interessante pois para todas as direções que eu olho, escuto a voz de meu orientador e penso:

"Espetáculo".

"I wonder if I've been changed in the night. Let me think. Was I the same when I got up this morning? I almost think I can remember feeling a little different. But if I'm not the same, the next question is 'Who in the world am I?' Ah, that's the great puzzle!"

— Lewis Carroll, Alice in Wonderland

"*And all the lives we ever lived and all the lives to be are full of trees and changing leaves.*"

— **Virginia Woolf, To the Lighthouse**

RESUMO

NAZAR, Bruno Palazzo. Transtornos Alimentares e o Transtorno do Déficit de Atenção / Hiperatividade. Rio de Janeiro, 2017. Tese (Doutorado em Psiquiatria) – Instituto de Psiquiatria. Universidade Federal do Rio de Janeiro, 2017.

Foi realizado um estudo com adultos jovens universitários, para avaliar se a presença de um Transtorno Alimentar poderia alterar o funcionamento cognitivo de sujeitos com Transtorno do Déficit de Atenção e Hiperatividade (TDAH). Não há estudos anteriores na literatura científica que avaliem comparativamente indivíduos com TDAH e aqueles com TDAH comórbido com Transtornos Alimentares. A justificativa dessa pesquisa se dá na investigação se há um perfil específico de funcionamento cognitivo desses pacientes que possa evidenciar possíveis focos de tratamento para este grupo. Foram analisados 90 indivíduos, sendo 35 portadores de TDAH, 16 portadores da comorbidade TDAH com Transtornos Alimentares e 39 Controles sem qualquer diagnóstico psiquiátrico. Todos os participantes realizaram entrevistas diagnósticas sobre TDAH, Transtornos Alimentares e outros diagnósticos psiquiátricos; responderam questionários sobre o comportamento alimentar, impulsividade, ansiedade e depressão, além de realizar testes neuropsicológicos para a avaliação de diferentes funções cognitivas. Evidenciou-se que o grupo com a comorbidade, quando comparado ao grupo TDAH e ao grupo Controle apresentava significativamente mais sintomas de hiperatividade/impulsividade, um índice de massa corporal maior e escores indicativos de impulsividade atencional, além de uma tendência a impulsividade cognitiva com pior capacidade de tomada de decisão. Finalmente, concluímos que a presença de um Transtorno Alimentar é capaz de prejudicar o funciomanto cognitivo e a regulação do peso dos sujeitos com TDAH

Palavras-Chave: Transtorno do Déficit de Atenção e Hiperatividade; Transtornos Alimentares; Impulsividade; Comorbidade; Diagnóstico

ABSTRACT

NAZAR, Bruno Palazzo. Eating Disorders and Attention-Deficit / Hyperactivity Disorder. Rio de Janeiro, 2017. Tese (Doutorado em Psiquiatria) – Instituto de Psiquiatria. Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2017.

A study was conducted to assess if the presence of an Eating Disorder could alter the cognitive functioning of Attention –Deficit / Hyperactivity Disorder of young adults. There are no previous studies in the scientific literature comparing ADHD with ADHD comorbid with Eating Disroder individuals. The justification for the present study is to investigate if ADHD comorbid with Eating Disorder individuals present a particular cognitive profile that can point towards possible new intervention domains. Ninety individuals were analysed within which, 35 were ADHD, 16 were ADHD comorbid with Eating Disorders and 39 were Controls without any psychiatric disorder. All participants were submitted to diagnostic interviews for ADHD, Eating Disorders and other psychiatric disorders, completed self report questionnaires on eating behaviour, impulsivity, anxiety and depression, performed neuropsychological tests investigating different cognitive domains. The group with ADHD comorbid with Eating Disorders, when compared to ADHD or to Controls, presented significantly more hyperactivity/impulsivity symptoms, higher body mass index, atentional impulsivity, as well as a tendency to cognitive impulsivity and decision making. Finally, we conclude that an Eating Disorder is capable of impairing cognitive functioning and weight regulation of ADHD subjects.

Keywords: Attention-Deficit / Hyperactivity Disorder; Eating Disorders; Impulsivity; Comorbidity; Diagnosis

Resumo geral da produção realizada durante o período do Doutorado

Os quatro capítulos de livro listados abaixo não foram replicados em sua integralidade na presente Tese mas foram utilizados no capítulo de Introdução. Em seguida, dos quinze artigos produzidos, a revisão sistemática e o estudo clínico sobre TDAH comórbido com Transtornos Alimentares foram descritos na Parte Textual da Tese. Dos treze artigos restantes, apenas os cinco já publicados que versavam sobre novas abordagens para o tratamento dos Transtornos Alimentares foram replicados nesta Tese, na seção de Anexos. Finalmente, os artigos restantes sobre Transtornos Alimentares (submetidos) ou sobre temas diversos em psiquiatria geral (independente do status) não foram reproduzidos na presente Tese em virtude do espaço que ocupariam. Na lista de artigos, aqueles que não foram reproduzidos na presente Tese encontram-se marcados em cinza.

Capítulos de Livros produzidos durante o período do Doutorado

Autores	Título	Status, Referência
Bruno Palazzo Nazar, Fabia Autuori	*TDAH em adultos*	Publicado em *Transtorno do Déficit de Atenção / Hiperatividade: Teoria e Clínica, Artmed*
Bruno Palazzo Nazar, Carolina Hanna Chaim, Nicola Worcman	*Anorexia Nervosa: Aspectos Diagnósticos e Prognósticos*	Publicado em *PRODIRETRIZES, Artmed*
JC Appolinario, Silvia Regina Freitas , **Bruno Palazzo Nazar**	*Transtornos Alimentares*	Publicado em *PROPSIQ, Artmed*
Bruno Palazzo Nazar, Janet Treasure	*Eating Disorders*	Publicado em *Human Nutrition 13th edition, Oxford Press*

Artigos produzidos durante o período do Doutorado			
Título do Artigo	**Periódico**	**Fator de Impacto**	**Status**
The risk of Eating Disorders comorbid with Attention-Deficit / Hyperactivity Disorder: A Systematic Review and Meta-Analysis	International Journal of Eating Disorders	4.06	Publicado
Influence of attention-deficit / hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women	Journal of Attention Disorders	2.37	Publicado
Can a Continuous Perfoemance Test help to assign innatention when mood and ADHD symptoms coexist?	Psychiatry Research	2.68	Publicado
Eating Disorders impair cognition and weight regulation of ADHD: a clinical and neuropsychological investigation			Em preparação
Early Response in Eating Disorders Treatment: A Systematic Review and Diagnostic Test Accuracy Meta-Analysis	European Eating Disorders Review	2.91	Publicado
Interventions for the carers of patients with eating disorders	Current Psychiatry Reports	3.28	Publicado
High-Frequency rTMS to Treat Refractory Binge Eating Disorder and Comorbid Depression: A Case Report	CNS Spectrum	3.40	Publicado
Testing the cognitive interpersonal model in adolescent anorexia nervosa: A pilot multicentre randomised trial to explore carer skills training on carer and patient behaviours			Submetido
Neural responses to taste stimuli in healthy controls and individuals with eating or weight disorders: A systematic review			Submetido
To go or not to go: A pilot study of food-specific inhibition training for people with bulimia nervosa and binge eating disorder			Em preparação
Misuse of sibutramine as a compensatory behavior in Bulimia Nervosa inducing psychosis			Submetido

Pathological gambling treated with Lithium: The role of assessing temperament	Addictive Behaviors	2.02	Publicado
Antidepressant induced excessive yawning and indifference	Brazilian Journal of Psychiatry	0.21	Publicado
Bilateral DMPFC-rTMS Leads to Sustained Remission in Geriatric Treatment-Resistant Depression: A Case Report			Submetido
Right Hemisphere Dominance for Language in a Woman with Schizophrenia and a Porencephalic Cyst of the Left Hemisphere	Neurocase	1.33	Publicado

Orientações de monografias junto ao programa de residência médica do IPUB-UFRJ realizadas durante o Doutorado

Nome do Aluno	Título da Monografia	Situação	Ano de Conclusão
Carolina Hanna Chaim	Jogo Patológico tratado com Lítio: o papel da avaliação do temperamento	Concluído	2014
Nicola Worcman	Skin Picking: Uma doença do impulso ou da ansiedade?	Concluído	2014
Amanda Pompeu Trindade	Transtornos Alimentares em estudantes universitários brasileiros: uma revisão da literatura	Concluído	2015
Paula Gibim Pacheco	Cisto Porencefálico e Esquizofrenia: Relato de Caso e Revisão da Literatura	Concluído	2015

FIGURAS

TABELAS

SUMÁRIO

1 INTRODUÇÃO

1.1 O Transtorno do Déficit de Atenção / Hiperatividade (TDAH)

Os estudos epidemiológicos indicam que aproximadamente 2 a 5% dos adultos apresentam o TDAH, com os estudos mais representativos descrevendo 4,4% da população adulta como sendo acometida pela forma completa do transtorno [1]. Ao contrário da distribuição por gênero encontrada em crianças, de 4 meninos para 1 menina, a distribuição em adultos é descrita na proporção de 1:1 [2].

A tríade sintomática característica do TDAH infantil - desatenção, impulsividade e hiperatividade [3] - também está presente em adultos, embora sintomas de hiperatividade-impulsividade sejam menos proeminentes e os sintomas de desatenção mais frequentemente observados. As manifestações em adultos tem características diferentes daquelas observadas em crianças, devido às diferenças dos contextos nos quais os sintomas aparecem (acadêmico, profissional, social, etc.) e um maior amadurecimento de sistemas cerebrais como aqueles do córtex pré-frontal.

É importante ressaltar que além dos sintomas nucleares, adultos com TDAH também apresentam dificuldades em lidar com frustrações, explosões de agressividade e aspectos relacionados à regulação do humor [4]. Além disso, apresentam outros déficits neuropsicológicos tais como os de funções executivas e percepção de tempo [5]. Estes sintomas podem resultar em prejuízos consideráveis em suas relações sociais [6].

O TDAH em adultos só foi reconhecido pelos sistemas classificatórios de saúde mental na terceira edição do Manual Estatístico e Diagnóstico da Associação Psiquiátrica Americana (DSM-III), com uma discreta indicação que o transtorno poderia persistir na vida adulta. Em sua versão subsequente, o DSM-IV [7], já descrevia alguns exemplos de sintomas em adultos, porém, indicava que:

"*Na maioria dos indivíduos, os sintomas atenuam-se durante o final da adolescência e idade adulta, embora uma minoria dessas pessoas experiencie o quadro sintomático completo ... até os anos intermediários da idade adulta*".

Esta afirmação da DSM-IV se contraria às evidências mais recentes sobre o curso evolutivo do transtorno. Na DSM-5 [8] foram realizadas mudanças para contemplar o diagnóstico em adultos, como a redução no número de sintomas para a realização do diagnóstico em adultos de 6 para 5 sintomas de desatenção e/ou hiperatividade-impulsividade. Apesar dos critérios para cada sintoma não terem mudado, foram adicionados exemplos que se aplicam melhor em adultos. Uma terceira mudança foi o aumento da idade de início dos sintomas para caracterizar comportamentos passados, de 7 para 12 anos, uma vez que os estudos sobre idade de início não demonstravam diferenças significativas entre os dois grupos. De acordo com os critérios da DSM-5, uma vez que os sintomas do TDAH são dimensionais e podem estar presentes em qualquer indivíduo, além de caracterizar uma agregação de sintomas acima do esperado para a maioria da população, estes sintomas precisam estar presentes em pelo menos duas áreas de funcionamento diferentes do indivíduo provocando prejuízo significativo, como por exemplo, na esfera conjugal e no trabalho. Os critérios diagnósticos para o TDAH na DSM-5 são apresentados na **Tabela 1**.

Os sintomas descritos na 10a Classificação Internacional de Doenças da Organização Mundial de Saúde (CID-10) [9] são semelhantes aos da DSM-IV mas o seu uso em adultos é difícil pois as situações descritas são mais adequadas para crianças.

O diagnóstico de TDAH em adultos é frequentemente realizado sem a presença de um informante colateral para corroborar a presença destes. Entretanto, alguns adultos não conseguem resgatar exemplos ou reconhecer a presença dos sintomas o que pode dificultar a entrevista. Apesar de podermos nos basear somente no relato do paciente adulto sobre os sintomas atuais e passados, a ausência de um relato colateral pode levar a um subdiagnóstico [10].

Independente da faixa etária, indivíduos com TDAH se apresentam com um diagnóstico psiquiátrico comórbido em aproximadamente 75% dos casos, sendo que em média três comorbidades psiquiátricas [11]. Os diagnósticos comórbidos mais comuns são os transtornos do humor e de ansiedade, sendo também frequentes outros transtornos do neurodesenvolvimento, como a dislexia. Outras comorbidades comuns incluem o transtorno por uso de substâncias, os transtornos alimentares (adiante) e as alterações do sono [12].

Tabela 1 - Critérios diagnósticos para TDAH pela DSM – 5

A. Um padrão persistente de desatenção e/ou hiperatividade-impulsividade que interfere no funcionamento ou desenvolvimento, caracterizado por (1) e/ou (2):

1. Desatenção: Seis (ou mais) dos seguintes sintomas de desatenção persistiram por pelo menos seis meses em grau mal-adaptativo e inconsistente com o nível de desenvolvimento, impactando negativa e diretamente em atividades sociais ou acadêmico/ocupacionais:

Nota: Os sintomas não se devem exclusivamente a manifestação de um transtorno de oposição, desafio, hostilidade ou falha em entender tarefas ou instruções. Para adolescentes mais velhos e adultos (17 anos ou acima), ao menos 5 sintomas são necessários.

a) freqüentemente deixa de prestar atenção a detalhes ou comete erros por descuido em atividades escolares, de trabalho ou outras (p.ex. não percebe ou deixa de perceber detalhes, o trabalho não é acurado)
b) com freqüência tem dificuldades para manter a atenção em tarefas ou atividades lúdicas (p.ex. tem dificuldade em se manter atento durante palestras, conversas ou leituras extensas)
c) com freqüência parece não escutar quando lhe dirigem a palavra (p.ex. parece estar com a cabeça em outro lugar mesmo que não haja uma distração óbvia)
d) com freqüência não segue instruções e não termina seus deveres escolares, tarefas domésticas ou deveres profissionais (não devido a comportamento de oposição ou incapacidade de compreender instruções)
e) com freqüência tem dificuldade para organizar tarefas e atividades (p.ex. tem dificuldade em realizar atividades sequenciais, em manter materiais e pertences organizados, realiza trabalhos de forma desordenada, apresenta um gerenciamento do tempo ruim, não consegue respeitar prazos)
f) com frequência evita, antipatiza ou reluta a envolver-se em tarefas que exijam esforço mental constante (p.ex. trabalhos escolares e deveres de casa; para adolescentes mais velhos e adultos, preparar relatórios, completar formulários revisar documentos extensos)
g) com freqüência perde coisas necessárias para tarefas ou atividades (p.ex. materiais escolares, lápis, livros, ferramentas, carteiras, chaves, material de escritório, óculos, telefone celular)
h) facilmente distraído por estímulos alheios à tarefa (para adolescentes mais velhos e adultos, também pode ser por pensamentos não relacionados à tarefa realizada)
i) com freqüência apresenta esquecimento em atividades diárias (p.ex. resolver atividades cotidianas; para adolescentes mais velhos e adultos, retornar ligações, pagar contas e manter compromissos)

2. Hiperatividade: Seis (ou mais) dos seguintes sintomas de desatenção persistiram por pelo menos seis meses em grau mal-adaptativo e inconsistente com o nível de desenvolvimento, impactando negativa e diretamente em atividades sociais ou acadêmico/ocupacionais:

Nota: Os sintomas não se devem exclusivamente a manifestação de um transtorno de oposição, desafio, hostilidade ou falha em entender tarefas ou instruções. Para adolescentes mais velhos e adultos (17 anos ou acima), ao menos 5 sintomas são necessários.

a) freqüentemente agita as mãos ou os pés ou se remexe na cadeira
b) freqüentemente abandona sua cadeira em situações nas quais se espera que permaneça sentado (p. ex. deixa o seu lugar na sala de aula, no escritório ou outro local de trabalho, ou em outras situações em que é requerido que se permaneça no lugar)
c) frequentemente escala ou corre em demasia, em situações nas quais isto é inapropriado (Nota: em adolescentes e adultos, pode estar limitado a sensações subjetivas de inquietação)
d) com freqüência tem dificuldade para brincar ou se envolver silenciosamente em atividades de lazer
e) está freqüentemente "a mil" ou muitas vezes age como se estivesse "a todo vapor" (p.ex. não consegue ou sente-se desconfortável ficando calmo por um período extenso de tempo, como num restaurante, numa reunião; pode ser percebido pelos outros como sendo incansável ou difícil de acompanhar).
f) freqüentemente fala em demasia

g) freqüentemente dá respostas precipitadas antes de as perguntas terem sido completadas (p.ex. completa as frases de outras pessoas; não espera o seu turno para falar numa conversa)
h) com freqüência tem dificuldade para aguardar sua vez (p.ex. quando precisa esperar numa fila)
i) freqüentemente interrompe ou se mete em assuntos de outros (p.ex. se intromete em conversas, jogos ou atividades; usa os objetos de outras pessoas sem pedir permissão; para adolescentes e adultos, pode se intrometer no que os outros estão fazendo)

B. Alguns sintomas de hiperatividade-impulsividade ou desatenção que causaram prejuízo estavam presentes antes dos 12 anos de idade.

C. Alguns sintomas de desatenção ou hiperatividade-impulsividade estão presentes em dois ou mais contextos (p.ex. em casa, na escola, no trabalho, em casa; com amigos ou parentes, em outras atividades).

D. Deve haver claras evidências de que os sintomas interferem ou reduzem a qualidade do funcionamento social, acadêmico ou ocupacional.

E. Os sintomas não ocorrem exclusivamente durante o curso de um Esquizofrenia ou outro Transtorno Psicótico e não são mais bem explicados por outro transtorno mental (por ex., Transtorno do Humor, Transtorno de Ansiedade, Transtorno Dissociativo, Transtorno da Personalidade, Intoxicação ou abstinência de Substâncias).

1.2 Os Transtornos Alimentares (TA)

1.2.1 Classificação e Quadro Clínico dos TA

A categoria diagnóstica dos TA é definida como um grupo de transtornos onde há grave comprometimento do comportamento alimentar [8]. As três principais síndromes definidas nesta categoria são a Anorexia Nervosa (AN), a Bulimia Nervosa (BN) e o Transtorno da Compulsão Alimentar (TCA). Os TA são síndromes complexas que prejudicam não apenas o comportamento alimentar propriamente dito, como também interferem na regulação do peso, na regulação dos sistemas apetitivos de recompensa e em outras redes neurais relacionadas a percepção corporal, funcionamento cognitivo e processamento emocional [13]. O DSM-5 descreve os quadros de AN, BN e TCA e seus critérios são apresentados, respectivamente nas **Figuras 1, 2 e 3**, numa comparação com os critérios da CID-10.

O DSM-5 também descreve uma outra categoria (Outros Transtornos Alimentares Específicos e Inespecíficos) incluindo, como por exemplo, a AN atípica, o TCA subclínico, o Transtorno Purgativo e a Síndrome do Comer Noturno. Em contrapartida, a CID-10, descreve apenas as síndromes da AN, BN e todos os outros quadros são classificados como formas atípicas de TA (TANE) [9].

As definições encontradas na literatura para este grupo mudam constantemente. Portanto, os limites externos para circunscrever essa categoria diagnóstica apresenta uma zona de penumbra mal definida, o que abre espaço para que entidades clínicas como a Ortorexia Nervosa, caracterizada por pensamentos obsessivos com comidas saudáveis e preparadas de acordo com crenças nutricionais distorcidas; a Dismorfia Muscular, um quadro marcado pela preocupação exagerada na obtenção de um corpo idealizado e musculoso associado à práticas alimentares distorcidas e manipulação hormonal para obtenção deste; e o Transtorno Purgativo, uma entidade clínica marcada pela prática de auto indução de vômitos sem a presença de episódios de compulsão alimentar ou outras características da BN, possam ser considerados parte dos TA em conjunto com as síndromes clássicas.

A AN é diagnosticada através da entrevista e exame clínico junto aos pacientes e seus familiares. O diagnóstico da AN pode ser caracterizada com a tríade descrita pelo psiquiatra britânico Gerald Russel [14]:

1. Perda de peso intencional com inanição: Existem diferentes definições para a determinação do que seria considerado uma perda de peso significativa. O DSM-5 determina que o paciente esteja 15% abaixo do peso esperado para a idade/altura/sexo em gráficos epidemiológicos [8], enquanto a CID-10 descreve um IMC de 17.5 kg/m^2 ou menos [9]. O DSM-5 menciona o uso do IMC apneas para estratificar a gravidade da AN.
2. Uma forma específica de psicopatologia: Diversos sintomas psíquicos expressando cognições e crenças distrocidas com temas relacionados à alimentação e peso e/ou forma do corpo podem se manifestar antes mesmo da perda de peso, apesar de também serem consequentes à desnutrição. Apesar da insatisfação com o peso ou com o corpo ser uma ideia frequente nas mulheres da sociedade atual, essas ideias tornam-se extremadas na AN.
3. Um distúrbio endocrinológico com funcionamento hormonal anormal: Expresso em mulheres por amenorreia e em homens por perda da libido e potência sexuais. A amenorreia foi um critério retirado na DSM-5.

A Bulimia Nervosa foi conceitualizada como uma entidade clínica distinta da AN no final da década de 70, com a sua principal característica sendo descrita como uma urgência incontrolável para comer, no original [15]:

"powerful and irresistible urges to overeat [...] there was often an all-or-none pattern to the sequences of eating [...] The amounts of food consumed at one sitting could be extraordinarily large".

"...their minds were filled almost constantly with thoughts of food with resulting impairment of concentration."

Além disso, essas pacientes apresentavam o uso de estratégias para prevenir o ganho de peso (*e.g.* auto indução de vômitos) e medo mórbido de engordar.

Como descrito acima, os episódios de compulsão alimentar apresentam aspecto central na psicopatologia da BN. Esses episódios referem-se à uma

sensação de perda de controle sobre o tipo ou a quantidade de comida a ser ingerida, associado ao consumo de uma grande quantidade de alimentos em um curto espaço de tempo, por exemplo, duas horas.

A caracterização de um episódio de compulsão alimentar é feita pela avaliação do critério subjetivo (sensação de perda de controle) e do critério objetivo (quantidade de alimento e espaço de tempo). Em associação aos episódios de compulsão alimentar, ocorrem práticas compensatórias inadequadas para prevenir o ganho de peso. Essas resultam num ciclo compulsão-compensação (ex. ciclos de compulsão-purgação). As estratégias para neutralizar os efeitos de superingestão podem ser danosos ao organismo e interferem com o funcionamento fisiológico, como a regulação da fome e saciedade, o que auxilia a manter o transtorno [16]. Outra característica marcante da BN é a auto avaliação indevida baseada no peso e na forma corporal. As alterações no funcionamento psicológico podem influenciar outras áreas do funcionamento como o funcionamento familiar e social.

O padrão alimentar das pacientes com BN é marcado por intensa restrição alimentar ou mesmo práticas de jejum, que se alternam com episódios de compulsão alimentar [17]. Uma composição pouco balanceada de nutrientes nas refeições de bulímicas pode constituir um dos fatores de manutenção do transtorno [18]. Os estudos utilizando recordatórios alimentares sugerem que as pacientes com BN consomem entre 3500 à 5000 kcal durante um episódio de compulsão [19].

A terceira síndrome descrita na DSM-5 é o Transtorno da Compulsão Alimentar. Este foi inicialmente descrito pelo psiquiatra americano Alfred Stunkard, na tentativa de diferenciar um subgrupo de pacientes obesos. Ele descreveu um grupo de pacientes que sofria episódios de compulsão alimentar, seguidos de intenso desconforto e auto condenação, no original [20]:

“ eating binges [...] with an orgiastic quality [...] followed by severe discomfort and expressions of self-condemnation”.

A ausência da prática de comportamentos compensatórios era um diferencial em relação aos pacientes com BN.

Há uma forte associação entre TCA e obesidade [8]. Tanto a obesidade pode preceder o TCA quanto o inverso. Geralmente, os pacientes com TCA ganham peso rapidamente e apresentam oscilações de peso mais frequente que obesos sem

TCA. Além disso, os portadores de TCA apresentam uma maior dificuldade em perder peso.

Mesmo que os episódios de compulsão alimentar do TCA tenham os mesmos critérios que os da BN, eles diferem em alguns pontos de sua caracterização. Os pacientes com TCA consomem menos calorias durante os episódios de compulsão (1500 à 3000 kcal), do que os pacientes com BN. Além disso, os episódios de compulsão de bulímicas tendem a ser mais ricos em carboidratos e açúcares [21] [22].

ANOREXIA NERVOSA	
DSM-5	***CID-10***
A. Restrição da ingestão alimentar relacionada às necessidades, levando a um peso corporal significativamente baixo, no contexto da idade, sexo, etapa do desenvolvimento e saúde física. Um peso significativamente baixo é definido como o peso que é menor que o minimamente normal, ou para as crianças e adolescentes, menor do que o mínimo esperado. B. Medo intenso de ganhar peso ou se tornar gordo, ou comportamentos persistentes que interferem com o ganho de peso, mesmo que com o peso significativamente baixo. C. Perturbação na forma que vivencia o peso e a forma corporais. Influencia indevida do peso ou forma corporal sobre a sua auto-avaliação ou persistente falta de reconhecimento da gravidade do baixo peso atual. Especificar o tipo atual: 1. Tipo restritivo – durante os últimos três meses o indivíduo não apresentou episódios de compulsão alimentar ou comportamentos purgativos (vômitos auto induzidos ou uso inapropriado de laxativos, diuréticos, ou enemas) 2. Tipo compulsão alimentar/purgação – durante os últimos três meses o indivíduo apresentou episódios de compulsão alimentar ou comportamento purgativos (vômitos auto induzidos ou uso inapropriado de laxativos, diuréticos, ou enemas). Especificar se: 1. Em remissão parcial: Depois de preencher todos os critérios de anorexia nervosa, o Critério A (baixo peso corporal) não esta sendo preenchido por um período de tempo mantido, mas ou o Critério B (intenso medo de ganhar peso ouse tornar gordo ou comportamento que interfira com o ganho de peso) ou o Critério C (distúrbio na auto-percepção do peso ou forma) é ainda preenchido. 2. Em remissão completa: Depois de preencher todos os critérios de anorexia nervosa, nenhum critério tem sido preenchido por um período de tempo mantido. Especificar gravidade atual: O nível mínimo de gravidade é baseado, para adultos, no índice de massa corporal atual (IMC) (veja abaixo) ou, para crianças e adolescentes, no percentil de IMC. As faixas abaixo são derivadas das categorias da Organização Mundial de Saúde para magreza em adultos: para crianças e adolescentes, os percentis de IMC devem ser usados. O nível de gravidade pode ser aumentado para refletir os sintomas clínicos, o grau de comprometimento funcional, e a necessidade de supervisão. Leve: IMC ≥ 17 Kg/m² Moderada: IMC 16-16.99 Kg/m² Grave: IMC 15-15.99 Kg/m² Extrema: IMC < 15 Kg/m²	A. O peso corporal é mantido em pelo menos 15% abaixo do esperado (tanto perdido como nunca alcançado) ou o índice de massa corporal de Quetelet em 17,5 ou menos. Pacientes pré-púberes podem apresentar falhas em alcançar o ganho de peso esperado durante o período do crescimento; B. A perda de peso é auto-induzida por abstenção de "alimentos que engordam" e um ou mais dos que se segue: vômitos auto induzidos, purgação auto induzida, exercício excessivo, uso de anorexígenos e/ou diuréticos; C. Há uma distorção da imagem corporal na forma de uma psicopatologia especifica por meio da qual um pavor de engordar persiste como uma idéia intrusiva e sobrevalorada, e o paciente impõe um baixo limiar de peso a si próprio; D. Um transtorno endócrino generalizado envolvendo o eixo hipotalâmico-hipofisário-gonodal é manifestado, em mulheres como amenorreia e, em homens, com a perda de interesse e potencia sexual (uma exceção aparente é a persistência de sangramentos vaginais em mulheres anoréticas que estão recebendo terapia de reposição hormonal, mais comumente tomada como uma pílula contraceptiva). Pode também haver níveis elevados de hormônio do crescimento, níveis aumentados de cortisol, alterações no metabolismo periférico do hormônio tireoidiano e anormalidades de secreção de insulina; E. Se o início é pre-puberal,a sequencia de eventos da puberdade é demorada ou mesmo detida (o crescimento cessa; nas garotas, os seios não se desenvolvem e há uma amenorreia primária; nos garotos, os genitais permanecem juvenis). Com a recuperação, a puberdade é com frequência completada normalmente, porém a menarca é tardia.

Figura 1 – Critérios diagnósticos da Anorexia Nervosa

BULIMIA NERVOSA	
DSM-5	***CID-10***
A. Episódios recorrentes de compulsão alimentar. Um episódio de compulsão alimentar é caracterizado por ambos: (1) comer, num período de tempo definido (por exemplo, dentro de um período de 2 horas), um montante de comida que é definitivamente maior do que a maioria pessoas come durante o mesmo período de tempo e em circunstâncias semelhantes, (2) um sentimento de falta de controle sobre a alimentação durante o episódio (por exemplo, um sentimento de que não consegue parar de comer ou controlar o que ou quanto está comendo). B. Recorrentes comportamentos compensatórios inadequados,a fim de evitar o ganho de peso, tais como a auto-indução devómitos; consumo de laxantes, diuréticos, enemas, ou outrosmedicamentos; jejum ou exercício excessivo. C. Ambos, a compulsão alimentar e os comportamentos compensatórios inadequados ocorrem, em média, pelo menos uma vez por semana durante três meses. D. A auto avaliação é indevidamente influenciada pela forma e peso corporal. E. A perturbação não ocorre exclusivamente durante episódios de Anorexia Nervosa. Especificar se: 1. Em remissão parcial: Depois de preencher todos os critérios de bulimia nervosa, alguns, mas não todos os critérios têm sido preenchidos por um período de tempo mantido. 2. Em remissão completa: Depois de preencher todos os critérios de bulimia nervosa, nenhum critério tem sido preenchido por um período de tempo mantido. Especificar gravidade atual: O nível mínimo de gravidade é baseado na frequência de comportamentos compensatórios inadequados (veja abaixo). O nível de gravidade pode ser aumentado para refletir outros sintomas e o grau de comprometimento funcional. Leve: Uma média de 1-3 episódios de comportamentos compensatórios inadequados por semana. Moderada: Uma média de 4-7 episódios de comportamentos compensatórios inadequados por semana. Grave Uma média de 8-13 episódios de comportamentos compensatórios inadequados por semana. Extrema: Uma média de 14 ou mais episódios de comportamentos compensatórios inadequados por semana.	A. Há uma preocupação persistente com o comer e um desejo irresistível por comida; o paciente sucumbe a episódios de hiperfagia, nos quais grandes quantidades de alimento são consumidas em curtos períodos de tempo. B. O paciente tenta neutralizar os efeitos de "engordar" dos alimentos através de um ou mais do que se segue: vômitos auto induzidos, abuso de purgantes, períodos alternados de inanição. Quando a bulimia ocorre em pacientes diabéticos, podem escolher negligenciar seu tratamento insulínico. C. A psicopatologia consiste de um pavor mórbido de engordar e o paciente coloca para si mesmo um limiar de peso nitidamente definido, bem abaixo do seu peso pré-mórbido que constitui o peso ótimo ou saudável na opinião do medico. Há frequentemente, mas não sempre, uma história de um episódio prévio de anorexia nervosa, o intervalo entre os dois transtornos variando de vários de poucos meses a vários anos. Esse episódio prévio pode ter sido completamente expressado ou pode ter assumido uma forma "disfarçada" menor, com uma perda de peso moderada e/ou uma fase transitória de amenorreia.

Figura 2 – Critérios diagnósticos da Bulimia Nervosa

CRITÉRIOS DIAGNÓSTICOS PARA O TRANSTORNO DA COMPULSÃO ALIMENTAR (TCA) NO DSM-5

A. Episódios recorrentes de compulsão alimentar. Um episódio de compulsão alimentar é caracterizado por ambos:
   (1) comer, num período de tempo definido (por exemplo, dentro de um período de 2 horas), um montante de comida que é definitivamente maior do que a maioria pessoas come durante o mesmo período de tempo e em circunstâncias semelhantes,
   (2) um sentimento de falta de controle sobre a alimentação durante o episódio (por exemplo, um sentimento de que não consegue parar de comer ou controlar o que ou quanto está comendo).

B. Os episódios de compulsão alimentar estão associados a três (ou mais) dos seguintes:
   1. Comer muito mais rapidamente do que o normal;
   2. Comer até sentir-se incomodamente repleto;
   3. Comer grandes quantidades de alimentos, quando não está fisicamente faminto;
   4. Comer sozinho por embaraço devido à quantidade de alimentos que consome;
   5. Sentir repulsa por si mesmo, depressão ou demasiada culpa após comer excessivamente.

C. Angústia acentuada relativa a presença de compulsão alimentar

D. A compulsão alimentar ocorre, na média, pelo menos uma vez por semana por três meses.

E. A compulsão alimentar não está associada ao uso recorrente de comportamentos compensatórios inadequados como na bulimia nervosa e nem ocorre durante o curso de bulimia nervosa ou anorexia nervosa.

Especificar se:

Em remissão parcial: Depois de preencher todos os critérios do transtorno da compulsão alimentar periódica, os episódios de compulsão alimentar ocorrem numa frequência média menor que um episódio por semana por um período de tempo mantido.

Em remissão completa: Depois de preencher todos os critérios de transtornos da compulsão alimentar, nenhum critério tem sido preenchido por um período de tempo mantido.

Especificar gravidade atual:

O nível mínimo de gravidade é baseado na frequência episódios de compulsão alimentar (veja abaixo). O nível de gravidade pode ser aumentado para refletir outros sintomas e o grau de comprometimento funcional.

Leve: 1-3 episódios de compulsão alimentar por semana.

Moderada: 4-7 episódios de compulsão alimentar por semana.

Grave: 8-13 episódios de compulsão alimentar por semana.

Extrema: 14 ou mais episódios de compulsão alimentar por semana.

Figura 3 – Critérios diagnósticos do Transtorno da Compulsão Alimentar

1.2.2 Epidemiologia dos TA

Os inquéritos epidemiológicos trazem diferentes estimativas para a AN de acordo com o desenho do estudo. A prevalência da AN varia de 0 até 0,9% na população geral, enquanto a ponto prevalência para AN em mulheres jovens é de 0,5% e a prevalência ao longo da vida varia de 1,2 à 2,2% [23]. A incidência da AN entre as mulheres sobe de 18.46 por 100.000 pessoas por ano em todas as faixas etárias, para 270 por 100.000 e mulheres na faixa de 15-19 [24 25]. A AN tem um pico bimodal de incidência aos 15 e aos 19 anos e as tendências históricas demonstram frequências relativamente estáveis em mulheres jovens apesar de terem sido relatados aumentos de até três vezes nos últimos 40 anos, nas mulheres da terceira e quarta décadas de vida [24]. Em vez de um aumento real no número de casos de TA, é possível que os aumentos nas taxas históricas se devam ao maior número de serviços especializados para TA, uma maior preocupação e disseminação de informações sobre a existência dos TA e a consequente identificação de casos na população, além das mudanças na estrutura demográfica da população.

A distribuição por gênero da AN é de 1:10 casos (homens:mulheres), com uma distribuição mais equilibrada entre os gêneros para os casos de AN pediátrica, com meninos representando 25% dos casos [26]. Vale ressaltar que os casos de TA pediátrico já são considerados mais frequentes que os casos de diabetes tipo 2 em crianças [27].

Apesar da BN ser mais comum do que a AN, essa síndrome é descrita como apresentando uma ponto prevalência que varia entre 0,9 a 1,5% em mulheres e de 0,1 a 0,5% em homens [28]. Utilizando os critérios da DSM-5, a prevalência é de 2,3% na população geral, com alguns estudos atingindo 2,9%. As formas atípicas (ou subclínicas) de BN são frequentes e sua prevalência pode chegar à 5,4% da população[25,29]. A incidência da BN tem se mantido relativamente estável desde a década de 90 até o início do ano 2000, em mulheres dos 16 aos 20 anos de idade. As análises de bancos de dados de clínicos gerais do Reino Unido demonstrou que a incidência da BN é de 20,7 em mulheres e 11,8 na população geral, para 100.000 pessoas por ano. Essa taxa aumenta para 46,8 no grupo de mulheres de 15 a 19 anos [30].

O TA mais comum na população geral é o TCA. Sua prevalência na população é de aproximadamente 3,5% em mulheres e 2% em homens [31]. Numa

avaliação nacional nos Estados Unidos, a taxa de incidência foi de 660 em homens e 1010 a cada 100.000 pessoas/ano em mulheres [32]. Por fim, é importante ressaltar que todos os TA podem ocorrer em ambos os gêneros, em qualquer faixa etária, em qualquer nível socioeconômico e país.

1.3 O conceito de comorbidade em Psiquiatria

O conceito de comorbidade em psiquiatria suscita uma discussão polêmica sobre a formação dos construtos diagnósticos que foge ao escopo da presente Tese. Entretanto, algumas considerações sobre a evolução deste conceito e o seu uso no campo da pesquisa psiquiátrica se fazem necessários para contextualizar o presente trabalho.

Devido a uma preocupação com as condições experimentais dos estudos de caso-controle, o médico e epidemiologista americano Alvan Feinstein investigou fatores que poderiam afetar o curso de uma doença índice ou mesmo o efeito de um tratamento sobre ela [33]. No conceito proposto por Feinstein, é considerada uma comorbidade, "*qualquer entidade clínica distinta e adicional, que seja pré-existente ou que passe a ocorrer durante o curso clínico de um paciente que possua a doença índice em estudo*" [34]. O autor classifica uma "*comorbidade funcional*", onde a doença adicional influencia o curso clínico da doença índice e uma "*comorbidade diagnóstica*", onde a doença adicional produz sintomas que simulam aqueles da doença índice e dificultam a sua identificação. As comorbidades poderiam ser avaliadas em diferentes pontos de observação temporais em relação à doença índice; exemplificando com um paciente portador de câncer de pulmão que podem ter tido como comorbidade pré-existente catapora na infância; pode apresentar como comorbidade atual uma pneumonia pneumocócia; e ainda, ter como comorbidade posterior ao início da doença índice, um acidente traumático. O autor salienta como o estudo das comorbidades poderia influenciar as taxas de morbi-mortalidade em estudos de saúde pública, demonstrando que a sua preocupação na definição deste conceito era especialmente epidemiológica [34].

A adaptação deste conceito para a psiquiatria foi definida por Cloninger como "um aumento no risco de dois transtornos mentais ocorrerem conjuntamente" e afirma que "para os transtornos mentais, a presença de uma comorbidade é mais uma regra do que uma exceção" [35]. O argumento de Cloninger está em

concordância com a maior parte da literatura que demonstra altas taxas de comorbidades psiquiátricas em indivíduos portando um transtorno psiquiátrico índice [31,36]. Entretanto, a valorização do conceito de comorbidade se faz em contrapondo ao conceito de diagnóstico diferencial. Segundo o psiquiatra iugoslavo Vladan Starcevic, a visão contemporânea em psiquiatria expõe que "A discussão atual sobre diagnóstico diferencial é conduzida de forma que o clínico pense em uma comorbidade, ou seja, se um diagnóstico principal alternativo seria melhor conceitualizado como um diagnóstico adicional" [37].

Entretanto, apesar do esforço de fenomenologistas de tentarem comprovar que a maior parte das comorbidades em psiquiatria seria melhor explicada pelo diagnóstico diferencial e uma avaliação de critérios relacionados a curso clínico da doença índice [38], a realização de subsequentes entrevistas diagnósticas por psiquiatras com um bom treinamento em psicopatologia levava a taxas de aproximadamente 25% dos pacientes sendo classificados como apresentando um transtorno atípico pois teria critérios para mais de um transtorno [38,39].

1.4 A comorbidade entre TDAH e TA

Uma proporção significativa dos pacientes com TA não apresenta remissão completa do transtorno com os tratamentos propostos[40], em estudos de seguimento.

A identificação de subgrupos de pacientes com quadros comórbidos ao TA pode ajudar na compreensão do motivo desses diferentes cursos clínicos para um mesmo transtorno [41] e auxiliar no planejamento terapêutico personalizado que atenda às necessidades individualizadas.

Existe interesse em avaliar se transtornos do desenvolvimento podem aumentar o risco para iniciar um TA. Por exemplo, há uma associação entre autismo e Anorexia Nervosa, especialmente no subtipo restritivo, [42], enquanto que o subtipo purgativo já foi associado ao TDAH [43].

A associação entre BN e TCA com TDAH já foi demonstrada repetidas vezes na literatura científica [44,45]. Mattos e cols. 1999 relataram uma alta frequência de TA, em especial de TCA, numa amostra de pacientes com TDAH que buscaram tratamento especializado, em 2004[45]. Esse resultado foi replicado em 6 outras amostras investigadas por outros grupos[43,46–50].

Na primeira revisão sistemática sobre o tema, publicada em 2008 [51], demonstramos que a BN foi o TA mais frequentemente encontrado em portadores com TDAH [51]. A gravidade e o número de sintomas de TDAH é mais elevado em portadores de BN ou TCA, quando comparados com portadores de AN [52].

O acompanhamento prospectivo de filhos de mulheres portadoras de AN e BN encontrou uma taxa significativamente maior de sintomas de hiperatividade em seus filhos, em relação ao encontrado em filhos de mulheres controles [53].

Os estudos investigando TA em portadores de TDAH encontraram prevalências de BN que variavam de 9 [46] até 11% [54], enquanto que as taxa de TCA variavam de 9,3 [36] até 11,4% [50], e a taxa de AN foi de 1% [49]. Em contrapartida, os estudos em portadores de TA encontraram que entre 3% [55] à 16,2% [31] dos pacientes com AN; de 9 [55] até 34,9% [31]; e 19,8% dos portadores de TCA [31] apresentavam diagnóstico de TDAH.

Uma associação positiva e significativa entre os sintomas de TDAH e os de TA já foi demonstrada em estudos correlacionais [52,56–62], com coeficientes de correlação que variavam de 0,23 [57] a 0,59 [60]. O número de sintomas de TDAH se correlaciona positivamente com a gravidade dos sintomas de TA em todos os pacientes com predominância de comportamentos compulsivos/purgativos [52]. Os sintomas de TDAH conseguem predizer a gravidade da compulsão alimentar [58,59,63] e de sintomas bulímicos, mesmo controlando para a influência de sintomas depressivos e ansiosos [57,63].

Em populações pediátricas, o comportamento de perda de controle da alimentação, do inglês "*Loss of Control eating*" (LOC), que é uma forma subclínica de compulsão alimentar, enfatiza o componente subjetivo de perda de controle, já anteriormente associado ao TDAH [64]. Talvez esse sintoma tenha sido mais estudado visto que quadros complexos de BN e TCA se desenvolvem em contextos onde há maior autonomia alimentar, ou seja, em idades posteriores como na adolescência onde é possível a obtenção de grande quantidade de alimento pelo indivíduo, sendo daí possível caracterizar o critério objetivo da compulsão [64].

Apesar da trajetória mais plausível ser aquela onde sintomas de TDAH precedem os de TA aumentando o risco do desenvolvimento de um comportamento alimentar alterado, é possível que as consequências de um TA no funcionamento cognitivo [65] possam produzir sintomas similares aos do TDAH.

A ligação entre esses transtornos ainda é pouco compreendida e possivelmente se deve a uma combinação de fatores genéticos e ambientais. A variabilidade genética em genes dopaminérgicos relacionados ao processamento de recompensas foi descrito em um paciente com TDAH comórbido com TCA [66], em um estudo caso-controle de portadores de TDAH comórbido com TCA [67] e numa coorte de mulheres com BN e histórico de TDAH na infância [68].

Alterações em mecanismos de controle da atenção e controle de impulsos são características comuns a ambos os transtornos. Os comportamentos impulsivos são uma característica fundamental do diagnóstico de TDAH [2] e déficits na sua regulação já foram demonstrados nestes indivíduos [69]. Além disso, a impulsividade pode ser um dos componentes da compulsão alimentar e da purgação [70]. A *urgência negativa* é um componente da regulação dos impulsos e já foi demonstrada como sendo um mediador entre compulsão alimentar e regulação emocional [71], o que também poderia auxiliar a explicar essa associação. Os pacientes com a comorbidade TDAH+TA apresentam escores mais elevados de autorrelato de traços impulsivos do que portadores de qualquer um desses transtornos isoladamente [60,63] .

Os pacientes com TA podem apresentar diferentes alterações no funcionamento atencional, tais como deficiência na atenção sustentada e deficiência na velocidade de processamento [65,72]. A codificação de recompensas também está alterada em pacientes com TA, havendo maior ativação atencional dirigida à estímulos que estão associados com comidas palatáveis. O desenvolvimento de vieses na ativação e no funcionamento atencional de portadores de TA também pode se associar a deficiências na capacidade de regular a motivação para a adoção de um padrão alimentar saudável ou outros cuidados com o corpo como a prática de atividade física [73]. Há propostas de treinamento para reforçar a atenção a estímulos neutros e não – relacionados à alimentação que podem ser benéficos na correção desses vieses [74,75]. Infelizmente, os estudos que avaliaram vieses atencionais não exploraram a presença do TDAH como um mediador da eficácia dos programas de treinamento cognitivo.

Os indivíduos com TDAH tipicamente apresentam dificuldades motivacionais e tem uma tendência a preferir recompensas imediatas, o que leva à uma dificuldade em postergar recompensas [76]. De acordo com este conceito, os indivíduos com TDAH estariam mais vulneráveis ao desenvolvimento de compulsão alimentar por apresentarem dificuldades em manter hábitos saudáveis no longo prazo

(recompensas tardias) em contraposição a buscarem alimentos que provêm uma sensação de prazer (recompensa imediata).

Em relação ao tratamento, a recente aprovação do uso de lisdexanfetamina para o tratamento do TCA pelo Food and Drug Administration nos Estados Unidos [77] ressalta o interesse em investigar o uso de psicoestimulantes no tratamento dos TA. Vários relatos de caso já foram publicados descrevendo melhoras no quadro clínico de pacientes com quadros refratários de BN, associados à história de TDAH na infância ou na vida adulta [78–83]. Entretanto, em um recente ensaio clínico utilizando lisdexanfetamina para o tratamento de TCA [77], o benefício clínico foi mantido mesmo excluindo os pacientes portadores de TDAH. Isso sugere que os psicoestimulantes podem auxiliar portadores com TA mesmo na ausência de TDAH. De fato, é bem documentado o efeito supressor do apetite pelos psicoestimulantes [84]. Portanto, é importante avaliar se a melhora dos TA com uso de psicoestimulantes se deve primariamente a este efeito, ressaltando-se ainda a preocupação de que pacientes impulsivos têm potencial para uso indevido deste grupo medicamentoso [85], com o objetivo de perda de peso. Um recente relato de caso ressalta que o tratamento de TDAH em pacientes com TA não diagnosticado anteriormente, pode levar a grave perda de peso, com importantes consequências clínicas [86].

O TDAH em adultos está relacionado a maiores taxas de obesidade em ambos os sexos. Alguns fatores explicando esta associação são a perturbação do comportamento alimentar, maiores taxas de distúrbios do sono ocasionando mudanças no apetite e uma desregulação do processamento de recompensas [87]. A associação entre obesidade e TA nos pacientes com TDAH ainda foi pouco estudada com apenas um estudo em crianças [64] e dois em adultos [62,88] explorando esta associação. Há dúvidas se a presença do TDAH em obesos com TA poderia mudar a apresentação clínica destes pacientes.

2 OBJETIVOS E JUSTIFICATIVA

2.1 Objetivo Primário do Estudo Clínico

O *objetivo primário* desta tese foi avaliar se a presença de um transtorno alimentar modifica o funcionamento cognitivo de portadores com TDAH. A importância disto recai na necessidade de avaliar se esses pacientes apresentariam diferentes necessidades de tratamento em relação aos portadores de TDAH isoladamente, ou se apresentariam um funcionamento cognitivo que potencialmente prejudicaria a resposta aos tratamentos usuais do TDAH.

2.2 Objetivos Primário e Secundário da Revisão Sistemática com Meta-análise

O *objetivo primário desta revisão sistemática* foi realizar uma meta-análise de estudos sobre o risco que portadores de TDAH apresentam de desenvolver algum dos TA (AN, BN ou TCA), e vice-versa;Os objetivos secundários foram atualizar a revisão sistemática publicada em 2008 [51], intitulada "Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders"; realizar uma meta-análise para sintetizar a força de associação dos estudos de correlação de sintomas de TDAH e TA; além de explorar num modelo de meta-regressão, fatores que pudessem explicar a variância do tamanho de efeito.

2.3 Apresentação da Tese

Na Parte Textual são apresentados dois estudos que aprofundam a investigação da comorbidade TDAH com TA. Estes dois estudos foram relatados conjuntamente sendo retirados do formato que seriam apresentados em um periódico. Apresentamos uma revisão sistemática com meta-análise sobre TDAH comórbido com TA e um estudo clínico onde avaliamos se a presença de TA poderia modificar o funcionamento cognitivo de alunos universitários portadores de TDAH.

Na seção de Anexos são apresentados seis artigos publicados durante o período do Doutorado. No primeiro artigo, reproduzimos a revisão sistemática com meta-análise, já descrita na Parte Textual, da maneira em que foi publicada no periódico *International Journal of Eating Disorders*.

No segundo artigo, intitulado "*Influence of attention-deficit / hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women",* realizamos novas análises na amostra estudada durante o Mestrado para avaliar como a presença da comorbidade TDAH com TA pode provocar mudanças na apresentação clínica e características psicopatológicas de mulheres obesas. Também demonstramos que sintomas depressivos e a os sintomas de desatenção são os melhores preditores da gravidade da compulsão alimentar nesta população.

No terceiro artigo, intitulado "*Can a Continuous Perfoemance Test help to assign innatention when mood and ADHD symptoms coexist?",* começamos a trabalhar com uma amostra não-clínica de universitários e investigamos a relação entre os sintomas de desatenção, os sintomas depressivos e uma medida neuropsicológica de atenção, através de um teste de performance contínua para avaliar se os sintomas de desatenção seriam primários ou melhor explicados por sintomas depressivos.

Em seguida são apresentados três artigos que exploram novas possibilidades de individualização para o tratamento dos pacientes com TA, para além da caracterização de uma comorbidade como o TDAH.

No quarto artigo da tese, realizamos uma revisão sistemática com meta-análise de como o ritmo de resposta aos tratamentos usuais para TA pode predizer quais pacientes vão atingir a remissão ao final deste. Também discutimos os diferentes conceitos e critérios utilizados na literatura para classificar os pacientes com AN, BN e TCA como respondedores precoces ao tratamento.

No quinto artigo da tese, apresentamos uma revisão sobre como novas técnicas de abordagem de cuidadores podem auxiliar no desfecho clínico de portadores de TA, especialmente AN.

Em seguida, no sexto da tese, apresentamos um relato de caso sobre o uso da estimulação magnética transcraniana em um paciente com TCA resistente ao tratamento.

3 METODOLOGIA

3.1 Metodologia utilizada na Revisão Sistemática e na meta-análise:

Nazar, B.P., Bernardes, C., Peachey, G., Sergeant, J., Mattos, P., Treasure, J. (2016). ***The risk of Eating Disorders comorbid with Attention-Deficit / Hyperactivity Disorder: A Systematic Review and Meta Analysis*****. International Journal of Eating Disorders, (publicado).**

Utilizamos as diretrizes descritas no "PRISMA statement" (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*) [89] para a realização desta revisão sistemática e para as meta-análises. Os seguintes unitermos em inglês foram utilizados para construir a estratégia de busca: [*("Eating Disorders"; "Anorexia Nervosa"; "Bulimia"; "Bulimia Nervosa"; "Binge Eating Disorder"; "Binge Eating"; "Overeating"*) *AND ("Hyperactivity with attention-deficit disorder"; "ADHD"; "ADD"; "Inattention"*)]. As buscas foram realizadas utilizando as bases de dados PubMed, Scielo, PsychINFO and ISI *Web of Knowledge*.

Dois pesquisadores (Bruno Palazzo Nazar e Camila Bernardes) realizaram as buscas de forma independente e os artigos foram considerados elegíveis para inclusão: (1) se publicados em inglês, português, espanhol, holandês, francês ou alemão; (2) se foram realizados com desenho caso-controle ou se consistiam num estudo de correlação de sintomas; (3) se apresentavam dados para o cálculo da razão de chance ou de correlação de sintomas; (4) se haviam sido publicados em periódicos com sistema de revisão por pares (*peer-reviewed*). Foram excluídos os estudos que não especificaram como o TDAH ou como o TA foram diagnosticados. Realizamos uma busca manual de artigos das listas de referências dos artigos selecionados na busca inicial para buscar outros estudos relevantes. Finalmente, as listas finais de artigos selecionados por cada avaliador foi comparada e itens discordantes discutidos. No caso dos dois avaliadores falharem em obter um consenso, a referência discordante seria submetida a avaliação de dois pesquisadores supervisores (Paulo Mattos e Janet Treasure). Após a discussão das listas finais de cada autor, uma lista síntese foi obtida após remoção de referências em duplicata utilizando o programa de referências bibliográficas *EndNote*.

O critério de eligibilidade para inclusão na meta-análise requeria que: a) o estudo indicasse a frequência de TA em uma amostra de TDAH e em Controles; b) ou que indicasse a frequência de TDAH em uma amostra de TA e em Controles; c) ou que o estudo indicasse o coeficiente de correlação entre os sintomas de TDAH e TA ou que houvesse publicado outro índice que pudesse ser transformado matematicamente num coeficiente de correlação.

Além disso, os autores principais dos artigos selecionados foram contactados para obtenção de dados que não haviam sido publicados em seus manuscritos. Assim, os dados utilizados para Mikami et. al., 2008 [90]; Mikami et. al., 2010 [91]; Docet et. al., 2012 [88]; Reinblatt et. al., 2015 [64]; Reinblatt et. al., 2015 (b) [92], Sonneville et. al., 2015 e Rojo-Moreno et al., 2015 [93] foram gentilmente cedidos pelos autores. O banco de dados de Nazar et. al., 2014 [63] estava disponível para extração das medidas necessárias. Adicionalmente, após contactar um dos autores (Ronald Kessler) do "*Collaborative Psychiatric Epidemiological Surveys* (CPES)", nós utilizamos as informações disponíveis do banco de dados indicado por este autor para a extração dos dados necessários para o estudo "*National Comorbidity Survey – Replication (NCS-R, 2001-2003)*" [94].

A razão de chance de um indivíduo com TDAH x Controles apresentar um TA, assim como, a razão de chance de um indivíduo com TA x Controles apresentar TDAH foi calculada utilizando um modelo de efeitos aleatórios, no programa *STATA 12 (Stata corporation, College Station, TX, USA)*. Utilizamos os comandos *Metan*, *Metabias* e *Metareg*.

Com a finalidade de obter o coeficiente de correlação sintético entre sintomas de TA e TDAH, inicialmente padronizamos os escores obtidos através de diferentes escalas transformando-os para a escala Z de Fisher, com a fórmula:

$$(Z = ½ \ln(^{1 + r}/_{1 - r}))$$

e o cálculo do seu desvio padrão calculado pela equação:

$$(SE_Z = 1/\sqrt{}(n-3)$$ [95]

Essa meta-análise utilizou o modelo Hedges-Olkin de efeitos aleatórios. Para calcular o coeficiente de correlação sintético de volta a escala normal, utilizamos a fórmula:

$$(e^{((2xZpool - 1)/ (2xZpool + 1)})$$

A heterogeneidade dos estudos foi calculada através da estatística Q de Cochran, expressa através do resultado em qui-quadrado. A inconsistência dos estudos foi investigada utilizando a estatística I^2 , calculada através da fórmula:

$$[(Q-df)/Q]$$ [96]

A avaliação de viés de publicação foi realizada utilizando o teste de Harbord, que explora o chamado "*small studies effect*" para explicar as variações na razão de chance. Este teste é mais adequado para dados binários pois resulta numa menor taxa de falsos positivos do que o rotineiramente utilizado teste de Egger [97]. Finalmente, realizamos a análise visual dos gráficos de dispersão em funil para inspecionar o viés de publicação.

Todos os estudos foram avaliados com a versão para estudos caso-controle da *Newcastle-Ottawa Quality Assessment Tool* [98]. A avaliação de qualidade dos artigos foi usada como um possível viés que explicasse a variância da razão de chance. Cada estudo poderia receber ao menos quatro pontos na subescala de seleção e dois pontos na subescala de comparabilidade, e três pontos na subescala de exposição dos resultados.

Realizamos uma meta-regressão para investigar se a média de idade; categoria de peso; proporção de participantes do sexo feminino; tamanho da amostra; método para a realização do diagnóstico de TDAH; método para a realização do diagnóstico de TA; país onde o estudo foi publicado; e qualidade do estudo poderiam explicar a variância da razão de chances.

3.2 Metodologia utilizada no estudo Clínico:

Nazar, B.P., Bernardes, C., Malloy-Diniz, L., Treasure, J., Sergeant, J., Mattos, P. *Eating Disorders impair cognition and weight regulation of ADHD: a clinical and neuropsychological investigation*. (em preparação)

3.2.1 Participantes

Foi selecionada uma amostra de alunos de Medicina do 9o período da Universidade Federal do Rio de Janeiro. A seleção foi realizadas ao longo de quatro anos, sendo cada novo recrutamento aqui denominado uma onda de recrutamento, sendo o total de oito ondas de recrutamento. Os alunos eram convidados a preencher um rastreio de TDAH (o ASRS-18), sendo convidados a participar do protocolo todos aqueles que apresentassem acima de cinco sintomas de desatenção e/ou hiperatividade (rastreios positivos); todos aqueles que pontuassem entre três e quatro sintomas (rastreios subclínicos); e um mesmo número randomizado de rastreios negativos eram convidados para participar do protocolo.

Todas as ondas de recrutamento mantiveram a mesma metodologia.

No presente estudo selecionamos para análise apenas os alunos com diagnóstico de TDAH; os alunos que apresentavam a comorbidade TDAH+TA e um número randomizado de estudantes sem qualquer outro diagnóstico psiquiátrico como Controles.

Todos os alunos assinaram consentimento informado e o projeto foi aprovado pelo comitê de ética do IPUB-UFRJ.

Os critérios de inclusão no estudo foram:

- estar regularmente matriculado como estudante da UFRJ
- ter compreendido o termo de consentimento e desejar participar voluntariamente da pesquisa

Os critérios de exclusão para a participação da pesquisa foram:

- presença de epilepsia ou outro transtorno neurológico
- presença de algum distúrbio endocrinológico descompensado que

sabidamente interfere com o apetite (ex. hipertireoidismo)

- presença de transtorno psicótico (ex. esquizofrenia, transtorno delirante persistente)
- uso atual de antipsicóticos ou estabilizadores do humor

O protocolo de pesquisa era completado em duas visitas, com uma semana de diferença. No primeiro dia de avaliação, era realizado uma entrevista clínica seguida de aplicação de entrevistas semi-estruturadas. Após um breve intervalo, os alunos retornavam para o preenchimento dos questionários. A primeira visita durava aproximadamente 1 hora. No segundo dia de avaliação, os alunos eram convidados a realizar uma bateria de testes neuropsicológicos com duração aproximada de duas horas.

3.2.2 Procedimentos durante a avaliação clínica

A avaliação de todos os participantes consistiu na realização de uma entrevista clínica para avaliação da presença dos critérios de exclusão, mensuração de peso e altura, seguida de entrevistas semi-estruturadas seguindo os critérios do DSM-5. Todas as entrevistas foram realizadas por psiquiatras. Os diagnósticos eram determinados após a entrevista semi-estruturada e complementados com discussão de dados clínicos para a definição da codificação final.

As seguintes entrevistas semi-estruturadas foram aplicadas:

- Módulo de TDAH do K-SADS adaptado para adultos [99]: O diagnóstico de TDAH era realizado se o indivíduo apresentasse ao menos 5 sintomas de desatenção e/ou 5 sintomas de hiperatividade/ impulsividade no presente; se apresentasse ao menos 5 sintomas de desatenção e/ou 5 sintomas de hiperatividade/impulsividade no passado, que se apresentassem antes dos 12 anos de idade; ocorrência dos sintomas em no mínimo dois ambientes diferentes da vida do sujeito; relatasse comprometimento significativa devido aos sintomas. Todas as avaliações de TDAH eram realizadas cegamente em relação ao resultado do rastreio, que era estudado, para a escolha e definição de status, por outro pesquisador. Se um diagnóstico positivo fosse realizado, ele seria discutido com o pesquisador coordenador do grupo.

- Módulo de Transtornos Alimentares da SCID-P [100]: Dentro desta entrevista eram contempladas as possibilidades diagnósticas de TA para o DSM-IV, que foram adaptadas para os critérios da DSM-5 de AN, BN e TCA. Adicionamos a possibilidade de BN subclínica (caso o critério de frequência para episódios de compulsão alimentar/uso de mecanismos compensatórios fosse menor que 1x semana porém maior do que 1x mês; ou que o critério de insatisfação com a imagem corporal não fosse atendido porém o critério de episódios de compulsão/uso de mecanismos compensatórios fosse atendido); e de TCA subclínico (caso a frequência de episódios de de compulsão alimentar fosse menor que 1x semana porém maior do que 1x mês; ou se o critério de impacto devido à ocorrência de compulsão não estivesse bem definido ou não fosse atendido).
- Mini-International Neuropsychiatric Interview (MINI-Plus) [101]: Todos os módulos foram utilizados com exceção dos módulos de Transtornos Alimentares, TDAH e Transtorno de Personalidade Anti-Social.

3.2.3 Questionários de autopreenchimento

Além das entrevistas semi-estruturadas, os participantes preencheram os seguintes questionários de auto-preenchimento na primeira visita. Todos os participantes receberam instruções sobre o preenchimento, nas quais eram explicados o tema principal de cada questionário e a necessidade de que revisassem a escala ao final do preenchimento:

- Adult Self-Rating Scale (ASRS-18) [102]: uma escala likert de 18 ítens utilizada como rastreio para o TDAH. Ela apresenta questões sobre cada um dos 18 sintomas de TDAH listados na DSM-5 e cada um dos sintomas pode ser marcado numa escala de frequência de 0 até 4. Os comportamentos são considerados “positivos para TDAH” quando iguais a 3 ou 4. A escala apresenta uma grupo de 9 sintomas de desatenção e outro grupo de 9 sintomas de hiperatividade/impulsividade. Todas as perguntas avaliam sintomas nos últimos 6 meses.
- *Binge Eating Scale* (BES) [104]: um questionário de 16 ítens, utilizado como rastreio de compulsão alimentar, assim como para avaliar a gravidade da

compulsão alimentar. Este questionário avalia o fenômeno da compulsão alimentar em maior profundidade do que os questionários para Bulimia Nervosa, levando em conta distorções cognitivas e comportamentais relacionadas a este fenômeno. Os escores acima de 17 são considerados positivos para compulsão alimentar.

- *Inventário de Depressão de Beck (IDB)* [105,106]: Esta escala foi desenvolvida para a avaliação da gravidade de sintomas depressivos e contem 21 questões numa escala do tipo likert de 0 a 3. Escores iguais ou acima de 10 são indicativos de depressão leve, escores iguais ou acima de 19 indicam depressão moderada e escores iguais ou acima de 30 são indicativos de depressão grave.
- *Inventário de Ansiedade Traço e Estado (IDATE-T e IDATE-E)* [107]: é um questionário composto de duas subescalas, uma avalia o traço de ansiedade ao longo da vida e a outra o estado de ansiedade atual. Possui 20 perguntas em cada subescala, numa escala likert de 1 a 4. Os escores variam de 20 a 80 com escores mais altos indicativos de maior presença de sintomas ansiosos.
- *Escala de Impulsividade de Barratt* (BIS-11)[108]: Essa escala mensura impulsividade em situações de vida consideradas cotidianas e com isso avalia o traço de impulsividade. Possui 30 ítens e e produz um escore total além de escores em subescalas. Na BIS-11 original são descritas 3 subescalas (atencional, motora e de planejamento), com escores para cada uma delas além do escore total. A análise utilizada no presente trabalho é a da versão brasileira [109] que após análise desta escala, a reconceitualizou como sendo melhor descrita com duas subescalas, não-planejamento (BIS-ATPLAN) e comportamentos impulsivos cognitivos e motores (BIS-CINI) [110].

3.2.4 Avaliação neuropsicológica

Todos os testes neuropsicológicos foram aplicados por um neuropsicólogo com experiência nos testes. As seguintes funções cognitivas foram avaliadas:

- **Quoeficiente de Inteligência (QI)**: foi calculado utilizando os quatro subtestes (blocos, vocabulário, matrizes e semelhanças) da bateria *Wechsler Abbreviated Intelligence Scale* (WASI) (Heck et al., 2009).

- **Atenção e impulsividade motora:** foi avaliada utilizando o teste de performance contínua *Conner's Continuous Performance Task II* (CPT-II) [111]: Os testes de performance contínua são os mais comumente utilizados na prática clínica [112] e possibilitam avaliar a habilidade do indivíduo em manter respostas cocnsitentes ao longo do tempo e com diferentes velocidades de apresentação de estímulos [113]. As variáveis de interesse para o presente estudo foram o número de erros por omissão (OMI); número de erros por ação, no inglês, *commission errors* (COM); e velocidade de respostas, no inglês, *hit reaction time* (HRT). OMI ocorre quando o indivíduo falha em responder adequadamente aos estímulos contendo a letra alvo (todas as letras, exceto a letra "X"); COM ocorre quando o indivíduo responde à apresentação da letra alvo (a letra "X"), situação em que ele deveria inibir a resposta. HRT é o tempo médio de ação para todas as respostas do indivíduo, quando letras diferentes do "X" são apresentadas.
- **Tomada de decisão e impulsividade de planejamento:** O *Iowa Gambling Task* (IGT) [114] foi utilizado em sua versão computadorizada na qual sujeitos precisam selecionar cartas dentre quatro possíveis blocos de cartas. Os sujeitos são instruídos que para ganhar a maior quantidade de dinheiro (virtual) devem selecionar cartas entre os blocos e que alguns blocos são mais vantajosos do que outros. Dois blocos de cartas trazem ganhos imediatos grandes porém, também promovem grandes perdas futuras (blocos A e B), enquanto que os outros dois blocos promovem ganhos pequenos associados a perdas futuras pequenas (Blocos C e D). Após 100 escolhas, um escore total, em inglês, *net score*, é calculado utilizando a equação [(Blocos C+D) – (Blocos A+B)]. Esse índice é uma avaliação do número de escolhas vantajosas menos o número total de escolhas desvantajosas. Esse índice total também é avaliado para cada um dos 5 blocos de vinte escolhas para avaliar o processo de aprendizagem ao longo do teste.

3.3 Análise Estatística

Os testes estatísticos foram realizados utilizando o programa estatístico SPSS v.20. Os sujeitos foram classificados em 3 grupos:

- Grupo Controle: consistindo de alunos que não apresentavam critérios para qualquer um dos diagnósticos psiquiátricos investigados.
- Grupo TDAH apenas (TDAHa): consistindo de alunos que apresentavam o diagnóstico de TDAH mas que não apresentavam qualquer um dos diagnósticos de TA investigados.
- Grupo TDAH comórbido com TA (TDAH+TA): consistindo de alunos que apresentavam o diagnóstico de TDAH e que também apresentavam ao menos um dos diagnósticos de TA investigados.

As diferenças entre os grupos foram consideradas significaivas se o p-valor fosse menor ou igual à .05 ($p \leq .05$). As características sociodemográficas, clínicas e neuropsicológicas foram testadas entre os grupos utilizando-se análise multivariada (MANOVA). Posteriormente, os grupos foram comparados em pares utilizando-se testes-*t* ou testes de Wilcoxon, de acordo com a distribuição, para obtenção dos contrastes. A análise dimensional de sintomas foi realizada utilizando-se coeficientes de correlação de Pearson ou Spearman, respeitando o perfil de dispersão dos dados.

Para a análise de mediação, o comando *paramed* do pacote estatístico STATA 12 foi utilizado. A significância direta e indireta e os efeitos totais foram testados pela correção de viés em *bootstrapping*, que é robusta à violações da assumpção de homocedasticidade.

4 RESULTADOS

4.1 Resultados da Revisão Sistemática:

Nazar, B.P., Bernardes, C., Peachey, G., Sergeant, J., Mattos, P., Treasure, J. (2016). *The risk of Eating Disorders comorbid with Attention-Deficit / Hyperactivity Disorder: A Systematic Review and Meta Analysis*. International Journal of Eating Disorders, (no prelo).

Um total de 5.122 referências foram identificadas utilizando a estratégia de busca, sendo que 59 eram elegíveis para análise do texto completo e apenas 22 possuíam dados para utilização na meta-análise. Os procedimentos de seleção dos artigos são demonstrados na **Figura 4**.

As características dos estudos caso-controle são apresentadas na **Tabela 2**, enquanto que as características dos estudos correlacionais são apresentadas na **Tabela 3**.

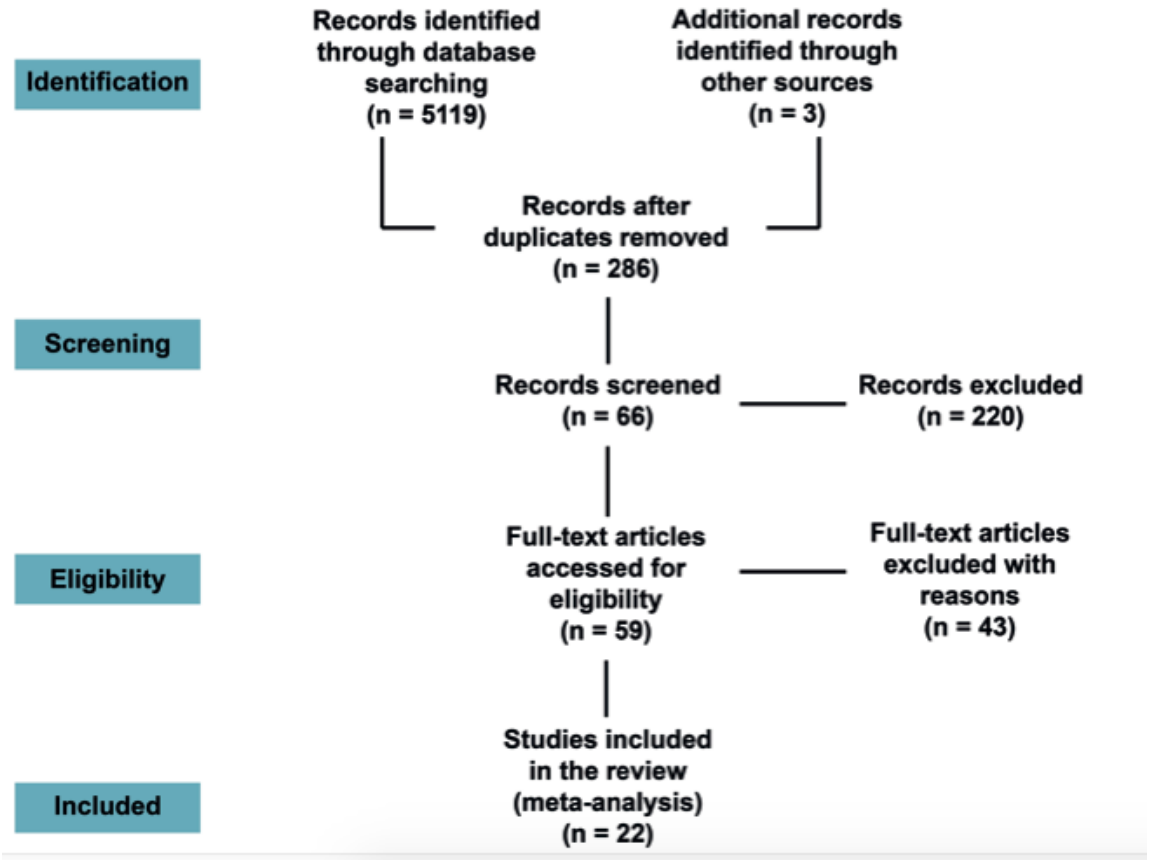


Figura 4 – Fluxograma da busca e procedimentos de seleção dos artigos

Tabela 2: Características dos estudos caso-controle na meta-análise de TDAH e TA

Autor, ano	País	Ambiente clínico	Desenho do Estudo	Amostra Total (Casos/ Controles)	Média de Idade	Gênero (N and %)	Categoria de IMC	Diagnóstico de TDAH	Diagnóstico de TA	Tipo de TA avaliado
Docet, 2012	Espanha	Amostra Clínica	SC	402 (172/ 230)	42.3	F = 45 (88,2%) M = 6 (11,8%)	Apenas obesos	Auto-relato	Entrevista semi-estruturada	TCA
Nazar, 2014	Brasil	Amostra Clínica	SC	131 (40/91)	38.2	F apenas = 131	Apenas obesos	Entrevista semi-estruturada	Entrevista semi-estruturada	BN + TCA

Biederman, 2007	EUA	Amostra Clínica	LGT	235 (123/112)	16.7	F apenas = 123	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	AN + BN
Bleck, 2013	EUA	Amostra não-clínica	SC	4862 (898/3964)	21.7	F = 2,619 (53.8%) M = 2.243 (46,2%)	Todas as categorias de peso	Auto-relato	Auto-relato	BN + TCA
Kessler, 2004	EUA	Amostra não-clínica	SC	3031 (153/ 2878)	de 18 à 44 anos	F = 4913 (52.9%) M = 4374 (47.1%)	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	BN + TCA
Reinblatt, 2015 (b)	EUA	Amostra Clínica	SC	252 (109/ 143)	10.8	F = 119 (47.2%) M= 133 (52.8%)	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	Compulsão alimentar

Sonneville, 2015	Reino Unido	Amostra não – clínica	LGT	3819 (233/ 3545)	11.7	F = 3847 (48.8%) M= 4037 (51.2%)	Todas as categorias de peso	Auto-relato	Entrevista semi-estruturada	Compulsão alimentar
Surnam, 2006	EUA	Amostra Clínica	SC	742 (320/ 422)	38.2	F = 315 (42.4%) M= 427 (57.5%)	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	BN
Biederman, 2002	EUA	Amostra Clínica	SC	522 (280/ 242)	11.3	F = 262 (50.1%) M= 260 (49.9%)	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	BN
Mikami 2008	EUA	Amostra Clínica	LGT	228 (140/ 88)	9.5	F apenas = 228	Todas as categorias de peso	Entrevista semi-estruturada	Entrevista semi-estruturada	BN
Mikami 2010	EUA	Amostra	LGT	696 (432/	16.3		Todas as	Entrevista	Entrevista	BN

		Clínica		264)		F = 148 (21.2%) M = 548 (78.8%)	categorias de peso	semi-estruturada	semi-estruturada	
Yoshimasu, 2012	EUA	Amostra não-clínica	LGT	1055 (343 / 712)	19	F = 214 (21.3%) M = 791 (78.7%)	Todas as categorias de peso	Database Registry	Database Registry	N.R.
Rastam, 2013	Suécia	Amostra não-clínica	LGT	11927 (903 / 11024)	10.5	F = 5885 (49.4%) M = 6042 (50.6%)	Todas as categorias de peso	Auto-relato	Auto-relato	Restrição alimentar
Seitz, 2013	Alemanha	Amostra Clínica	SC	97 (57 / 40) *	21	F apenas = 97	Peso normal e baixo peso	Semi-structured Interview	Semi-structured Interview	BN

Rojo-Moreno, 2015	Espanha	Amostra não-clínica	LGT	993 (35 / 958)*	14	F = 475 (47.8%) M = 518 (52.2%)	Todas as categorias de peso	Semi-structured Interview	Semi-structured Interview	AN + BN
Welch, 2016	Suécia	Amostra Clínica sample	LGT	9350 (850 / 8500)*	22[§]	F = 811 (95.4%)[§] M = 39 (4.6%)[§]	Todas as categorias de peso	Análise retrospectiva de prontuários	Análise retrospectiva de prontuários	TCA

Legenda: N.R. = Não Reportado; SC = Seccional; LGT = Longitudinal; * Os números significam: Amostra total (Transtorno Alimentar / Controles); [§] = Dados relatados apenas para o grupo Transtorno Alimentar; F = Feminino; M = Masculino

Tabela 3 – Características dos estudos de correlação de sintomas na meta-análise de TDAH e TA

Autor, ano	País	Perfil da amostra	Média de idade	Média de IMC (kg/m^2)	Gênero	Questionário de TA	Questionário de TDAH
Strimas, 2008	Canada	Amostra não – clínica	34.2	28.1	M apenas = 145	BEQ	CAARS
Steadman, 2014	EUA	Amostra não – clínica	19.2	22.4	F = 36 (72%) M= 14 (28%)	BES	BAARS-IV
Liao, 2015	China	Amostra não – clínica	21.8	21.86	F = 181 (44.3% M = 228 (55.7%)	BITE	ASRS
Nazar, 2014	Brasil	Amostra clínica	38.2	39.1	F apenas = 171	BITE e BES	ASRS
Cortese, 2007	França	Amostra clínica	14.2	37	F = 65 (65.6%) M = 34 (34.4%)	BITE	CPRS
Seitz, 2013	Alemanha	Amostra clínica	21.9	20.7	F apenas = 57	EDI-II	ADHS-SB
Férnandez-Aranda, 2013	Espanha	Amostra clínica	28.3	23.6	F apenas = 191	EDI-II	ASRS

Legenda: BEQ = Binge Eating Questionnaire ; CAARS = Coner's Adult ADHD Rating Scale;
BES = Binge Eating Scale; BAARS-IV = Barkley Adult ADHD Scale ; BITE = Bulimic Inventory Test, Edinburgh;
ASRS = Adult Self Report Scale; CPRS = Conner's Parent Rating Scale ; EDI-II = Eating Disorders Inventory II ;
ADHS-SB = ADHD self rating scale

4.1.1 O risco de portadores de TDAH desenvolverem Transtornos Alimentares quando comparados a Controles

Nos doze estudos investigando Transtornos Alimentares em coortes de TDAH x Controles, foram avaliados 33.417 indivíduos (TDAH = 4.013 / Controles = 29.404). Os estudos em populações pediátricas mensuravam sintomas alimentares como a perda de controle sobre o comer, em inglês "*Loss of Control Eating*"(LOC) [64], os episódios de compulsão alimentar [92,115] ou os comportamentos alimentares restritivos [61]. Em contrapartida, os estudos em adultos avaliaram síndromes de TA (AN, BN ou TCA). Dois estudos foram considerados como apresentando valores extremos ("*outliers*") [92,116], visto que o seu tamanho de efeito possuía um intervalo de confiança amplo, com o limite superior maior do que aquele da maioria dos outros estudos, e foram excluídos da análise. Todos os estudos demonstraram níveis significativamente mais altos de diagnósticos de TA ou sintomas de TA em portadores de TDAH, quando comparados com o grupo controle.

A meta-análise desses 12 estudos [48,49,63,64,88,90,91,115,117,118], após a exclusão dos dois com valores extremos, indicou que havia um risco significativo ($p<.001$) de que indivíduos com TDAH apresentassem um diagnóstico de TA (AN, BN ou TCA) ou sintomas alimentares (comer restritivo, episódios de compulsão alimentar ou LOC), com um tamanho de efeito global de OR = 3.81 (95% IC: 2.31 - 6.21) (**Figura 5**). Os resultados das principais meta-análises em subgrupos de participantes, assim como os testes de heterogeneidade e o viés de publicação, são apresentadas na **Tabela 4**.

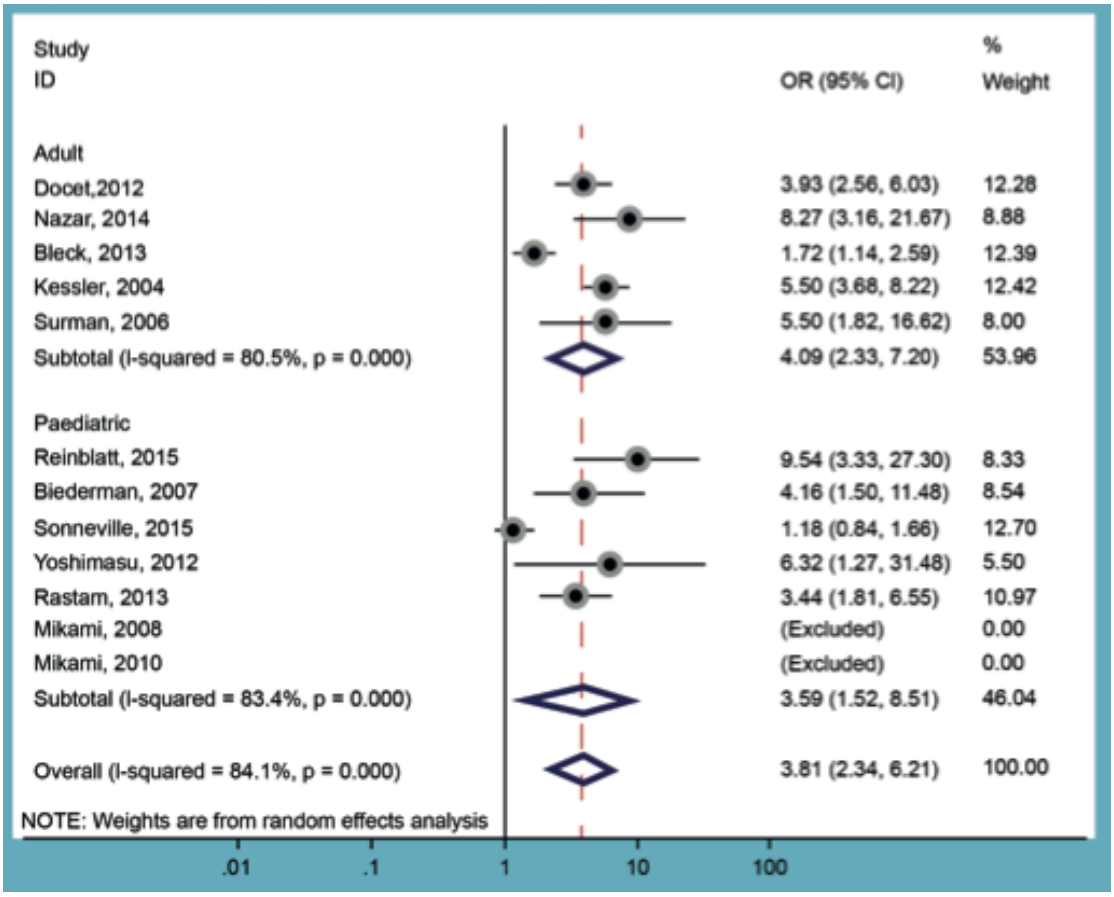


Figura 5 – Gráfico de floresta da meta-análise dos estudos caso-controle em TDAH x Controles

Tabela 4 – Resultados das meta-análises em estudos caso-controle

							estatística Q			teste de Harbord	
	Grupo analisado	Desfecho primário	N amostral	Razão de Chance	95% IC	p-valor	X^2	p-valor	I^2	Coef. do viés	p-valor
	Todos os estudos	Sintomas ou diagnóstico de TA	12	3.81	(2.33-6.21)	<,001	56.50	<.001	84,1%	4.83	,03
	Todos os estudos	AN ou restrição alimentar	3	4.28	(2.24-8-16)	<,001	2.00	.36	0%	3.66	,70
			6		(3.56-						

	Todos os estudos	BN e TCA	4	4.13	(3.00-5.67)	<,001	3.27	.35	8,2%	2.81	,32
	Todos os estudos	Compulsão objetiva (qualquer TA)	7	4.67	(3.58-6.10)	<,001	2.10	.71	0%	2.05	,56
	Apenas estudos com obesos	Sintomas (LOC) ou diagnóstico (BN ou TCA)	3	5.81	(3.15-10.71)	<,001	3.71	.156	46,1%	2.66	,02
	Estudos usando todas as categorias de peso	Sintomas ou diagnóstico de TA	9	3.10	(1.71-5.64)	<,001	40.94	<.001	85,3%	5.63	,05
ED in ADHD x Controls	Amostras pediátricas	Sintomas de TA	7	3.59	(1.51-8.50)	,013	24.10	.004	83,4%	4.65	,01
	Amostras com adultos	Qualquer diagnóstico de	5	4.09	(2.32-7.20)	<,001	20.49	<.001	80,5%	5.93	,28

	TA									
Apenas participantes do gênero feminino	Sintomas ou diagnóstico de TA	9	3.46	(2.00-5.98)	<.001	15.05	,02	60,1%	1.23	,50
Apenas mulheres	Diagnóstico de TA	3	4.35	(1.67-11.27)	.002	7.85	,02	74,5%	4.04	,36
Apenas meninas	Sintomas de TA	6	2.96	(1.32-6.65)	.008	6.98	,07	57%	2.57	,49
Apenas participantes do gênero masculino	Sintomas ou diagnóstico de TA	6	3.37	(1.46-7.77)	.004	11.67	,02	65,7%	2.53	,12
TDAH por entrevista diagnóstica	Sintomas ou diagnóstico de TA	8	5.89	(4.32 – 8.04)	<.001	0.65	,72	0%	-1.9	,70

	TDAH por entrevista diagnósticas em adultos	Diagnóstico de TA	3	5.80	(4.08 – 8.25)	<,001	1.25	,53	0%	-12.2	,72
	TDAH por entrevista diagnósticas em amostras pediátricas	Sintomas ou diagnóstico de TA	5	6.22	(3.20 – 12.11)	<,001	1.90	,86	0%	1.45	,71
	TDAH por auto-relato de sintomas	Sintomas ou diagnóstico de TA	4	2.23	(1.23 – 4.03)	.008	21.82	<,001	86,2%	4.99	,38
	Todos os estudos de TA x Controles	Diagnóstico de TDAH	5	2.57	(1.30-5.11)	.007	14.04	,007	71,5%	8.66	,43

ADHD in ED x Controls	Qualquer TA em adultos	Diagnóstico de TDAH	3	1.58	(.78-3.19)	,195	4.67	,09	57,2%	-1.68	,76
	Apenas pacientes com compulsão alimentar	Diagnóstico de TDAH	3	5.77	(2.35-14.18)	<.001	11.43	,003	82,5%	-43.69	,20

Legenda: Sintomas de TA = a não ser que seja especificado, representa LOC, compulsão alimentar e restrição alimentar; Diagnóstico de TA = a não ser que seja especificado, representa AN, BN e TCA

Para investigar o risco individual em cada um dos diagnósticos de TA, realizamos análises separadas para estudos que reportaram AN [49,94] ou sintomas relacionados à AN (comer restritivo) [61]; BN (todos os estudos estudaram pacientes com a síndrome completa [48,49,63,94]); e TCA (síndrome completa [63,88,94], episódios de compulsão alimentar isolados [115] ou LOC [64]). Também realizamos uma análise com os estudos que investigaram pacientes com episódios de compulsão alimentar objetivos (critério subjetivo associado ao critério objetivo pela DSM), independente da síndrome de TA a que eles pertenciam (BN ou TCA) [48,49,63,88,94]. As análises de subgrupo por diagnósticos de TA demonstrou um risco de OR = 4.28 (95% IC: 2.24-8.16) para AN (n=3);OR = 5.71 (95% IC: 3.56-9.16) para BN (n=4); OR = 4.13 (95% IC: 3-5.67) para TCA (n=4) e OR = 4.67 (95% IC: 3.58-6.10) para os episódios objetivos de compulsão alimentar (n=5), em portadores de TDAH.

Na análise do subgrupo de participantes adultos, (n= 5) [48,63,88,94,118] a razão de chance para um diagnóstico de TA foi de OR = 4.09 (95% IC: 2.32–7.20). A análise de subgrupo em amostras pediátricas, encontrou um risco aumentado significativo (p = ,013) risk (n= 7) [49,61,64,91,115,119,120], OR = 3.59 (95% IC: 1.51 – 8.50). A análise de subgrupo de estudos contendo apenas pacientes obesos (n=3 studies) [63,64,88], também encontrou um risco aumentado para obesos com TDAH desenvolverem um TA, quando comparados com obesos sem TDAH, OR = 5.81 (95% IC: 3.15-10.7).

Na análise de subgrupo por gênero, a avaliação apenas de participantes do sexo feminino (n=9) [48,49,61,63,64,91,115,118,120] apresentou um risco de OR = 3.46 (95% IC: 2.00 – 5.98). Em mulheres (n= 3) [48,63,118], o risco foi similar OR = 4.35 (95% IC: 1.67 – 11.27). Nas amostras avaliando meninas (n=6) [49,61,64,90,91,115] o risco para qualquer TA foi de OR = 2.96 (95% IC: 1.32-6.65). Na análise de subgrupo de participantes do sexo masculino (n=6) [48,61,64,91,115,118], o risco foi de OR = 3.37 (95% IC: 1.46 – 7.77).

Uma vez que os estudos utilizaram diferentes estratégias para classificar os participantes, realizamos uma análise com o subgrupo de estudos que utilizou apenas questionários ou apenas entrevista semi-estruturada para realizar o diagnóstico de TDAH. A análise do subgrupo de

estudos onde o TDAH foi diagnosticado por entrevista (n=8) [48,49,63,64,90,91,94,119] resultou num risco significativo de encontrar um TA, OR = 5.89 (95% IC: 4.32 – 8.04), com uma sub análise de apenas adultos (n=3) [48,63,94] de5.80 (95%CI: 4.04 – 8.25) e uma sub análise de apenas pediátricos (n=5) [49,64,90,91,119] de 6.22 (95% CI: 3.20 – 12.11).

Os resultados obtidos com entrevistas semi-estruturadas eram significativamente maiores do que aqueles obtidos com o diagnóstico do TDAH através de questionários de auto preenchimento (n=4) [61,88,115,118]. Estes por sua vez, demonstraram um risco de OR = 2.23 (95% IC: 1.23 – 4.03).

De maneira geral, os estudos mostraram inconsistência substancial (**Tabela 4**). Portanto, realizamos uma meta regressão para avaliar quais variáveis poderiam influenciar na variância da razão de chance. Apesar das variáveis incluídas no modelo terem alcançado um R^2 de 63.64%, esse achado não foi significativo (p = 0,49).

4.1.2 O risco de portadores de Transtornos Alimentares desenvolverem TDAH quando comparados a Controles

Obtivemos os resultados de 12.336 indivíduos (TA = 1.044 / Controles = 11.292), em 5 estudos para análise. Novamente, dois estudos [60,63] foram excluídos pois o tamanho de efeito foi considerados como sendo de valores extremos ("*outliers*"), visto que o seu tamanho de efeito possuía um intervalo de confiança amplo, com o limite superior maior do que aquele da maioria dos outros estudos. A maioria dos estudos [64,93,121] encontrou taxas de TDAH em portadores de TA significativamente maiores do que em Controles, mesmo com dois estudos tendo encontrado resultados nulos [122,123]. Assim como nos estudos de TDAH, alguns autores não relataram qual a síndrome de TA que foi estudada (**Tabela 2**). Infelizmente, o pequeno número de estudos não possibilitava a realização de um modelo estável de meta-regressão.

O risco combinado de diagnosticar TDAH nos 5 estudos com portadores de TA foi significativo (p = .007), OR = 2.57 (95% IC: 1.30 – 5.11)

(**Tabela 4)**. A análise do subgrupo de estudos com adultos (n=3) [121–123], resultou em um risco não-significativo de 1.58 (95% IC: .78-3.19) (**Figura 6**).

A análise de subgrupo de pacientes que apresentam episódios de compulsão alimentar (n=3) (com indivíduos de todas as síndromes de TA [64,121,122122], produziu um risco significativo de 5.77 (95% IC: 2.35-14.18).

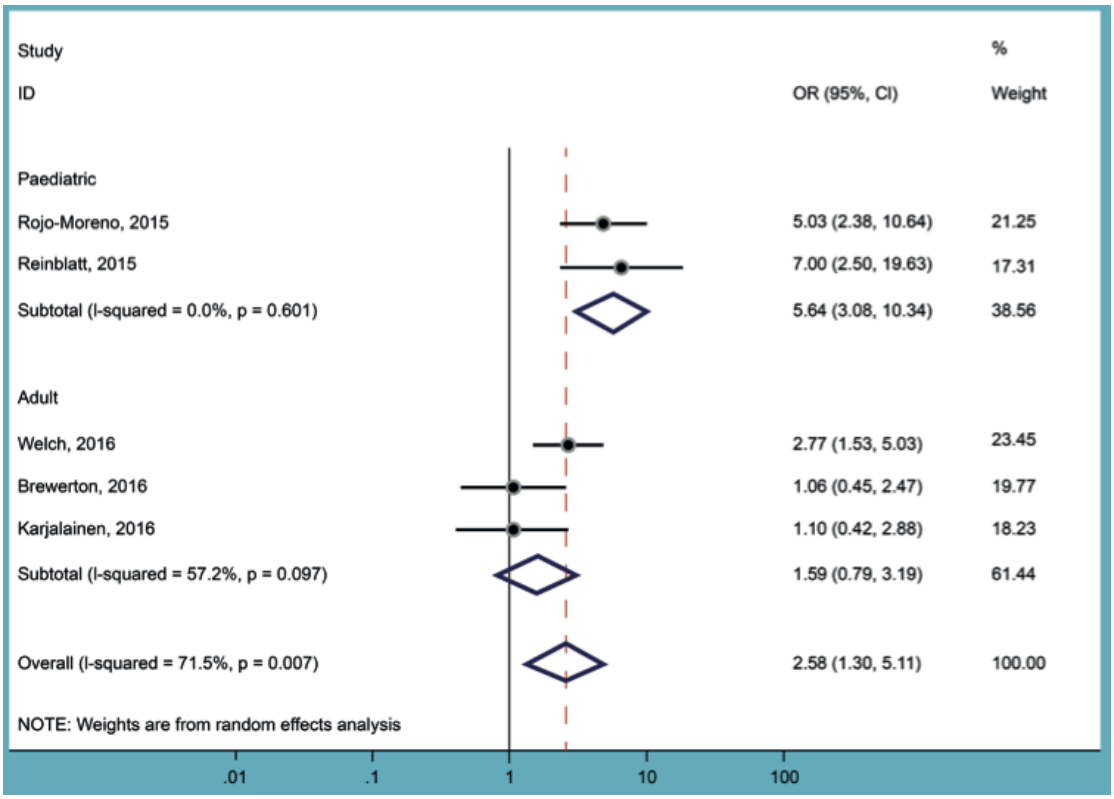


Figura 6 – Gráfico de floresta dos estudos caso-controle de TA x Controles

4.1.3 A força de associação entre os sintomas de TDAH e de Transtornos Alimentares

A síntese dos coeficientes de correlação resultou em um coeficiente de r = .43 (95% IC: .33 – .52) utilizando sete estudos [52,57–60,63,124] (**Figura 7**). A análise do subgrupo de estudos que avaliou questionários específicos sobre sintomas da BN (n=4) [52,57,63,124] resultou em um coeficiente de r= .38 (95% IC: .28 - .49), enquanto que a análise do subgrupo de estudos que avaliou

questionários específicos sobre episódios de compulsão alimentar (n=3) [58,59,63] resultou em um coeficiente r = .47 (95% IC: .31 - .59).

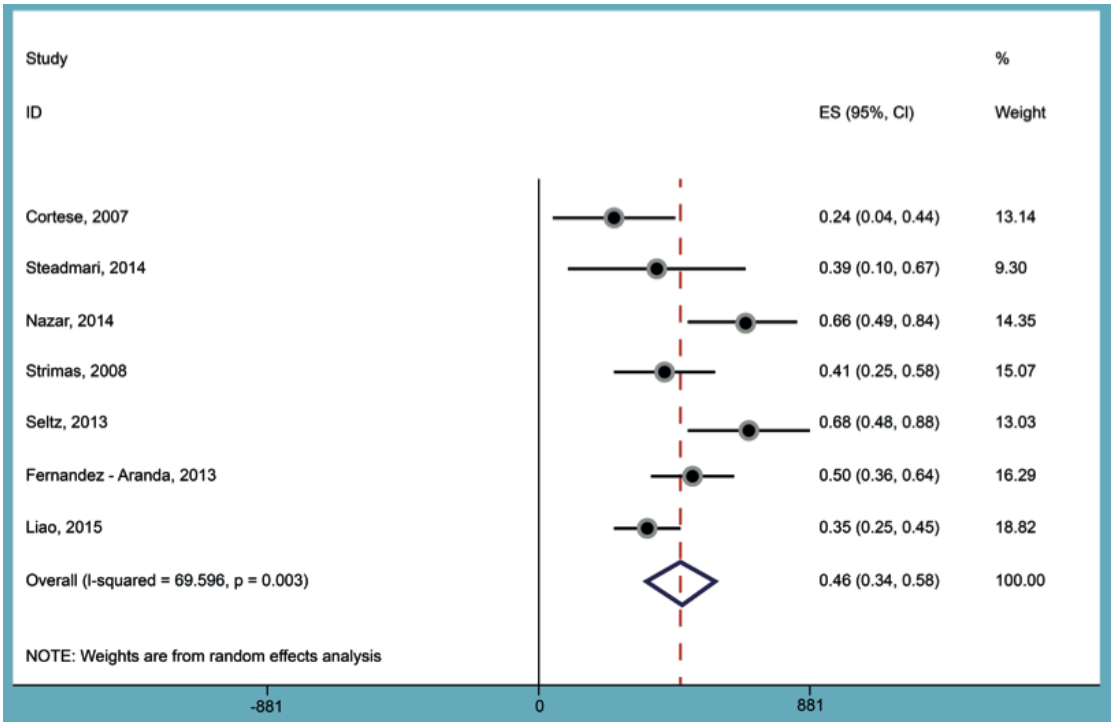


Figura 7 – Gráfico de floresta da meta-análise dos estudos de correlação de sintomas de TDAH e TA

4.2 Resultados do Estudo Clínico

No total, 726 estudantes completaram o rastreio para TDAH nas oito ondas de recrutamento (47% homens e 53%mulheres; média de idade = 23.6 ± 2 anos). Apenas 64 estudantes (8.81%) estavam ausentes nos dias dos rastreios e foram excluídos do estudo. De acordo com a meta proposta inicialmente, nenhum aluno da oitava onda de recrutamento foi excluído. Além disso, nenhum aluno que realizou o rastreio se recusou a participar do estudo. Não havia diferenças significativas na média de idade e proporção entre os gêneros nos estudantes que completaram ou que não completaram o rastreio. Essa avaliação foi possível pela análise do diário de presença de classe e consulta da idade dos alunos que faltaram o rastreio. De acordo

com os objetivos do estudo, a amostra final analisada no estudo clínico consistia de 90 estudantes

4.2.1 Características da amostra

As características sociodemográficas da amostra de alunos analisado neste estudo clínico são apresentadas na **Tabela 5**. Os três grupos eram semelhantes e não apresentavam diferenças significativas em relação à proporção por gênero (p = ,215), nível socio-econômico (p = ,184) e QI total (p = ,46). Nenhum dos sujeitos com TDAH do grupo TDAHa ou do grupo TDAH+TA estavam em uso de psicoestimulantes. Um sujeito do grupo TDAHa já havia recebido o diagnóstico de TDAH e feito uso prévio de psicoestimulantes.

Os diagnósticos de TA no grupo TDAH+TA consistiam de: cinco sujeitos com BN; três sujeitos com TCA; três sujeitos com BN subclínica; cinco sujeitos com TCA subclínico.

A proporção de alunos com obesidade e sobrepeso no grupo TDAH+TA era significativamente maior do que nos outros dois grupos (p=,004). Além disso, a média de IMC neste grupo era significativamente maior do que os outros dois grupos, sendo 4.1 pontos maior do que controles e 3.9 pontos maior do que o grupo TDAHa. Analisando-se o peso, o grupo TDAH+TA era 13kg mais pesado do que Controles e 12.7kg mais pesado do que o grupo TDAHa (**Tabela 5**).

A análise de sintomas de TDAH pelo K-SADS demonstrou que o grupo TDAH+TA apresentava uma contagem significativamente maior de sintomas de Hiperatividade/Impulsividade do que o grupo TDAHa. Todas as outras comparações demonstraram que não haviam diferenças significativas entre esses grupos, porém, o grupo TDAH+TA também demonstrou uma tendência para um maior número de sintomas de Desatenção no passado (**Tabela 6**).

Tabela 5 - Características sociodemográficas da amostra

[a] Análise univariada. *Omnibus* pd valor tamanhos de efeito. correção pós hoc LSD. [b] Controle=TDAH, p=,889; Controle<TDAH+TA e TDAH<TDAH+TA, p < ,001

[c] Controle=TDAH, p=,786; Controle<TDAH+TA e TDAH<TDAH+TA, p < ,001

	Total (n= 90)	**Controles (n=39)**	**TDAH (n= 35)**	**TDAH+TA (n=16)**	***p*-valor[a]**	**Effect-Size (Partial Eta²)[a]**
Idade	23,71 (±1.9)	23,3 (1±.2)	24 (±2,3)	24 (±1.,)	,215	,035
Sexo: % (n)					,976	,001
Feminino	75,5% (68)	69,2% (27)	80% (28)	81,3% (13)		
Peso, kgs	62,6 (±12.2)	60,2 (±9)	60,5 (±9.7)	73,2 (±17.5)	<,0001 [b]	,167
IMC	22,37 (±3.4)	21,6 (±2.7)	21,8 (±2.8)	25,7 (±4.3)	<,001 [c]	,205
Sobrepeso	12,2% (n=11)	10,4% (4)	8,7% (3)	37,8% (6)		
Obeso	2% (n=2)	0% (0)	2,9% (1)	6,3% (1)		
Nível SE: % (n)					,184	,038
(A1)	67% (n = 6)	7,7% (3)	8,6% (3)	0% (0)		
(A2)	11,1% (10)	2,6% (1)	20% (7)	12,5% (2)		
(B 1 e 2)	30% (27)	28,2% (11)	28,6% (10)	37,5% (6)		
(C e D)	52,2% (n=47)	61,5% (24)	42,9% (15)	50% (8)		
QI Global	113 (9)	112 (10)	113 (8)	116 (8.2)	,46	,021

4.2.2 Resultados dos questionários de auto-preenchimento

Os escores médios e a análise comparativa dos questionários de auto preenchimento é apresentada na **Tabela 6**. O grupo TDAH+TA apresentou escores significativamente maiores na escala BES quando comparado aos outros grupos (p< ,001). Vale ressaltar que o escore médio de 18 ± 5.3 apresentado por este grupo o classificaria como sendo portador de compulsão alimentar moderada.

Encontramos uma diferença significativa entre os escores do IDB entre os participantes (p=,03), com os grupos TDAHa e TDAH+TA apresentando um escore médio maior do que Controles e sem diferenças significativas entre si.

Em relação às medidas de ansiedade, o IDATE-T foi significativamente diferente entre os grupos (p= ,039), enquanto o IDATE-E não apresentou diferença (p=,23).

Na análise do auto relato de sintomas impulsivos, apenas os escores da BIS-Total (p< ,001) e da BIS-CINI (p<,001) apresentaram diferenças significativas, com os grupos TDAH+TA e TDAHa apresentando escores mais elevados do que o grupo Controle, porém, sem diferenças entre si.

Tabela 6 – Características clínicas e resultados dos questionários da amostra

	Total (n=90)	Controles (n=39)	TDAH (n= 35)	TDAH+TA (n=16)	*Omnibus* *p*-valor[a]	Contrastes	*Omnibus* Effect-Size (Partial Eta²)[a]
Desatenção atual	N.A.	1,5 (±1,9)	5,9 (±1,5)	6,8 (±1,3)	<,001	1<2=3[b]	,657
H/I atual	N.A.	1,2 (±1,2)	4 (±2,2)	5,6 (±2,7)	<,001	1<2<3[c]	,433
Desatenção passada	N.A.	1,1 (±1,3)	5 (±1,9)	6,1 (±1,9)	<,001	1<2=3[d]	,607
H/I passada	N.A.	1,1 (±1,4)	4,2 (±2,4)	4,4 (±2,8)	<,001	1<2=3[e]	,349
BIS – Total	66,6 (±12)	58,9 (±8,8)	71,8 (±10,3)	71,4 (±15,8)	<,001	1<2=3[f]	,256
BIS-ATTPL	18,3 (±4,1)	17,9 (±4.,)	18,8 (±3,9)	18 (±3,6)	,73	1=2=3	,010
BIS-CINI	43,5 (±8,4)	36 (±4,8)	48 (±6,6)	50 (±5,2)	<,001	1<2=3[g]	,547
IDATE-T	41,7 (±9,9)	38,4 (±9,4)	44,2 (±9,6)	44,6 (±9,8)	,032	1<2[h]	,089
IDATE-E	42,2 (±10,4)	38 (±8,7)	45,3 (±11,5)	44,5 (±8,1)	,23	1<2[i]	,087
BES	8,7 (6,3)	6,22 (5,3)	8,82 (6)	15 (5,3)	<,001	1=2<3[j]	,234
IDB	7 (±6,9)	4,5 (±4,5)	8,8 (±7,2)	8,5 (±9,1)	,03	1<2=3[l]	,092

Legenda: N.A. = Não Aplicável; H/I = sintomas de Hiperatividade/Impulsividade pelo K-SADS;

Contrastes:
1= Controles; 2= TDAH; 3= TDAH+TA

[a] Análise univariada. Omnibus pd valor. correção pós hoc LSD.
[b] 1<2, p<,001; 1< 3, p<,001; 2=3, p=,11
[c] 1<2, p<,001; 1< 3, p<,001; 2<3, p=,007
[d] 1<2, p<,001; 1< 3, p<,001; 2=3, p=,53
[e] 1<2, p<,001; 1< 3, p<,001; 2=3, p=,75 [f]
1<2, p<,001; 1< 3, p=,002; 2=3, p=,92 [g]
1<2, p<,001; 1< 3, p<,001; 2=3, p,34 [h]
1<2, p=,01; 1=3, p=,052; 2=3, p=,89
[i] 1=2, p=,059; 1=3, p=,065; 2=3, p=,69 [j]
1=2, p=,07; 1<3, p < ,001; 2<3, p = ,002 [l]
1<2, p=,025; 1<3, p=,031; 2=3, p=,757

4.2.3 Avaliação dos dados da testagem neuropsicológica

Os resultados referentes ao QI verbal, QI não-verbal e QI Total, não demonstraram diferenças significativas entre os grupos (**Tabela 5**). Os resultados individuais sobre a escolha em cada uma das pilhas de cartas do do IGT (**Tabela 7**) também não apresentaram diferenças significativas. Entretanto, percebemos uma tendência à realização de mais escolhas desvantajosas no *net score* e no bloco B, o que sugere uma curva de aprendizagem prejudicada ao longo do tempo no grupo TDAH+TA, quando comparado aos outros dois grupos, que não diferiram entre si (**Figura 8**). Vale ressaltar que apenas o bloco B do IGT demonstrou diferenças significativas entre o grupo TDAH+TA e Controles (p= ,05).

Na avaliação de atenção com as medidas do CPT, foram demonstradas diferenças significativas nos escores de erros por omissão (OMI). Houve uma diferença significativa entre OMI do grupo TDAH+TA vs Controles (p=,031) e do grupo TDAH+TA vs TDAHa (p=,042). Essa diferença apresentava um pequeno tamanho de efeito em ambos os contrastes. Todas as outras medidas do CPT não apresentaram diferenças significativas (**Tabela 8**).

Tabela 7. Resultados do *Iowa Gambling Test* (IGT)

	***Omnibus* F (Eta²), pa valor**	**TDAH vs. Controle** Diferença de médias (d de Cohen)	**TDAH+TA vs. Controle** Diferença de médias (d de Cohen)	**TDAH+TA vs. TDAH** Diferença de médias (d de Cohen)
IGT pilha A	,32(,009), p=,727	,049 (-,75)	1,63 (-,29)	1,13 (-,20)
IGT pilha B	2,50(,067), p=,089	-2,8 (,37)	5 (-,71) *	2,25 (-,33)
IGT pilha C	1,65(,045), p=,19	-2,46 (,34)	-3,8 (,34)	-1,33 (,19)
IGT pilha D	,48(,014), p=,61	-61 (,07)	-2,67 (,35)	-2,05 (,26)
IGT bloco 1	,90(,025), p=,412	-,53 (,08)	2,31 (-,41)	2,83 (-,44)
IGT bloco 2	(,054), p=,14	,14 (-,02)	-3,48(,69)	-3,62 (,66)[a]
IGT bloco 3	,98 (,027), p=,37	-1,6 (,22)	-3,09 (,41)	-1,49 (,23)
IGT bloco 4	2,12 (,057), p=,12	-3,15 (,35)	-5,19 (,70)	-2,03 (,29)
IGT bloco 5	1,07 (,03), p=,34	-,76 (,09)	-3,67 (,53)	2,91 (,42)
Net score	2,12 (,057), p=,12	-6,98 (,30)	-13,77 (,73)	-6,79 (,37)[b]

Legenda: * = p<,05; [a] p = ,068; [b] p = ,053
Pilhas A e B = desvantajosas; Pilhas C e D = vantajosas;
Net score de 100 tentativas = [(Pilhas C+D) – (Pilhas A+B)];
Um Bloco é referente ao *Net score* de apenas 20 tentativas.

Tabela 8 í Resultados do teste de performance contínua (Conner's Continuous Performance Test - CPT)

	***Omnibus* F (Eta²), p-valor**	**TDAH vs. Controle** Diferença de médias (d de Cohen)	**TDAH+TA vs. Controle** Diferença de médias (d de Cohen)	**TDAH+TA vs. TDAH** Diferença de médias (d de Cohen)
Erros por Omissão	2,65 (,072), p=,07	-,02 (,009)	9,05 (-,42)[a]	9,07 (-,42)[b]
Erros por ação (COM)	1,45 (,040), p=,24	2,56 (-,31)	4,26 (-,50)	1,69 (-,19)
Tempo de reação (HRT)	,01 (0), p=,98	-285,13 (,04)	-130,20 (,02)	154,92(-,02)

Legenda: [a] p= .035; [b] p= .041

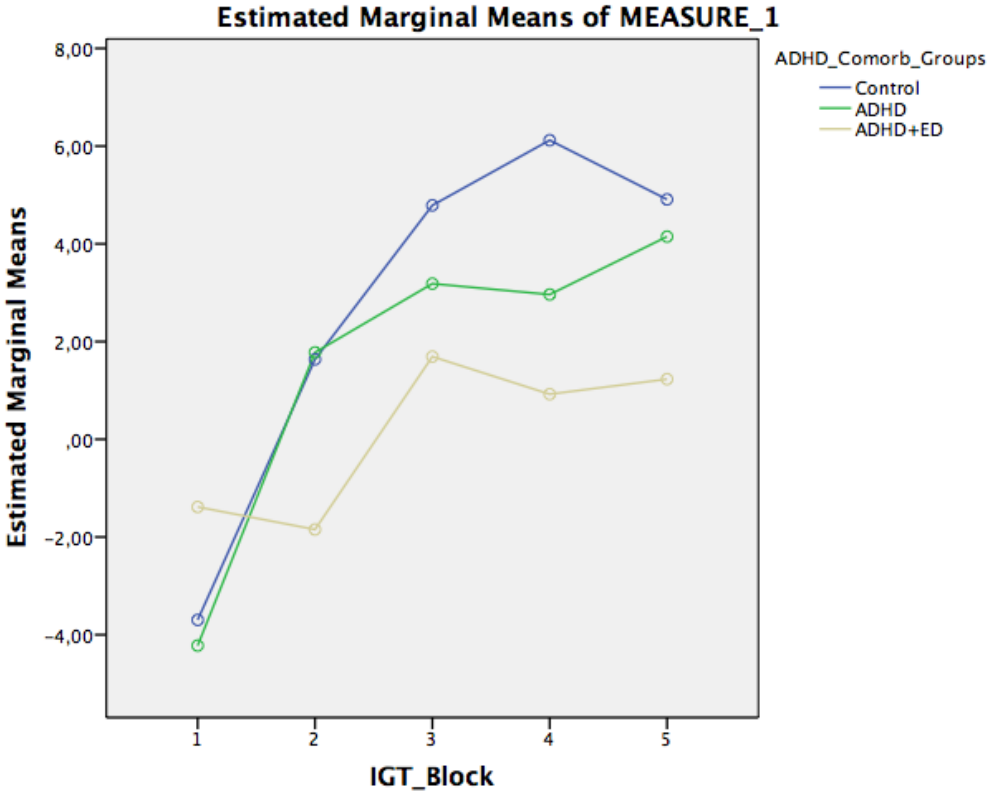


Figura 8 – Gráfico da performance do Iowa Gambling test - IGT ao longo do teste

Legenda:
Control = Controle; ADHD = TDAHa; ADHD+ED = TDAH+TA

4.2.4 Análise de mediação explorando IMC

O primeiro modelo de mediação testado apresentava como variável dependente o IMC e análise de mediação através do BES, IDB e sintomas atuais do K-SADS como preditores.

As correlações de Pearson entre IMC, BES, IDB e K-SADS (escore composto pela soma de Desatenção + Hiperatividade/Impulsividade, no inglês, *composite score* (CS)) demonstram que a BES se correlaciona positivamente com o IDB (r= ,025; p< ,05) e com o K-SADS CS (r=,43; p<,001) com um tamanho de efieto moderado. A BES se correlacionou positivamente com IMC com um forte tamanho de efeito (r=0,48; p< ,001). Os sintomas de TDAH atuais pela K-SADS CS se correlacionaram positivamente com depressão mas com um tamanho de efeito moderado (r=0,33; p< ,01) e não se correlacionaram com o IMC (r= ,23, p >,05). Nenhuma das correlações foi alta a ponto de sugerir redundância entre si (todas as correlações < |,8|).

As premissas para a análise de mediação foram testadas utilizando uma regressão bivariada do BES no status diagnóstico de TA (codificado em TA presente ou TA ausente) e no IDB (*path a'*) e uma regressão múltipla de IMC no BES e IDB (*path b'*), e status diagnóstico de TA (*path c'*). Tanto o *path a'* (β = 7,86, SE = 1,76, 95% CI [4,34, 11,38]) e o *path b'* (β = 0,13, 0,05, 95% CI [0,04, 0,23]) estavam associados com tamanhos de efeito positivos, porém, significativos.

A análise demonstrou que possuir um diagnóstico de TA estava associado de modo positivo e significativo a maiores escores de IMC (efeito total = 3,31, erro padrão da correção em *bootstrap* = 0,63; 95% IC: [2,06, 4,52]). A BES mediava significativamente este efeito (efeito indireto = 1,04, erro padrão da correção em *bootstrap* = 0,58; 95% IC: [0,09, 2,30]).

4.2.5 Análise de mediação explorando a compulsão alimentar

No segundo modelo, analisamos um modelo mediacional com a compulsão alimentar mensurada pela BES como variável dependente e com sintomas depressivos, traços impulsivos e sintomas atuais de TDAH como variáveis independentes. Para esta regressão, o IDB, BIS-Total, e sintomas atuais da K-SADS Desatenção (K-SADS D) e sintomas atuais da K-SADS para Hiperatividade/Impulsividade (K-SADS HI) foram adicionados no método de *forced entry*. Esse modelo predizia a BES a partir dos sintomas de TDAH e da presença de um TA de forma significativa (R^2 = ,21, Adj. R^2 = ,16, *SE* = 5,88, Δ*F*(4,60) = 9,64, *p* = ,006). Nenhuma das variáveis predizia significativamente a BES.

5 DISCUSSÃO

5.1 Discussão sobre a revisão sistemática e a meta-análise

O risco de portadores de TDAH apresentarem um TA está aumentado três vezes, enquanto que portadores de TA tem duas vezes mais chance de apresentar TDAH do que Controles. A força de associação entre os sintomas de TDAH e de TA é moderada. Nenhuma das variáveis exploradas na meta-regressão explicou a variância no tamanho de efeito. A divisão das amostras apresentadas em subgrupos de interesse clínico falhou em demonstrar que o tamanho do risco em potencial poderia diferir de modo significativo. Por exemplo, o risco de TA em portadores de TDAH do sexo masculino e do sexo feminino foi significativo mas com intervalos de confiança que se sobrepunham. O tamanho de efeito para alterações do comportamento alimentar encontrava-se aumentado na população pediátrica, mas esse risco foi semelhante àquele encontrado em adultos. Conjuntamente, esses resultados sugerem que o risco para todas as síndromes em portadores de TDAH é semelhante, com uma tendência não–significativa favorecendo taxas maiores de BN.

O fato de que o diagnóstico de TDAH por entrevista semi-estruturada ao invés de questionário autopreeenchido levou a uma diferença significativa no risco de TA, reforça a ideia de que a associação é mais forte quanto mais bem caracterizado é o quadro do TDAH. A maioria dos estudos não indicou se o diagnóstico do TDAH se utilizou de informações de colaterais. A informação de colaterais é sugerida como parte das melhores práticas diagnósticas para o TDAH adulto [125], entretanto, as taxas de concordância de relato de sintomas entre adultos e seus parentes variam de moderadas [125] a altas [126], o que sugere que os adultos são bons informantes para os próprios sintomas de TDAH.

Os sintomas de TDAH estão positivamente associados com os de TA. Tanto a desatenção como a impulsividade são preditores de sintomas bulímicos [60,63,91,120], enquanto que a hiperatividade e a desatenção são preditores de fissura por alimentos [64,115]. É digno de nota enfatizar que a

edição mais recente da DSM (DSM-5)[8] está retirando a ênfase nos subtipos de TDAH visto que a literatura recente sobre o assunto tem demonstrado baixas taxas de estabilidade dos subtipos ao longo do tempo [127,128].

Outra possibilidade é que o TDAH esteja associado com um risco aumentado de distúrbios na percepção corporal [129] como demonstrado por Fernandez-Aranda et al., 2013, onde a percepção interoceptiva estava correlacionada positivamente com sintomas de TDAH. Outros autores já apontaram para o fato do processo atencional dominar a resposta fisiológica de pacientes com BN quando são expostos a imagens dos seus próprios corpos. Nestas pacientes, ocorre uma reação de alerta com sentimentos negativos em relação a si, provavelmente devido a produção de vieses atencionais [130].

É digno de nota que o risco para a associação entre TDAH e TA é mais do que o dobro daquele encontrado entre obesidade e TDAH. Em duas recentes revisões sistemáticas, o risco de obesidade em portadores de TDAH variou de 1.37 [131] até 1.55 [132] em adultos, quando comparados a Controles, enquanto que em crianças o risco variou de 1.13 [131] até 1.22 [132]. Os sujeitos obesos com TDAH diferem daqueles sem o transtorno pois apresentam uma frequência mais elevada de distúrbios do comportamento alimentar [62], de diagnósticos de TA, além de maiores taxas de comorbidades psiquiátricas [63], e é sugerido que o mecanismo subjacente para esta associação se dê através da participação da compulsão alimentar. A obesidade é uma consequência de longo prazo dos sujeitos com TCA em estudos epidemiológicos [133] e um estudo demonstrou que LOC é um mediador entre o o TDAH e aumentos no IMC de crianças [64]. Outros estudos longitudinais são necessários para testar se o comportamento alimentar transtornado e outros fatores como uso de medicação psicoestimulante em crianças até a idade adulta, atuam alterando a regulação do peso ao longo do tempo.

A síndrome de Deficiência de Recompensa (RDS) é um conceito que associa alterações genéticas em genes dopaminérgicos com fenótipos comportamentais. É possível que essa síndrome represente uma característica transdiagnóstica entre o TDAH [134], TA, obesidade [135] e o transtorno pelo uso de substâncias [136]. Não existem estudos utilizando a técnica de *genome wide association studies (GWAS)* para BN e TCA, que

tenham analisado o escore de risco poligênico entre essas condições. A análise genética específica de perfis genéticos poderia auxiliar na compreensão de subgrupos diagnósticos dentro de um determinado transtorno.

Em termos de estudos de neuroimagem, Seymour et al., 2015, demonstrou numa revisão descritiva, que há uma sobreposição em anomalias de circuitos cerebrais relacionados ao controle cognitivo e emocional. Curiosamente, uma dissociação foi percebida no processamento de recompensas de portadores de TDAH quando comparada com portadores de TA. Enquanto que os portadores de TDAH demonstraram um recrutamento neural deficiente na antecipação de recompensas e um recrutamento neural exacerbado durante o recebimento de recompensas [137], os portadores de compulsão alimentar foram descritos como apresentando uma hiperresponsividade para estímulos relacionados à comida, tanto na fase de antecipação como no recebimento de recompensas [138]. Até o momento, não existem estudos demonstrando se o cérebro de pacientes com a comorbidade TDAH+TA funciona de forma diferente dos portadores de um desses transtornos isoladamente.

Apesar de diferentes estudos terem encontrado que os portadores da comorbidade TDAH+TA apresentavam níveis mais elevados de traços impulsivos em questionários de auto preenchimento, quando comparados com portadores de um desses transtornos isoladamente [58,60,62,63], esses resultados não foram replicados com o uso de testes neuropsicológicos que mensuravam impulsividade [60,64,139]. Por exemplo, a mediação entre sintomas de TDAH e compulsão não foi explicada pelos resultados de um teste do tipo Go/No-Go [58]. Além disso, não foram encontradas diferenças significativas em testes de impulsividade em pacientes bulímicas com ou sem uma história prévia de TDAH na infância [60].

As possíveis explicações para a comorbidade TDAH+TA mencionadas anteriormente são baseadas em fatores únicos (por exemplo, impulsividade, anormalidades genéticas) que possivelmente não conseguem contemplar a complexidade de comportamentos exibidos por estes pacientes. Algumas hipóteses que vislumbra um processo dual ou mesmo uma conceitualização em três níveis de funcionamento poderia auxiliar na compreensão desta

comorbidade. Strack & Deutsch [140] propuseram um modelo de processamento cerebral dual de formação do hábito, através da integração de determinantes reflexivos e impulsivos. Dentro desse modelo, seria possível que um sistema distorcido de crenças e cognições (TA) interagisse com uma resposta distorcida e impulsiva aos estímulos ambientais (TDAH), levando à ativação de esquemas comportamentais automáticos disfuncionais. Em outra proposta conceitual, Sergeant, 2000 [141] conceitualizou o modelo cognitivo energético para TDAH, onde o primeiro nível de processamento de informações pelo cérebro, dependeria de um segundo nível de fatores determinantes do estado de ativação fisiológica da consciência (vigília, nível de esforço), ambos regulados por um terceiro nível que seriam as funções executivas. Utilizando este modelo, poderíamos sugerir que o funcionamento neuropsicológico afetado pelo TDAH poderia alterar o funcionamento de informações e decisões relacionadas à comida e no sentido oposto, que as alterações nutricionais e de regulação emocional decorrentes do TA poderiam prejudicar ainda mais o funcionamento cognitivo de portadores de TDAH.

5.2 Discussão sobre o estudo clínico

Demonstramos numa amostra não-clínica e majoritariamente virgem de tratamento, que a presença de um TA em portadores de TDAH pode provoca impulsividade atencional no *Continuous Performance Test* e gera uma tendência a maior impulsividade cognitiva por aumento de escolhas de risco e pior tomada de decisão no *Iowa Gambling Task*. Além disso, também demonstramos pela análise de mediação que a presença de um TA é um mediador do aumento de peso em portadores de TDAH.

5.2.1 Achados neuropsicológicos

A hipótese de que tanto a impulsividade atencional, como a cognitiva e a motora diferenciariam o grupo TDAH+TA do grupo TDAHa apresentou resultados com um tamanho de efeito pequeno e que por vezes era contraditório. Apesar do grupo com a comorbidade ter apresentado

significativamente mais erros por omissão no CPT que o grupo TDAHa, indicando maior impulsividade atencional, eles não apresentaram maiores escores na subescala de atenção/planejamento da BIS-11, nem mesmo maiores do que os Controles. O achado de um maior número de erros por omissão no CPT está de acordo com os achados de um estudo anterior [60] onde foram avaliadas mulheres bulímicas com ou sem histórico de TDAH na infância. Uma possibilidade para explicar este achado é que a irregularidade no comportamento alimentar com a prática de dietas restritivas e jejuns em pacientes com TA, especialmente com síndromes bulímicas, prejudique de forma significativa sujeitos que já apresentam um funcionamento cognitivo de base prejudicado.

Na demonstração da impulsividade motora o grupo TDAH+TA não apresentou mais erros por ação no CPT em relação a qualquer um dos outros dois grupos, apesar de ter apresentado na subescala de controle inibitório da BIS-11 escores significativamente maiores do que Controles, porém, igual ao grupo TDAHa.

Em relação ao IGT, houve uma tendência para uma pior curva de aprendizagem com mais escolhas de risco ao longo do tempo. Isto poderia sugerir que os indivíduos com TDAH+TA tenham uma maior dificuldade em controlar impulsos e planejar estratégias eficientes mediante a possibilidade de recompensas imediatas. Além disso, todos os escores brutos do IGT demonstravam um padrão de piora de performance do grupo TDAHa em relação a Controles, e do grupo TDAH+TA em relação ao TDAHa. isto demonstra que talvez a alteração em impulsividade motora se deva apenas ao TDAH e não à comorbidade. Vale ressaltar que o IGT é baseado na teoria do marcador somático, onde o processamento emocional dos indivíduos participa do processo de tomada de decisão. São bem documentados os déficits de processamento emocional em portadores de TA[142] sendo que alguns autores inclusive os relacionam como sendo nucleares aos sintomas destas síndromes[143]. É possível que seja através deste componente que os TA prejudiquem a capacidade de tomada de decisão de portadores de TA mas estudos posteriores seriam necessários para comprovar esta hipótese.

Garon e cols. (2006) [144] avaliou o efeito da comorbidade da comorbidade de sintomas depressivo-ansiosos na performance do IGT de

crianças com TDAH e, contrário à sua hipótese, encontrou que a presença da comorbidade aproximava os pacientes dos escores de Controles. Narvaez e cols. (2014) [145] encontraram que a presença de TDAH comórbido com Transtorno Bipolar em crianças e adolescentes, provocava uma pior performance no *Stroop test* mas não no CPT ou no *Wisconsin Card Sorting Test*. Portanto, os estudos de comorbidades no TDAH que buscaram determinar um perfil neuropsicológico específico encontraram alterações que não foram replicadas em outros estudos, que por vezes eram contrárias a impressão clínica e que podem se dever ao acaso sendo necessários mais estudos replicando estes experimentos.

5.2.2 Achados clínicos

Em relação aos sintomas psiquiátricos avaliados, as únicas diferenças significativas encontradas foram que o grupo TDAH+TA apresentou um maior escore na escala de compulsão BES, como esperado, e um maior número de sintomas de Hiperatividade/Impulsividade atual, quando comparado ao grupo TDAHa. Como os escores de hiperatividade e impulsividade foram mensuradas dentro de uma mesma dimensão, uma possibilidade seria que este achado fosse explicado pelo componente impulsivo. Como exposto acima, dois achados enfraquecem esta possibilidade, visto que tanto a medida de impulsividade motora no CPT como a avaliação de traços de impulsividade pela BIS-11 não apresentaram diferenças significativas que pudessem diferenciar os dois grupos de TDAH. Levando-se em conta que é o componente de hiperatividade que explicaria a diferença, é necessário avaliar a possibilidade de que os sintomas ansiosos possam explicar o achado, já que em adultos, ambos podem se sobrepor. Visto que não houve diferenças significativas nos escores do IDATE, podemos inferir que a hiperatividade apresentada não seja uma expressão de ansiedade mas a própria dimensão de hiperatividade primária do TDAH. Talvez ela esteja relacionada à impulsividade cognitiva ou mesmo outras funções cognitivas que não foram investigadas neste estudo, como funções executivas.

Os estudos sobre TDAH e obesidade sugerem que o aumento de peso em portadores de TDAH esteja relacionado aos transtornos do sono (e.g.

apnéia do sono) ou variantes genéticas relacionadas à impulsividade e um funcionamento prejudicado de sistemas de recompensa [87,132]. Nós apresentamos evidência, pela análise de mediação, de que a presença de um TA pode mediar o aumento de peso no TDAH. Mesmo com um escore médio considerado leve de compulsão alimentar na escala BES, os sujeitos com TDAH+TA apresentaram um IMC significativamente maior que os sujeitos com TDAHa. Esse achado está em consonância com os estudos epidemiológicos sobre o TCA, onde os portadores apresentam um risco de 4.9 vezes mais chance de desenvolver a obesidade [146].

6 LIMITAÇÕES

6.1 Limitações referentes a revisão sistemática e meta-análise.

O número de estudos encontrados para esta revisão da literatura foi pequeno. Dentre os 12 estudos de caso-controle em portadores de TDAH x Controles explorando a comorbidade, 5 focaram em populações pediátricas com uma faixa etária variando entre 10 e 17 anos. As definições de TA na população pediátrica eram amplas, incluindo LOC [64], comportamentos alimentares alterados [90,92] além das síndromes de TA descritas na DSM-5. Uma vez que a média de idade para a busca pelo tratamento na BN é aos 18 anos e no TCA aos 22 anos, é provável que as coortes pediátricas não tenham avaliado a faixa de idade onde a maior parte dos sujeitos desenvolve algumas das síndromes de TA, o que explicaria o uso de outras definiçãos ou mesmo o uso de sintomas ao invés de síndromes [30]. Isso também explicaria porque dois estudos não encontraram qualquer caso de portadores de BN em suas populações pediátricas [90,91]. Adicionalmente, poucos estudos exploraram a presença de TDAH em populações de portadores de TA x Controles, o que nos impediu a realização de uma meta-regressão com estes dados. Levando-se em conta a recente aprovação do uso de lisdexanfetamina pelo FDA americano [77] seria interessante saber se o uso de psicoestimulantes diminui a prevalência destes transtornos em estudos longitudinais mas o uso de medicações psicoestimulantes não foi descrito por estudos suficientes para realizar esta análise.

6.2 Limitações referentes ao estudo clínico

Vale ressaltar que a amostra consistia de universitários de alta performance acadêmica e alto QI. O papel da inteligência em avaliações neuropsicológicas foi estudado por Warner e cols. (1987) [147], que demonstraram que o QI se relacionava a melhores escores em tarefas com medidas auditivo-linguísticas, solução de problemas, memória e percepção tátil. O nosso grupo TDAHa também apresentava alta performance cognitiva, com uma menor diferenciação do grupo Controle do que seria o esperado e

pode representar um viés de seleção por serem os portadores de TDAH com maiores fatores de resiliência.

Webb e cols. (2014) [148] demonstraram que o nível de inteligência cognitiva pode explicar a maior parte da variabilidade do IGT, enquanto que medidas de inteligência emocional explicariam a menor parte. Esse achado se contradiz à *teoria do marcador somático* na qual o teste é baseado e que postula sobre o efeito das emoções na tomada de decisão. É possível que em sujeitos com alto nível de inteligência o IGT talvez deva ser adaptado, mudando a frequência de mudanças no estilo de resposta ou velocidade de apresentação de novas rodadas do teste, de forma a dificultar a sua aplicação.

Outra limitação importante é o tamanho da amostra e talvez a significância estatística não tenha sido alcançada nas análises dos escores dos testes neuropsicológicos entre grupos pois o tamanho do grupo TDAH+TA era pequeno. Além disso, a amostra de portadores da comorbidade TDAH+TA apresentava sintomas e quadros considerados leves, contribuindo para a falta de constraste entre os grupos.

7 CONCLUSÃO

A associação entre o TDAH e os Transtornos alimentares ocorre tanto com essas síndromes avaliadas de forma categorias, em formato de avaliação diagnóstica, como de forma dimensional, em formato de avaliação de sintomas. A presença de um Transtorno Alimentar prejudica o funcionamento atencional e de tomada de decisão de portadores de TDAH, além de estar associado a um índice de massa corporal maior e à presença de mais comportamentos hiperativos/impulsivos em adultos. Os Transtornos Alimentares pioram o funcionamento cognitivo dos portadores de TDAH, mesmo quando estes apresentam alta performance e não diferem significativamente de controles. Mais estudos são necessários para avaliar o impacto longitudinal dessas alterações tanto no prognóstico como na resposta terapêutica desses indivíduos.

8 REFERÊNCIAS BIBLIOGRÁFICAS

1. POLANCZYK, G.; ROHDE, L. A. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Current opinion in psychiatry, v. 20, n. 4, p. 386–92, jul. 2007.

2. VOLKOW, N. D.; SWANSON, J. M.; PH, D. Clinical Practice: Adult Attention Deficit – Hyperactivity Disorder. New England Journal of Medicine, v. 369, n. 20, p. 1935–1944, 2013.

3. MATTOS, P. et al. Painel brasileiro de especialistas sobre diagnóstico do transtorno de déficit de atenção/hiperatividade (TDAH) em adultos. Revista de Psiquiatria do Rio Grande do Sul, v. 28, n. 1, p. 1–19, abr. 2006.

4. MCKAY, K. E.; HALPERIN, J. M. ADHD, aggression, and antisocial behavior across the lifespan. Interactions with neurochemical and cognitive function. Annals of the New York Academy of Sciences, v. 931, p. 84–96, jun. 2001.

5. HERVEY, A. S.; EPSTEIN, J. N.; CURRY, J. F. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology, v. 18, n. 3, p. 485–503, jul. 2004.

6. BIEDERMAN, J. et al. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. The Journal of clinical psychiatry, v. 67, n. 4, p. 524–40, abr. 2006.

7. AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Vol 1. 4ta ed. Arlington, VA: American Psychiatric Association; 2000.

8. AMERICAN PSYCHIATRIC ASSOCIATION. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5*. 5tA ed. Arlington, VA: American Psychiatric Association; 2013.

9. WORLD HEALTH ORGANIZATION, ed. *World Health Organization: The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research*. 1a ed. Geneva, Switzerland; 1993.

10. DANCKAERTS, M. et al. Self-report of attention deficit and hyperactivity disorder in adolescents. Psychopathology, v. 32, n. 2, p. 81–92, 1999.

11. CUMYN, L.; FRENCH, L.; HECHTMAN, L. Comorbidity in adults with attention-deficit hyperactivity disorder. Canadian journal of psychiatry. Revue canadienne de psychiatrie, v. 54, n. 10, p. 673–83, out. 2009.

12. KOOIJ, S. J. J. et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC psychiatry, v. 10, n. 1, p. 67, jan. 2010.

13. TREASURE, J.; CARDI, V.; KAN, C. Eating in eating disorders. European Eating Disorders Review, v. 20, n. 1, p. e42–e49, jan. 2012.

14. RUSSELL, G. The management of anorexia nervosa. In: *Royal College of Physicians of Edinburgh, Symposium: Anorexia Nervosa and Obesity (Publication No. 42)*. Endinburgh: T. and A. constable Ltd.; 1973.

15. RUSSELL, G. Bulimia nervosa: an ominous variant of anorexia nervosa. Psychological medicine, v. 9, n. 3, p. 429–48, ago. 1979.

16. PRINCE, A. C. et al. Systematic review and meta-analysis of the baseline concentrations and physiologic responses of gut hormones to food in eating disorders. The American journal of clinical nutrition, v. 89, n. 3, p. 755–65, mar. 2009.

17. FAIRBURN, C. G. et al. The natural course of bulimia nervosa and binge eating disorder in young women. Archives of general psychiatry, v. 57, n. 7, p. 659–65, jul. 2000.

18. WELTZIN, T. E. et al. Feeding patterns in bulimia nervosa. Biological psychiatry, v. 30, n. 11, p. 1093–110, 1 dez. 1991.

19. DAVIS, R.; FREEMAN, R. J.; GARNER, D. M. A naturalistic investigation of eating behavior in bulimia nervosa. Journal of consulting and clinical psychology, v. 56, n. 2, p. 273–9, abr. 1988.

20. STUNKARD AJ. Eating patterns and obesity. *Psychiatr Q*. 1959;33:284-295.

21. FITZGIBBON, M. L.; BLACKMAN, L. R. Binge eating disorder and bulimia nervosa: differences in the quality and quantity of binge eating episodes. The International journal of eating disorders, v. 27, n. 2, p. 238–43, mar. 2000.

22. MASHEB, R. M.; GRILO, C. M.; WHITE, M. A. An examination of eating patterns in community women with bulimia nervosa and binge eating disorder. The International journal of eating disorders, v. 44, n. 7, p. 618–24, nov. 2011.

23. HOEK, H. W. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Current opinion in psychiatry, v. 19, n. 4, p. 389–94, jul. 2006.

24. PAWLUCK, D. E.; GOREY, K. M. Secular trends in the incidence of anorexia nervosa: integrative review of population-based studies. The

International journal of eating disorders, v. 23, n. 4, p. 347–52, maio 1998.

25. KESKI-RAHKONEN, A. et al. Epidemiology and course of anorexia nervosa in the community. The American journal of psychiatry, v. 164, n. 8, p. 1259–65, ago. 2007.

26. ROSEN, D. S.; AMERICAN ACADEMY OF PEDIATRICS COMMITTEE ON ADOLESCENCE. Identification and management of eating disorders in children and adolescents. Pediatrics, v. 126, n. 6, p. 1240–53, dez. 2010.

27. CAMPBELL, K.; PEEBLES, R. Eating Disorders in Children and Adolescents: State of the Art Review. PEDIATRICS, v. 134, n. 3, p. 582–592, 1 set. 2014.

28. PRETI, A. et al. The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project. Journal of psychiatric research, v. 43, n. 14, p. 1125–32, set. 2009.

29. DANCYGER, I. F.; GARFINKEL, P. E. The relationship of partial syndrome eating disorders to anorexia nervosa and bulimia nervosa. Psychological medicine, v. 25, n. 5, p. 1019–25, set. 1995.

30. MICALI, N. et al. The incidence of eating disorders in the UK in 2000-2009: findings from the General Practice Research Database. BMJ open, v. 3, n. 5, 2013.

31. HUDSON, J. I. et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biological psychiatry, v. 61, n. 3, p. 348–58, fev. 2007.

32. SMINK, F. R. E.; VAN HOEKEN, D.; HOEK, H. W. Epidemiology, course, and outcome of eating disorders. Current opinion in psychiatry, v. 26, n. 6, p. 543–8, nov. 2013.

33. ANDREWS, J.; FEINSTEIN, A. Importance of clinical and co-morbid features in the staging of cancer. Clin Res, v. 16, p. 356, 1968.

34. FEINSTEIN, A. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis, v. 23, p. 455–468, 1970.

35. CLONINGER, C. Implications of comorbidity for the classification of mental disorders: the need for a psychobiology of coherence. In: Maj M, Gaebel W, Lopez-ibor J, Sartorius N, eds. *Psychiatric Diagnosis and Classification*. 1a ed. Chichester, UK: Wiley; 2002:79-105.

36. KESSLER, R. C. et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. The American journal of psychiatry, v. 163, n. 4, p. 716–23,

abr. 2006.

37. STARCEVIC, V. Psychiatric comorbidity: concepts, controversies and alternatives. Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists, v. 13, n. 4, p. 375–8, dez. 2005.

38. ROBINS, E.; GUZE, S. B. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. The American journal of psychiatry, v. 126, n. 7, p. 983–7, jan. 1970.

39. FEIGHNER, J. P. et al. Diagnostic criteria for use in psychiatric research. Archives of general psychiatry, v. 26, n. 1, p. 57–63, jan. 1972.

40. MCALEAVEY, K. Ten years of treating eating disorders: what have we learned? A personal perspective on the application of 12-step and wellness programs. Advances in mind-body medicine, v. 23, n. 2, p. 18–26, 2008.

41. MISCHOULON, D. et al. Depression and eating disorders: treatment and course. Journal of affective disorders, v. 130, n. 3, p. 470–7, maio 2011.

42. WESTWOOD, H. et al. Using the Autism-Spectrum Quotient to Measure Autistic Traits in Anorexia Nervosa: A Systematic Review and Meta-Analysis. Journal of autism and developmental disorders, v. 46, n. 3, p. 964–77, mar. 2016.

43. WENTZ, E. et al. Childhood onset neuropsychiatric disorders in adult eating disorder patients. A pilot study. European child & adolescent psychiatry, v. 14, n. 8, p. 431–7, dez. 2005.

44. NAZAR, B. P. et al. ADHD rate in Obese Women with Binge Eating and Bulimic Behaviours from a Weight Loss Clinic. Journal of Attention Disorders, 28 ago. 2012.

45. MATTOS, P. et al. [Comorbid eating disorders in a Brazilian attention-deficit/hyperactivity disorder adult clinical sample]. Revista brasileira de psiquiatria (São Paulo, Brazil : 1999), v. 26, n. 4, p. 248–50, dez. 2004.

46. KOOIJ, J. J. S. et al. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychological medicine, v. 34, n. 6, p. 973–82, ago. 2004.

47. AGRANAT-MEGED, A. N. et al. Childhood obesity and attention deficit/hyperactivity disorder: a newly described comorbidity in obese hospitalized children. The International journal of eating disorders, v. 37, n. 4, p. 357–9, maio 2005.

48. SURMAN, C. B. H.; RANDALL, E. T.; BIEDERMAN, J. Association between attention-deficit/hyperactivity disorder and bulimia nervosa: analysis of 4 case-control studies. The Journal of clinical psychiatry, v. 67, n. 3, p. 351–4, mar. 2006.

49. BIEDERMAN, J. et al. Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study. Journal of developmental and behavioral pediatrics : JDBP, v. 28, n. 4, p. 302–7, ago. 2007.

50. SOBANSKI, E. Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). European archives of psychiatry and clinical neuroscience, v. 256 Suppl, p. i26-31, set. 2006.

51. NAZAR, B. P. et al. Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders. Revista Brasileira de Psiquiatria, v. 30, n. 4, p. 384–9, dez. 2008.

52. FERNÁNDEZ-ARANDA, F. et al. ADHD symptomatology in eating disorders: a secondary psychopathological measure of severity? BMC psychiatry, v. 13, p. 166, 2013.

53. MICALI, N. et al. The effects of maternal eating disorders on offspring childhood and early adolescent psychiatric disorders. The International journal of eating disorders, v. 47, n. 4, p. 385–93, maio 2014.

54. BIEDERMAN, J. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. The Journal of clinical psychiatry, v. 65 Suppl 3, p. 3–7, jan. 2004.

55. BLINDER, B. J.; CUMELLA, E. J.; SANATHARA, V. A. Psychiatric comorbidities of female inpatients with eating disorders. Psychosomatic medicine, v. 68, n. 3, p. 454–62, 2006.

56. STULZ, N. et al. The severity of ADHD and eating disorder symptoms: a correlational study. BMC psychiatry, v. 13, p. 44, 2013.

57. CORTESE, S. et al. Association between symptoms of attention-deficit/hyperactivity disorder and bulimic behaviors in a clinical sample of severely obese adolescents. International journal of obesity (2005), v. 31, n. 2, p. 340–6, fev. 2007.

58. STEADMAN, K. M.; KNOUSE, L. E. Is the Relationship Between ADHD Symptoms and Binge Eating Mediated by Impulsivity? Journal of attention disorders, 7 maio 2014.

59. STRIMAS, R. et al. Symptoms of attention-deficit/hyperactivity disorder, overeating, and body mass index in men. Eating Behaviors, v. 9, n. 4, p. 516–518, dez. 2008.

60. SEITZ, J. et al. The Role of Impulsivity, Inattention and Comorbid ADHD in Patients with Bulimia Nervosa. PLoS ONE, v. 8, n. 5, p. e63891, 20 maio 2013.

61. RÅSTAM, M. et al. Eating problems and overlap with ADHD and autism spectrum disorders in a nationwide twin study of 9- and 12-year-old children. TheScientificWorldJournal, v. 2013, p. 315429, 2013.

62. NAZAR, B. P. et al. ADHD rate in Obese Women with Binge Eating and Bulimic Behaviours from a Weight Loss Clinic. Journal of Attention Disorders, 28 ago. 2012.

63. NAZAR, B. P. et al. Influence of attention-deficit/hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women. Comprehensive psychiatry, v. 55, n. 3, p. 572–8, abr. 2014.

64. REINBLATT, S. P. et al. Pediatric loss of control eating syndrome: Association with attention-deficit/hyperactivity disorder and impulsivity. International Journal of Eating Disorders, v. 48, n. 6, p. 580–588, set. 2015.

65. DUCHESNE, M. et al. Neuropsychology of eating disorders: a systematic review of the literature. Revista brasileira de psiquiatria Sao Paulo Brazil 1999, v. 26, n. 2, p. 107–117, 2004.

66. PORFIRIO, M. C. et al. Attention-deficit hyperactivity disorder and binge eating disorder in a patient with 2q21.1–q22.2 deletion. Psychiatric Genetics, v. 22, n. 4, p. 202–205, ago. 2012.

67. DAVIS, C. et al. A psycho-genetic study of associations between the symptoms of binge eating disorder and those of attention deficit (hyperactivity) disorder. Journal of psychiatric research, v. 43, n. 7, p. 687–96, abr. 2009.

68. YILMAZ, Z. et al. Possible association of the DRD4 gene with a history of attention-deficit/hyperactivity disorder in women with bulimia nervosa. International Journal of Eating Disorders, v. 45, n. 4, p. 622–625, maio 2012.

69. FARAONE, S. V. et al. Attention-deficit/hyperactivity disorder. Nature Reviews Disease Primers, p. 15020, 6 ago. 2015.

70. WONDERLICH, S. A; CONNOLLY, K. M.; STICE, E. Impulsivity as a risk factor for eating disorder behavior: assessment implications with adolescents. The International journal of eating disorders, v. 36, n. 2, p. 172–82, set. 2004.

71. FISCHER, S. et al. The role of negative urgency and expectancies in problem drinking and disordered eating: testing a model of comorbidity in pathological and at-risk samples. Psychology of addictive behaviors :

journal of the Society of Psychologists in Addictive Behaviors, v. 26, n. 1, p. 112–23, mar. 2012.

72. SVALDI, J. et al. Information processing of food pictures in binge eating disorder. Appetite, v. 55, n. 3, p. 685–94, dez. 2010.

73. SCHMITZ, F. et al. Attentional bias for food cues in binge eating disorder. Appetite, v. 80, p. 70–80, set. 2014.

74. RENWICK, B.; CAMPBELL, I. C.; SCHMIDT, U. Review of attentional bias modification: a brain-directed treatment for eating disorders. European eating disorders review : the journal of the Eating Disorders Association, v. 21, n. 6, p. 464–74, nov. 2013.

75. BOUTELLE, K. N. et al. An open trial evaluating an attention bias modification program for overweight adults who binge eat. Journal of Behavior Therapy and Experimental Psychiatry, v. 52, p. 138–146, set. 2016.

76. LEMIERE, J. et al. Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: an fMRI pilot study. Brain research, v. 1450, p. 57–66, 23 abr. 2012.

77. MCELROY, S. L. et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA psychiatry, v. 72, n. 3, p. 235–46, mar. 2015.

78. SOKOL, M. S. et al. Methylphenidate treatment for bulimia nervosa associated with a cluster B personality disorder. The International journal of eating disorders, v. 25, n. 2, p. 233–7, mar. 1999.

79. SCHWEICKERT, L. A.; STROBER, M.; MOSKOWITZ, A. Efficacy of methylphenidate in bulimia nervosa comorbid with attention-deficit hyperactivity disorder: a case report. The International journal of eating disorders, v. 21, n. 3, p. 299–301, abr. 1997.

80. DRIMMER, E. J. Stimulant treatment of bulimia nervosa with and without attention-deficit disorder: three case reports. Nutrition (Burbank, Los Angeles County, Calif.), v. 19, n. 1, p. 76–7, jan. 2003.

81. DUKARM, C. P. Bulimia nervosa and attention deficit hyperactivity disorder: a possible role for stimulant medication. Journal of women's health (2002), v. 14, n. 4, p. 345–50, maio 2005.

82. IOANNIDIS, K.; SERFONTEIN, J.; MÜLLER, U. Bulimia nervosa patient diagnosed with previously unsuspected ADHD in adulthood: clinical case report, literature review, and diagnostic challenges. The International journal of eating disorders, v. 47, n. 4, p. 431–6, maio 2014.

83. KESHEN, A.; IVANOVA, I. Reduction of bulimia nervosa symptoms after psychostimulant initiation in patients with comorbid ADHD: five case reports. Eating disorders, v. 21, n. 4, p. 360–9, 2013.

84. KOCIANCIC, T.; REED, M. D.; FINDLING, R. L. Evaluation of risks associated with short- and long-term psychostimulant therapy for treatment of ADHD in children. Expert opinion on drug safety, v. 3, n. 2, p. 93–100, mar. 2004.

85. WILENS, T. E. et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. Journal of the American Academy of Child and Adolescent Psychiatry, v. 47, n. 1, p. 21–31, jan. 2008.

86. PENNELL, A. et al. Severe avoidant/restrictive food intake disorder and coexisting stimulant treated attention deficit hyperactivity disorder. The International journal of eating disorders, 13 ago. 2016.

87. CORTESE, S.; MORCILLO PEÑALVER, C. Comorbidity between ADHD and obesity: exploring shared mechanisms and clinical implications. Postgraduate medicine, v. 122, n. 5, p. 88–96, set. 2010.

88. DOCET, M. F. et al. Attention deficit hyperactivity disorder increases the risk of having abnormal eating behaviours in obese adults. Eating and weight disorders : EWD, v. 17, n. 2, p. e132-6, jun. 2012.

89. MOHER, D. et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine, v. 6, n. 7, p. e1000097, 21 jul. 2009.

90. MIKAMI, A. Y. et al. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. Journal of Abnormal Psychology, v. 117, n. 1, p. 225–235, 2008.

91. MIKAMI, A. Y. et al. Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD. The International journal of eating disorders, v. 43, n. 3, p. 248–59, abr. 2010.

92. REINBLATT, S. P. et al. Association between binge eating and attention-deficit/hyperactivity disorder in two pediatric community mental health clinics. International Journal of Eating Disorders, v. 48, n. 5, p. 505–511, jul. 2015.

93. ROJO-MORENO, L. et al. Prevalence and comorbidity of eating disorders among a community sample of adolescents: 2-year follow-up. Psychiatry Research, v. 227, n. 1, p. 52–57, maio 2015.

94. KESSLER, R. C.; MERIKANGAS, K. R. The National Comorbidity Survey Replication (NCS-R): background and aims. International journal of methods in psychiatric research, v. 13, n. 2, p. 60–8, 2004.

95. FISHER, R. A. Frequency Distribution of the Values of the Correlation Coefficient in Samples from an Indefinitely Large Population. Biometrika, v. 10, n. 4, p. 507, maio 1915.

96. HIGGINS, J. P. T. et al. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed.), v. 327, n. 7414, p. 557–60, 6 set. 2003.

97. HARBORD, R. M.; EGGER, M.; STERNE, J. A. C. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Statistics in medicine, v. 25, n. 20, p. 3443–57, 30 out. 2006.

98. WELLS, G. et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Disponível em: <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>.

99. KAUFMAN, J. et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry, v. 36, n. 7, p. 980–8, jul. 1997.

100. FIRST MB, SPITZER RL, GIBBON M, W. J. Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCIDI/ P, Version 2.0, 4/97 revision). New York: Biometrics Research Department, 1997.

101. AMORIM, P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. Revista Brasileira de Psiquiatria, v. 22, n. 3, set. 2000.

102. KESSLER, R. C. et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychological medicine, v. 35, n. 2, p. 245–56, fev. 2005.

103. FREITAS, S. et al. Tradução e adaptação para o português da Escala de Compulsão Alimentar Periódica Translation and adaptation into Portuguese of the Binge-Eating Scale. Revista Brasileira de Psiquiatria, v. 23, n. 4, p. 215–220, 2001.

104. GORMALLY, J. et al. The assessment of binge eating severity among obese persons. Addictive behaviors, v. 7, n. 1, p. 47–55, jan. 1982.

105. BECK, A. T.; BEAMESDERFER, A. Assessment of depression: the depression inventory. Modern problems of pharmacopsychiatry, v. 7, p. 151–69, jan. 1974.

106. GORENSTEIN, C. et al. Psychometric properties of the Portuguese version of the Beck Depression Inventory on Brazilian college students. Journal of clinical psychology, v. 55, n. 5, p. 553–62, maio 1999.

107. ANDRADE, L. et al. Psychometric properties of the Portuguese version of the State-Trait Anxiety Inventory applied to college students: factor analysis and relation to the Beck Depression Inventory. Brazilian journal of medical and biological research = Revista brasileira de pesquisas médicas e biológicas / Sociedade Brasileira de Biofísica ... [et al.], v. 34, n. 3, p. 367–74, mar. 2001.

108. PATTON, J. H.; STANFORD, M. S.; BARRATT, E. S. Factor structure of the Barratt impulsiveness scale. Journal of clinical psychology, v. 51, n. 6, p. 768–74, nov. 1995.

109. MALLOY-DINIZ, L. F. et al. Tradução e adaptação cultural da Barratt Impulsiveness Scale (BIS-11) para aplicação em adultos brasileiros. J Bras Psiquiatria, v. 59, n. 2, p. 99–105, 2010.

110. VASCONCELOS, A. G. et al. Impulsivity components measured by the Brazilian version of the Barratt Impulsiveness Scale (BIS-11). Psicologia: Reflexão e Crítica, v. 28, n. 1, p. 96–105, mar. 2015.

111. CONNERS B. Conners ' Continuous Performance Test II (CPT II, V.5). 2004.

112. RABIN, L. A.; BARR, W. B.; BURTON, L. A. Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, v. 20, n. 1, p. 33–65, jan. 2005.

113. ROBERTSON, I. H. et al. “Oops!”: performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia, v. 35, n. 6, p. 747–58, jun. 1997.

114. BECHARA A. *Iowa Gambling Task Professional Manual*. Lutz, FL: Psychological Assessment Resources; 2007.

115. SONNEVILLE, K. R. et al. Childhood hyperactivity/inattention and eating disturbances predict binge eating in adolescence. Psychological Medicine, v. 45, n. 12, p. 2511–2520, 22 set. 2015.

116. BIEDERMAN, J. et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. The American journal of psychiatry, v. 159, n. 1, p. 36–42, jan. 2002.

117. ALEGRIA M, Jackson JS, Kessler RC, Takeuchi D. Collaborative Psychiatric Epidemiology Survey (CPES). ICPSR20240-v8. *Inter-university Consort Polit Soc Res 2015-12-09*. http://doi.org/10.3886/ICPSR20240.v8.

118. BLECK, J. R.; DEBATE, R. D.; OLIVARDIA, R. The Comorbidity of ADHD and Eating Disorders in a Nationally Representative Sample.

The journal of behavioral health services & research, 10 jul. 2014.

119. YOSHIMASU, K. et al. Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: a population-based birth cohort study. Journal of Child Psychology and Psychiatry, v. 53, n. 10, p. 1036–1043, out. 2012.

120. MIKAMI, A. Y. et al. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. Journal of Abnormal Psychology, v. 117, n. 1, p. 225–235, 2008.

121. WELCH, E. et al. Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical course and psychiatric comorbidity. BMC Psychiatry, v. 16, n. 1, p. 163, 26 dez. 2016.

122. BREWERTON, T. D.; DUNCAN, A. E. Associations between Attention Deficit Hyperactivity Disorder and Eating Disorders by Gender: Results from the National Comorbidity Survey Replication. European eating disorders review : the journal of the Eating Disorders Association, 2 ago. 2016.

123. KARJALAINEN, L. et al. Eating disorders and eating pathology in young adult and adult patients with ESSENCE. Comprehensive Psychiatry, v. 66, p. 79–86, abr. 2016.

124. LIAO, Y.-T. et al. Association between Attention Defi cit Hyperactivity Disorder Symptoms and Bulimia among College Students. Taiwanese Journal of Psychaitry, v. 29, n. 2, p. 98–108, 2015.

125. FISCHER, M.; BARKLEY, R. A. The Persistence of ADHD into Adulthood: (Once Again) It Depends on Whom You Ask. The ADHD Report, v. 15, n. 4, p. 7–16, ago. 2007.

126. DIAS, G. et al. Agreement Rates Between Parent and Self-Report on Past ADHD Symptoms in an Adult Clinical Sample. Journal of Attention Disorders, v. 12, n. 1, p. 70–75, 11 jan. 2008.

127. WILLCUTT, E. G. et al. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. Journal of abnormal psychology, v. 121, n. 4, p. 991–1010, nov. 2012.

128. WAGNER, F. et al. Attention-deficit/hyperactivity disorder dimensionality: the reliable “g” and the elusive “s” dimensions. European child & adolescent psychiatry, v. 25, n. 1, p. 83–90, jan. 2016.

129. WILLIAMSON, D.; JOHNSTON, C. Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review. Clinical psychology review, v. 40, p. 15–27, ago. 2015.

130. ORTEGA-ROLDÁN, B. et al. The emotional and attentional impact of

exposure to one's own body in bulimia nervosa: a physiological view. PloS one, v. 9, n. 7, p. e102595, 2014.

131. NIGG, J. T. et al. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. Clinical psychology review, v. 43, p. 67–79, fev. 2016.

132. CORTESE, S. et al. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. The American journal of psychiatry, v. 173, n. 1, p. 34–43, jan. 2016.

133. KESSLER, R. C. et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biological psychiatry, v. 73, n. 9, p. 904–14, 1 maio 2013.

134. BLUM, K. et al. Attention-deficit-hyperactivity disorder and reward deficiency syndrome. Neuropsychiatric disease and treatment, v. 4, n. 5, p. 893–918, out. 2008.

135. BLUM, K. et al. Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant. Advances in therapy, v. 23, n. 6, p. 1040–51, 2006.

136. BLUM, K. et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine, v. 89, n. 7, p. 396–400, jul. 1996.

137. SEYMOUR, K. E. et al. Overlapping neurobehavioral circuits in ADHD, obesity, and binge eating: evidence from neuroimaging research. CNS spectrums, v. 20, n. 4, p. 401–11, ago. 2015.

138. CARNELL, S. et al. Neuroimaging and obesity: current knowledge and future directions. Obesity reviews : an official journal of the International Association for the Study of Obesity, v. 13, n. 1, p. 43–56, jan. 2012.

139. HARTMANN, A. S.; RIEF, W.; HILBERT, A. Impulsivity and negative mood in adolescents with loss of control eating and ADHD symptoms: an experimental study. Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, v. 18, n. 1, p. 53–60, 3 mar. 2013.

140. STRACK, F.; DEUTSCH, R. Reflective and impulsive determinants of social behavior. Personality and social psychology review : an official journal of the Society for Personality and Social Psychology, Inc, v. 8, n. 3, p. 220–47, 2004.

141. SERGEANT, J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neuroscience and biobehavioral reviews, v. 24, n. 1, p. 7–12, jan. 2000.

142. CAGLAR-NAZALI, H. P. et al. A systematic review and meta-analysis of

"Systems for Social Processes" in eating disorders. Neuroscience and biobehavioral reviews, v. 42, p. 55–92, maio 2014.

143. PENNESI, J.-L.; WADE, T. D. A systematic review of the existing models of disordered eating: Do they inform the development of effective interventions? Clinical psychology review, v. 43, p. 175–92, fev. 2016.

144. GARON, N. Decision Making in Children With ADHD Only, ADHD-Anxious/Depressed, and Control Children Using a Child Version of the Iowa Gambling Task. Journal of Attention Disorders, v. 9, n. 4, p. 607–619, 1 maio 2006.

145. NARVAEZ, J. C. et al. Does comorbid bipolar disorder increase neuropsychological impairment in children and adolescents with ADHD? Revista Brasileira de Psiquiatria, v. 36, n. 1, p. 53–59, mar. 2014.

146. WELCH, E. et al. Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical course and psychiatric comorbidity. BMC psychiatry, v. 16, p. 163, 26 maio 2016.

147. WARNER, M. H. et al. Relationships between IQ and neuropsychological measures in neuropsychiatric populations: within-laboratory and cross-cultural replications using WAIS and WAIS-R. Journal of clinical and experimental neuropsychology, v. 9, n. 5, p. 545–62, out. 1987.

148. WEBB, C. A.; DELDONNO, S.; KILLGORE, W. D. S. The role of cognitive versus emotional intelligence in Iowa Gambling Task performance: What's emotion got to do with it? Intelligence, v. 44, p. 112–119, 2014.

Parte Pós - Textual

9 ANEXOS

9.1 Artigo:

The risk of Eating Disorders comorbid with Attention-Deficit / Hyperactivity Disorder

REVIEW

The Risk of Eating Disorders Comorbid with Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis

Bruno Palazzo Nazar, MD, MSc[1,2]*
Camila Bernardes, BA[3]
Gemma Peachey, MBBS[4]
Joseph Sergeant, PhD[5]
Paulo Mattos, MD, MSc, PhD[1,3]
Janet Treasure, OBE, PhD, FRCP, FAED[2,4]

ABSTRACT

Objective: There has been interest in whether people with Attention-Deficit/Hyperactivity Disorder (ADHD) are at higher risk of developing an Eating Disorder (ED). The aim of this study was estimate the size of this association with a meta-analysis of studies.

Methods: We retrieved studies following PRISMA guidelines from a broad range of databases.

Results: Twelve studies fitted our primary aim in investigating ED in ADHD populations (ADHD = 4,013/Controls = 29,404), and five exploring ADHD in ED populations (ED = 1,044/Controls = 11,292). The pooled odds ratio of diagnosing any ED in ADHD was increased significantly, 3.82 (95% CI:2.34–6.24). A similar level of risk was found across all ED syndromes [Anorexia Nervosa = 4.28 (95% CI:2.24–8.16); Bulimia Nervosa = 5.71 (95% CI: 3.56–9.16) and Binge Eating Disorder = 4.13 (95% CI:3–5.67)]. The risk was significantly higher if ADHD was diagnosed using a clinical interview [5.89 (95% CI:4.32–8.04)] rather than a self-report instrument [2.23 (95% CI:1.23–4.03)]. The pooled odds ratio of diagnosing ADHD in participants with ED was significantly increased, 2.57 (95% CI:1.30–5.11). Subgroup analysis of cohorts with binge eating only yielded a risk of 5.77 (95% CI:2.35–14.18). None of the variables examined in meta-regression procedures explained the variance in effect size between studies.

Discussion: People with ADHD have a higher risk of comorbidity with an ED and people with an ED also have higher levels of comorbidity with ADHD. Future studies should address if patients with this comorbidity have a different prognosis, course and treatment response when compared to patients with either disorder alone.

Resumen: Objetivo: Ha habido interés en saber si la gente con Trastorno por Déficit de Atención e Hiperactividad (TDAH) están en mayor riesgo de desarrollar un Trastorno de la Conducta Alimentaria (TCA). El objetivo de este estudio fue estimar el tamaño de esta asociación con un meta-análisis de los estudios. Métodos: Recuperamos estudios de una amplia gama base de datos, que siguen los lineamientos PRISMA. Resultados: Doce estudios encajaron con nuestro objetivo primario de investigar los TCA en poblaciones con TDAH (TDAH = 4,013/Controles = 29,404), y 5 exploraron TDAH en poblaciones con TCA (TCA = 1,044/Controles = 11,292). El odds ratio (OR) agrupado de diagnosticar cualquier TCA en el TDAH se incrementó significativamente, 3.82 (95% CI:2.34–6.24). Un nivel de riesgo similar fue encontrado en todos los síndromes de TCA [Anorexia Nervosa = 4.28 (95% CI:2.24–8.16); Bulimia Nervosa = 5.71 (95% CI:3.56–9.16) y Trastorno por Atracón = 4.13 (95% CI: 3–5.67)]. El riesgo fue significativamente mayor si el TDAH fue diagnosticado utilizando una entrevista clínica [5.89 (95% CI:4.32–8.04)] en lugar de un instrumento de auto-reporte [2.23 (95% CI:1.23–4.03)]. El odds ratio (OR) agrupado de diagnosticar TDAH en participantes con TCA fue significativamente incrementado, 2.57 (95% CI:1.30–5.11). El análisis de los subgrupos de cohort con atracones solamente produjo un riesgo de 5.77 (95% CI:2.35–14.18). Ninguna de las variables examinadas en los procedimientos de meta-regresión explicaron la varianza en el tamaño del efecto entre los estudios. Discusión: La gente con TDAH tiene un mayor riesgo de comorbilidad

Accepted 9 October 2016
Additional Supporting Information may be found in the online version of this article.
*Correspondence to: Bruno Palazzo Nazar, E-mail: bruno.nazar@gmail.com
[1] Institute of Psychiatry (IPUB-UFRJ), Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[2] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IOPPN), King's College, London
[3] D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil
[4] South London and the Maudsley National Health Trust (SLaM – NHS), London
[5] Vrjie Universiteit, Amsterdam, The Netherlands
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/eat.22643

con un TCA y la gente con un TCA también tiene niveles altos de comorbilidad con TDAH. Los estudios futuros deberán abordar si los pacientes con esta comorbilidad tienen diferente pronóstico, curso y respuesta a tratamiento cuando son comparados con pacientes que solamente tienen uno de los trastornos. © 2016 Wiley Periodicals, Inc.

Keywords: eting disorders; ADHD; binge eating; obesity; attention deficit-hyperactivity disorder; comorbidity; impulsivity; reward; bulimia nervosa; anorexia nervosa

(Int J Eat Disord 2016; 00:000-000)

A proportion of people with Eating Disorders (ED) have poor treatment outcomes.[1] Identifying subgroups of patients with comorbid disorders may help explain differences in disease trajectories[2] and aid the process of tailoring treatments to match individual needs.

There has been interest in whether developmental disorders might increase ED risk. For example, Anorexia Nervosa (AN), especially the restrictive subtype, has been linked to autism[3] and the purging subtype of AN has been associated with ADHD.[4] The association of Bulimia Nervosa (BN) and Binge Eating Disorder (BED) with ADHD has been repeatedly demonstrated.[5,6] We reported a higher prevalence of ED, in particular BED, in a lean ADHD cohort in 2004.[6] This result was further replicated in six samples.[4,7–11] A systematic review of all studies found that BN was the most frequent form of ED seen among people with ADHD.[12] The frequency of ADHD symptoms is higher in BN or BED when compared to AN.[13] We have published the first systematic review about ADHD comorbid with ED[12] in 2008 but this field of research was still in its infancy limiting us to perform a qualitative review of studies. Thus, there is the need to extend the previous systematic research and complement it with a meta-analysis of studies to measure the risk of the association between ADHD and ED.

The studies of ADHD patients found that the prevalence of BN ranged from 9%[7] up to 11%,[14] whereas that of BED ranged from 9.3%[15] up to 11.4%,[11] and that of AN was 1%.[10] Conversely, when the prevalence of ADHD was investigated in ED, studies in AN patients found rates ranging from 3%[16] up to 16.2%,[17] while for BN patients it ranged from 9%[16] up 34.9%,[17] and for BED patients it was 19.8%.[17] The positive association of ADHD and ED traits has also been demonstrated in correlational studies,[13,18–24] with a correlation coefficient ranging from[19] 0.23 to 0.59.[22] The number of ADHD symptoms correlate with ED symptom severity in all binge/purge ED subtypes.[13] ADHD symptoms have been found to predict binge eating severity[20,21,25] and bulimic symptoms even after controlling for anxiety and depression.[19,25]

In the paediatric population, the symptom of Loss of Control Eating (LOC), a subclinical form of binge eating is also associated with ADHD rather than the full BN and BED syndromes, probably because the two latter only evolve in the context of greater autonomy in food choice and consumption.[26]

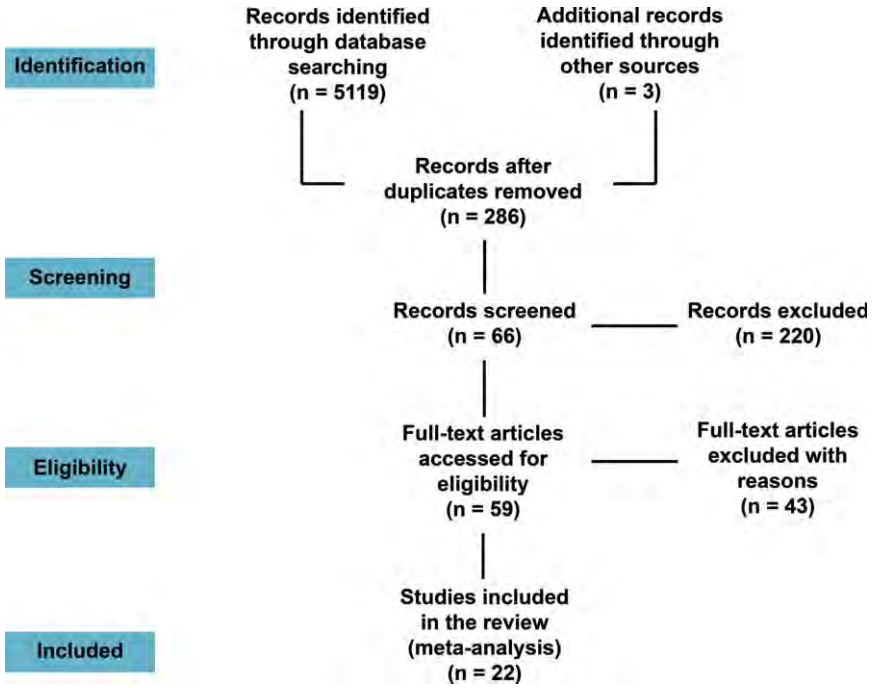
Although the most likely trajectory is for ADHD symptoms to precede the development of an ED it is possible that secondary consequences of an eating disorder on attentional and impulsive behaviors[27] lead to de novo ADHD traits, and to an ADHD-like syndrome.

The link mediating the association of ADHD and ED is still not clear and is possibly a combination of genetic and environmental mechanisms. Genetic variability in dopaminergic genes related to reward processing have been described in a patient with comorbid ADHD and BED,[28] in a case control study of obese BED comorbid with ADHD[29] and in BN women with a childhood history of ADHD.[30]

Anomalies in attentional and impulsive mechanisms could explain the link between ADHD and ED. Impulsive behaviors constitute a core ADHD symptom domain[31] and deficits in its regulation have been demonstrated in this population.[32] Also, impulsivity plays a role in binge eating and purging behaviors.[33] Negative urgency, an aspect of impulsivity, that has been shown to relate binge eating to emotional regulation[34] could also play a role in explaining this association. Patients with ADHD + ED have higher levels of impulsive traits than patients with either of those conditions alone.[22,25]

Changes in different aspects of attentional functioning have been reported in ED. Patients with AN, BN, and BED have deficits in both sustained attention and processing speed.[27,35] The disturbed reward encoding in ED patients increases salience towards food cues. This leads to the development of attentional bias towards food and an altered motivational control.[36] Programs that train attention towards neutral stimuli are beneficial in correcting these disturbances.[37,38] ADHD individuals typically have motivational difficulties since they prefer immediate and small rewards instead of

FIGURE 1. Selection procedures flowchart for the systematic review and meta-analysis.



delaying gratification to obtain larger rewards.[39] In concert with this style, ADHD individuals would be vulnerable for developing binge eating and would have difficulties in maintaining long lasting healthy habits. It is unfortunate that the presence of ADHD as a possible mediator explaining attentional deficits in ED has not yet been considered in the neuropsychological or attentional bias studies.

In terms of treatment, the recent approval of psychostimulants for the treatment of Binge Eating Disorder (BED)[40] raises the question as to whether improvements in an undiagnosed Attention-Deficit/Hyperactivity Disorder (ADHD) syndrome could lead to additional benefits to the ED symptoms. Several case reports have described that patients with refractory Bulimia Nervosa (BN), associated with either a current or a past history of ADHD, improved their ED when treated with psychostimulants.[41–46] However, in a recent lysdexamphetamine trial for BED, even excluding ADHD participants, significant improvements in eating behavior were observed. It is well documented that psychostimulants can promote appetite loss and weight loss.[47] Thus, it is a clinical concern that the use of psychostimulants could improve ED symptoms largely by a primary effect on appetite. In this case, the use of psychostimulants to treat ADHD in individuals with an undiagnosed ED could lead to severe weight loss,[48] specially in impulsive individuals with risk of psychostimulant misuse.[49]

The aim of this study was to update and expand the previous systematic review and perform a meta-analysis of studies to investigate the risk of comorbidity with an ED (AN, BN, or BED) in ADHD individuals or eating disorder symptoms (binge eating or LOC eating) in ADHD paediatric samples. The risk of diagnosing ADHD in ED patients was also investigated. Furthermore, we explored the strength of association between ADHD and ED symptoms when those were measured dimensionally. Additionally, we explored confounding factors, which might explain the variability in ED prevalence in this population.

Methods

The systematic review and meta-analysis were conducted following PRISMA statement guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[50] Selection procedures are presented in Figure 1. The following key terms were used: ("Eating Disorders"; "Anorexia Nervosa"; "Bulimia"; "Bulimia Nervosa"; "Binge Eating Disorder"; "Binge Eating"; "Overeating") AND ("Hyperactivity with attention-deficit disorder"; "ADHD"; "ADD"; "Inattention"), to search for articles in PubMed, Scielo, PsychINFO, and ISI Web of Knowledge databases.

Studies were searched independently by both the first (BPN) and second (CB) authors and were considered eligible if published in English, French, German, Dutch, Spanish, or Portuguese languages; if they were of a case-control design; if they reported measures to calculate

TABLE 1. Summary of the case-control studies included in the meta-analysis of Eating Disorders in ADHD individuals, and the meta-analysis of ADHD in ED individuals

Author, year	Country	Clinical Setting	Study Design	Total Sample (ADHD/Controls)	Mean age	Gender (N and %)	BMI category	ADHD diagnosis	ED diagnosis	Reported ED result
Docet, 2012	Spain	Outpatient	CRS	402 (172/230)	42.3	F = 45 (88,2%) M = 6 (11,8%)	Obese	Self-Report	Clinical Interview	BED
Nazar, 2014	Brazil	Outpatient	CRS	131 (40/91)	38.2	F only = 131	Obese	Semi-structured Interview	Semi-structured Interview	BN + BED
Reinblatt, 2015	USA	Clinical sample	CRS	79 (44/35)	11	F = 38 (48.1%) M= 41 (51.9%)	Obese	Semi-structured Interview	Semi-structured Interview	LOC
Biederman, 2007	USA	Clinical sample	LGT	235 (123/112)	16.7	F only = 123	All weight categories	Semi-structured Interview	Semi-structured Interview	AN + BN
Bleck, 2013	USA	Community	CRS	4862 (898/3964)	21.7	F = 2619 (53.8%) M = 2243 (46,2%)	All weight categories	Self-Report	Self-Report	AN + BN + BED
Kessler, 2004	USA	Community	CRS	3031 (153/2878)	range: 18–44	F = 4913 (52.9%) M = 4374 (47.1%)	All weight categories	Semi-structured Interview	Semi-structured Interview	AN + BN + BED
Reinblatt, 2015 (b)	USA	Clinical sample	CRS	252 (109/143)	10.8	F = 119 (47.2%) M= 133 (52.8%)	All weight categories	Semi-structured Interview	Semi-structured Interview	Binge eating
Sonneville, 2015	UK	Community	LGT	3819 (233/3545)	11.7	F = 3847 (48.8%) M= 4037 (51.2%)	All weight categories	Self-Report	Semi-structured Interview	Binge eating
Surnam, 2006	USA	Clinical sample	CRS	742 (320/422)	38.2	F = 315 (42.4%) M= 427 (57.5%)	All weight categories	Semi-structured Interview	Semi-structured Interview	BN
Biederman, 2002	USA	Clinical sample	CRS	522 (280/242)	11.3	F = 262 (50.1%) M= 260 (49.9%)	All weight categories	Semi-structured Interview	Semi-structured Interview	BN
Mikami 2008	USA	Clinical sample	LGT	228 (140/88)	9.5	F only = 228	All weight categories	Semi-structured Interview	Semi-structured Interview	BN
Mikami 2010	USA	Clinical sample	LGT	696 (432/264)	16.3	F = 148 (21.2%) M = 548 (78.8%)	All weight categories	Semi-structured Interview	Semi-structured Interview	BN
Yoshimasu, 2012	USA	Community	LGT	1055 (343/712)	19	F = 214 (21.3%) M = 791 (78.7%)	All weight categories	Database Registry	Database Registry	N.R.
Rastam, 2013	Sweden	Community	LGT	11927 (903/11024)	10.5	F = 5885 (49.4%) M = 6042 (50.6%)	All weight categories	Self-Report	Self-Report	Restrictive Eating
Seitz, 2013	Germany	Clinical sample	CRS	97 (57/40) *	21	F only = 97	NonOverweight/Obese	Semi-structured Interview	Semi-structured Interview	BN
Rojo-Moreno, 2015	Spain	Community	LGT	993 (35/958)*	14	F = 475 (47.8%) M = 518 (52.2%)	All weight categories	Semi-structured Interview	Semi-structured Interview	AN and BN
Welch, 2016	Sweden	Clinical sample	LGT	9350 (850/8500)*	22§	F = 811 (95.4%) § M = 39 (4.6%)§	All weight categories	Database Registry	Database Registry	BED

Legend: CRS, Cross-Sectional; LGT, Longitudinal; *Numbers mean: Total Sample (Eating Disorder/Controls); § =Data reported only for the ED group.

TABLE 2. Summary of correlational studies included in the meta-analysis

Author, year	Country	Sample type	Mean age (years)	Mean BMI (kg/m^2)	Gender	ED instrument	ADHD instrument
Strimas, 2008	Canada	Community	34.2	28.1	M only = 145	BEQ	CAARS
Steadman, 2014	USA	Community	19.2	22.4	F = 36 (72%) M= 14 (28%)	BES	BAARS-IV
Liao, 2015	China	Community	21.8	21.86	F = 181 (44.3%) M = 228 (55.7%)	BITE	ASRS
Nazar, 2014	Brazil	Clinical	38.2	39.1	F only = 171	BITE and BES	ASRS
Cortese, 2007	France	Clinical	14.2	37	F = 65 (65.6%) M = 34 (34.4%)	BITE	CPRS
Seitz, 2013	Germany	Clinical	21.9	20.7	F only = 57	EDI-II	ADHS-SB
Fernandez-Aranda, 2013	Spain	Clinical	28.3	23.6	F only = 191	EDI-II	ASRS

Legend: BEQ, Binge Eating Questionnaire; CAARS, Coner's Adult ADHD Rating Scale; BES, Binge Eating Scale; BAARS-IV, Barkley Adult ADHD Scale; BITE, Bulimic Inventory Test, Edinburgh; ASRS, Adult Self Report Scale; CPRS, Conner's Parent Rating Scale; EDI-II, Eating Disorders Inventory II; ADHS-SB, ADHD self rating scale.

odds ratio; if they reported any statistical result measuring the association between eating disorders and ADHD symptoms; and if they had been peer-reviewed for publishing. Studies that did not specify how ADHD or ED was diagnosed were excluded. A hand-search from reference lists of selected articles was performed to find additional relevant studies. Finally, the lists of selected articles were compared and discordant references discussed. If both authors failed to reach a consensus this was later discussed with both principal authors (PM and JT). Finally, references were added to EndNote where duplicates were removed. All case-control studies characteristics are summarized in Table 1, while correlational studies are summarized in Table 2.

Statistical Analysis

The eligibility criteria for inclusion in meta-analytic procedures required that studies reported either: (a) the ED frequency in an ADHD versus a Control group, (b) ADHD frequency in an ED versus Control group, (c) a correlation coefficient between ADHD and ED symptoms, (d) a statistical result that could be transformed into a correlation coefficient. Moreover, authors were contacted in order to obtain unpublished quantitative data. Thus, the data used on Mikami et al.[51]; Mikami et al.[52]; Docet et al.[53]; Reinblatt et al.[26]; Reinblatt et al.,[54] Sonneville et al., and Rojo-Moreno et al.[55] were kindly provided after direct contact with authors. The database from Nazar et al.[25] was available for direct extraction of necessary outcomes. Additionally, after contacting one of the authors (Kessler RC) from the Collaborative Psychiatric Epidemiological Surveys (CPES), we used the available information from the National Comorbidity Survey—Replication (NCS-R, 2001–2003) dataset to extract results relevant for the purpose of the present analysis.[56]

The Odds Ratio of having an ED amongst ADHD versus Control groups, and the odds ratio of having ADHD amongst ED versus Control groups was calculated using a random effects model. STATA 12 (Stata corporation, College Station, TX, USA) was used for this purpose as well as building all graphics. The user-written commands for STATA *Metan, Metabias* and *Metareg* were used.

The pooled correlation coefficient among ED and ADHD symptoms measured in different rating scales was obtained by using the transformed value on a standardized Fisher's Z scale with the formula ($Z = 1/2\ \ln(1 + r\ /\ 1 - r)$) and its standard error by ($SE_Z = 1/\sqrt{(n-3)}$.[57] This meta-analytic model used the Hedges-Olkin random-effects model and was performed using STATA 12. To calculate the correlation coefficient back to a nonstandardized scale the formula $(e^{((2xZpool-1)/(2xZpool+1))}$ was used.

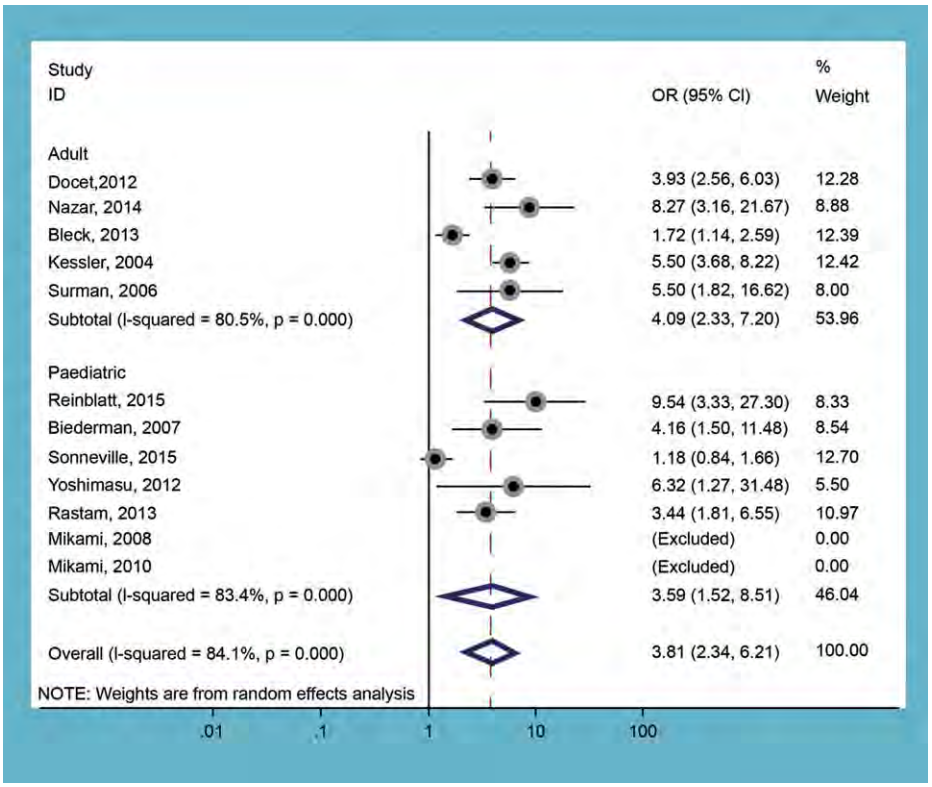
Heterogeneity across studies was calculated using Cochran's Q statistics, expressed in a χ^2 result. Inconsistency across studies was investigated through publication bias with I^2 statistics $[(Q\text{-}df)/Q]$.[58]

The assessment of publication bias was done with the Harbord's test of bias, which was chosen for exploring "small studies effect" explaining the OR variance, as it is better suited for binary data and results in less false positive outcomes than the Eggers' Test.[59] Also, informal visual inspections of funnel plots were performed.

All studies were assessed with the case control version of the Newcastle-Ottawa Quality Assessment Tool.[60] Quality assessments were used to investigate risk of bias. Each study could receive at least four points in the selection, two points in the comparability and three points in the exposure subescale.

Metaregression was used to investigate if mean age; weight category; proportion of females; sample size; method for ADHD diagnosis; method for ED diagnoses, study country or study quality would account for differences in studies results.

FIGURE 2. Meta-analysis of studies investigating ED in ADHD individuals. [Color figure can be viewed at wileyonlinelibrary.com]



Results

The Risk of Eating Disorders in People with ADHD versus Controls

Outcomes for 33,417 individuals (ADHD = 4,013/Controls = 29,404), across 12 retained studies were available. Most paediatric studies measured symptoms such as LOC,[26] binge eating episodes[54,61] or restrictive behaviors,[23] whereas all adult studies reported on syndromes (AN, BN, and BED). Two studies were considered outliers[54,62] since their effect size had a wide confidence interval that had an upper bound that was much bigger than all others,[54,62] and were excluded from the analysis. Results including these two studies are presented in the online **Supporting Information**. All of the studies demonstrated higher levels of either ED diagnosis or disordered eating behaviors in the ADHD group compared with the control group.

The meta-analysis from pooling all 12 studies,[9,10,25,26,51–53,56,61,63] after the exclusion of the two outliers, yielded a significant risk ($P<.001$) of diagnosing either an ED syndrome (AN, BN, or BED) or ED symptoms (restrictive eating, binge eating episodes, or LOC) within ADHD individuals, with an overall random effect OR of 3.81 (95% CI: 2.31–6.21) (**Fig. 2**). The results of the key subgroup meta-analyses, heterogeneity tests, and publication bias, are presented in **Table 3**.

To disentangle the individual risk for each ED, analyses were carried out for studies that reported AN (either full syndrome[10,64] or AN-related symptoms[23]), BN (all studies reported full syndrome[9,10,25,64]) and BED (either full syndrome[25,53,64] or LOC[26]). A separate analysis with studies that reported outcomes for binge eating episodes that fulfilled DSM criteria (Objective Binge Eating), regardless of the ED syndrome,[9,10,25,53,64] was also performed. The subgroup analysis yielded a risk of 4.28 (95% CI: 2.24–8.16) for AN ($n=3$); 5.71 (95% CI: 3.56–9.16) for BN ($n=4$); 4.13 (95% CI: 3–5.67) for BED ($n=4$); and of 4.67 (95% CI: 3.58–6.10) for objective binge eating episodes ($n=5$), in ADHD.

In adults ($n=5$)[9,25,53,63,64] the OR for ED syndromes was 4.09 (95% CI: 2.32–7.20). The subgroup analysis in the paediatric samples, also found an increased significant ($P=.013$) risk ($n=7$),[10,23,26,52,61,65,66] OR of 3.59 (95% CI: 1.51–8.50) (**Fig. 3**). The subgroup analysis in the obese only samples, also found an increased risk in the obese-ADHD ($n=3$ studies),[25,26,53] OR of 5.81 (95% CI: 3.15–10.7).

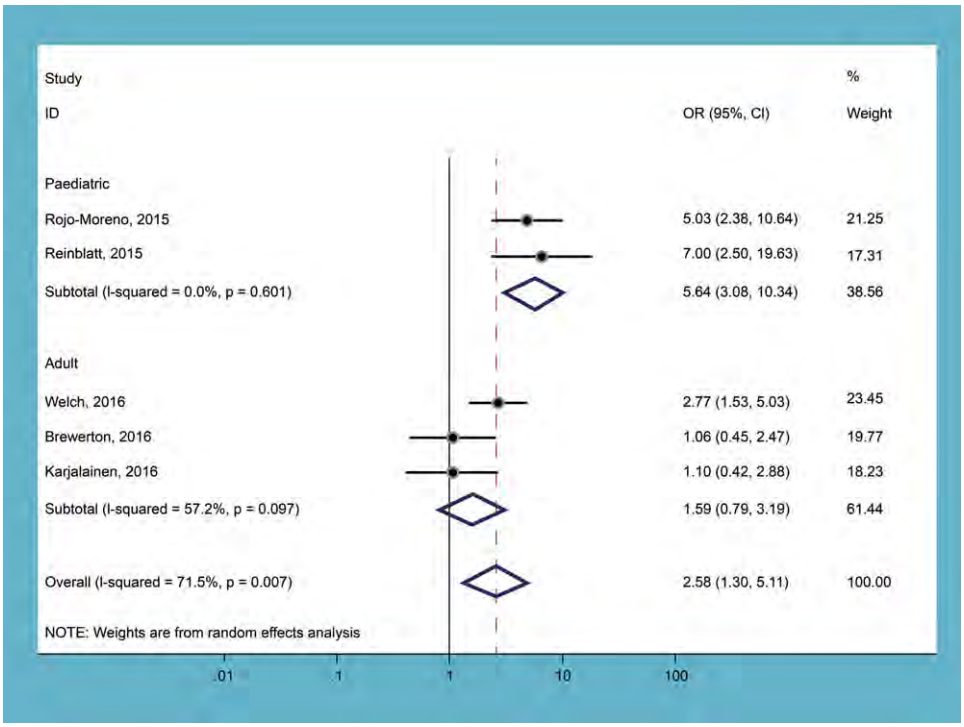
In the subgroup analysis by gender, females only ($n=9$)[9,10,23,25,26,52,61,63,66] presented an OR of 3.46

TABLE 3. Summary of the results for all meta-analysis using case-control studies

							Q statistics			Harbord test	
	Group analysed	Main Outcome	Sample Size	Odds Ratio	95% CI	p values	X^2	*P* values	I^2	Bias Coef.	*P* values
ED in ADHD x Controls	All studies	ED symptoms or syndromes	12	3.81	(2.33–6.21)	<.001	56.50	<.001	84.1%	4.83	.03
	All studies	AN (full or subclinical)	3	4.28	(2.24–8.16)	<.001	2.00	.36	0%	3.66	.70
	All studies	BN (full)	6	5.71	(3.56–9.16)	<.001	3.20	.36	6.1%	13.02	.19
	All studies	BED (full or subclinical)	4	4.13	(3.00–5.67)	<.001	3.27	.35	8.2%	2.81	.32
	All studies	Objective Binge Eating (any ED syndrome)	7	4.67	(3.58–6.10)	<.001	2.10	.71	0%	2.05	.56
	Obese only studies	ED symptoms (LOC) or syndromes (BN or BED)	3	5.81	(3.15–10.71)	<.001	3.71	.156	46.1%	2.66	.02
	Studies using all weight categories	ED symptoms or syndromes	9	3.10	(1.71–5.64)	<.001	40.94	<.001	85.3%	5.63	.05
	Paediatric subjects	ED symptoms	7	3.59	(1.51–8.50)	.013	24.10	.004	83.4%	4.65	.01
	Adult subjects	ED syndromes	5	4.09	(2.32-7.20)	<.001	20.49	<.001	80.5%	5.93	.28
	Female only subjects	ED symptoms or syndromes	9	3.46	(2.00-5.98)	<.001	15.05	.02	60.1%	1.23	.50
	Adult Female only subjects	ED syndromes	3	4.35	(1.67–11.27)	.002	7.85	.02	74.5%	4.04	.36
	Paediatric Female Only subjects	ED symptoms or syndromes	6	2.96	(1.32–6.65)	.008	6.98	.07	57%	2.57	.49
	Male only subjects	ED symptoms or syndromes	6	3.37	(1.46–7.77)	.004	11.67	.02	65.7%	2.53	.12
	ADHD through diagnostic interview	ED symptoms or syndromes	8	5.89	(4.32–8.04)	<.001	0.65	.72	0%	−1.9	.70
	Adult ADHD through diagnostic interview	ED syndromes	3	5.80	(4.08–8.25)	<.001	1.25	.53	0%	−12.2	.72
	Paediatric ADHD through diagnostic interview	ED symptoms or syndromes	5	6.22	(3.20–12.11)	<.001	1.90	.86	0%	1.45	.71
	ADHD through Self - Report	ED symptoms or syndromes	4	2.23	(1.23–4.03)	.008	21.82	<.001	86.2%	4.99	.38
	All Eating Disorder x Control studies	ADHD diagnosis	5	2.57	(1.30–5.11)	.007	14.04	.007	71.5%	8.66	.43
ADHD in ED x Controls	Any Adult Eating Disorder	ADHD diagnosis	3	1.58	(0.78–3.19)	.195	4.67	.09	57.2%	−1.68	.76
	Binge Eating patients only	ADHD diagnosis	3	5.77	(2.35–14.18)	<.001	11.43	.003	82.5%	−43.69	.20

Legend: ED symptoms, unless otherwise stated represent LOC, binge eating and restrictive eating; ED syndromes, unless otherwise stated represent AN, BN and BED; AN, anorexia nervosa; BN, bulimia nervosa; BE, binge eating episodes; BED, binge eating Disorder; LOC, loss of control eating;.

FIGURE 3. Meta-analysis of studies investigating ADHD in ED individuals. [Color figure can be viewed at wileyonlinelibrary.com]



(95% CI: 2.00–5.98). Adult females ($n = 3$)[9,25,63] had a similar sized risk OR of 4.35 (95% CI: 1.67–11.27). In the paediatric female subgroup ($n = 6$) ([10,23,26,51,52,61] the risk for any ED was 2.96 (95% CI: 1.32–6.65). The subgroup consisting only of males ($n = 6$),[9,23,26,52,61,63] had an OR of 3.37 (95% CI: 1.46–7.77).

Since studies differed in how they diagnosed ADHD we analyzed results for subgroups that did so by using a semi-structured interview or by using questionnaires. The analysis of ADHD diagnosis by interview ($n = 8$)[9,10,25,26,51,52,64,65] yielded a significant risk of ED, 5.89 (95% CI: 4.32–8.04), with a subset for adults only ($n = 3$)[9,25,64] of 5.80 (95% CI: 4.04–8.25) and a subset for paediatric only ($n = 5$)[10,26,51,52,65] of 6.22 (95% CI: 3.20–12.11). These results significantly differed from those that diagnosed ADHD through questionnaires ($n = 4$),[23,53,61,63] which resulted in a significant risk of 2.23 (95% CI: 1.23 – 4.03).

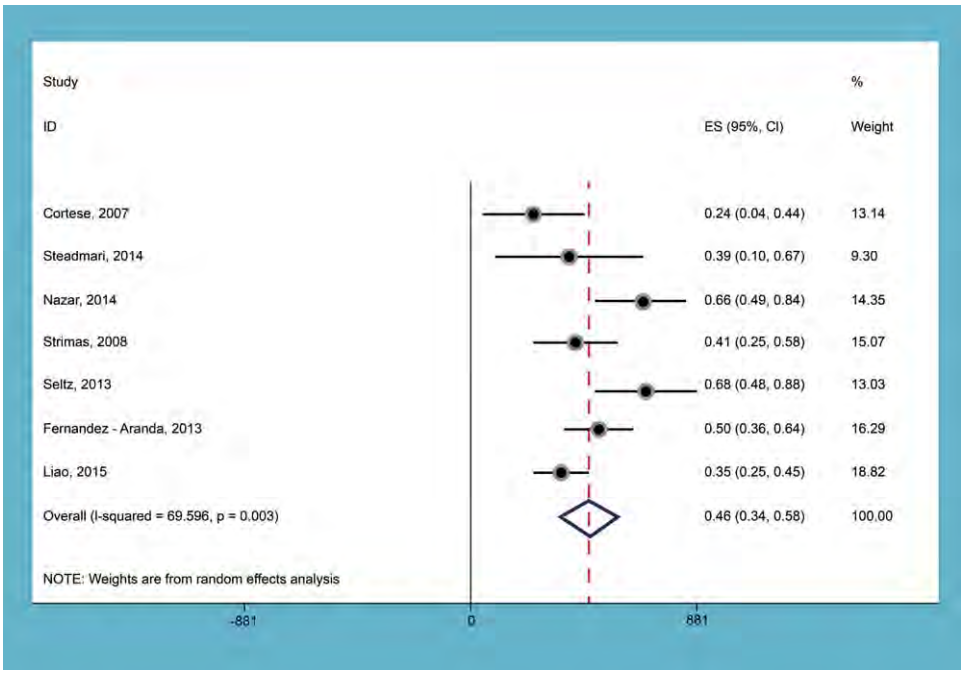
The overall analysis resulted in substantial inconsistency across studies (**Table 2**). Thus, we performed a meta-regression analysis to investigate whether age group (paediatric or adult), BMI class (obese only or all weight categories), percentage of female participants, country where research was conducted, study quality rating, method for diagnosing ED, and method for diagnosing ADHD (self-report or clinical interview) might have contributed to the findings. Although these variables resulted in an adjusted R^2 of 63.64%, this was not significant ($P = 0.49$).

The Risk of ADHD in People with Eating Disorders versus Controls

A total of 12,336 individuals (ED = 1,044/Controls 11,292), across five retained studies were available. Again, two studies[22,25] were excluded for their effect size, which again, had a wide confidence interval that had an upper bound that was much bigger than all others. Results including these two studies are presented in the online **Supporting Information**. Most studies[26,55,67] found higher rates of ADHD in ED populations, although the results did not reach formal levels of significance in two.[68,69] As in the ADHD studies, not all authors reported which type of ED syndrome was comorbid with ADHD in their samples (**Table 1**). There were not enough observations to run a model of meta-regression.

The combined risk of diagnosing ADHD in the five ED studies was significant ($P = .007$), 2.57 (95% CI: 1.30–5.11) (**Table 3**). The analysis of the adult subgroup ($n = 3$)[67–69] resulted in a nonsignificant risk of 1.58 (95% CI: .78–3.19).

FIGURE 4. Meta-analysis of correlational studies of ED and ADHD symptoms. [Color figure can be viewed at wileyonlinelibrary.com]



A subgroup analysis of patients with binge eating[68] (including BED[67] or LOC only[26] patients), produced ($n = 3$)[26,67,68] a significant risk of 5.77 (95% CI: 2.35–14.18).

The Strength of Association between ADHD and ED Symptoms

A pooled correlation coefficient of $r = .43$ (95% CI: .33–.52). was found from the association of ADHD and ED symptoms in seven studies.[13,19–22,25,70] The subgroup using bulimc symptom questionnaires ($n = 4$)[13,19,25,70]) yielded a pooled correlation coefficient of .38 (95% CI: .28–.49), while the subgroup using binge eating questionnaires ($n = 3$)[20,21,25] resulted in a pooled r of .47 (95% CI: .31–.59).

Discussion

The aim of this study was to provide an update on a previous systematic review of the literature examining the comorbidity between ADHD and ED[12] and to perform a meta-analysis. To the best of our knowledge this is the first meta-analysis investigating the risk of the ADHD + ED comorbidity.

The risk of ADHD individuals having an ED is increased three-fold and the risk of ED individuals also having ADHD is increased two-fold. The strength of association between ADHD and ED symptoms is moderate. No variables in our meta-regression explained the effect size variance. The sample division into clinically relevant subgroups failed to show that size of the potential risk differed significantly. For example, the risk of ED in males and females were both significant with overlapping confidence intervals. The size of the increased risk for disordered eating in paediatric samples was similar to the risk of ED in adult samples. The results from the meta-analysis suggested that the risk for all ED syndromes in ADHD is similar, with a nonsignificant trend for a higher risk of BN.

The significantly higher risk of ADHD when the diagnosis was made by using a semi-structured interview suggests that the association with ADHD is robust. Most studies didn't report if collateral information was used to define ADHD cases. Collateral reports are suggested as best practice for making adult ADHD diagnosis,[71] however, agreement rates between adults and their parents range from moderate[71] to high.[72] Finally, adult patients diagnosed with ADHD by self-report whose informants did not report ADHD symptoms in childhood have similar clinical profiles and treatment response as those who did.[73]

Most ADHD symptom domains have been found to be associated with ED behaviors. Both inattention and impulsivity predicts bulimic symptoms,[22,25,52,66] while both inattention and hyperactivity predicts craving,[26,61] Of note, the most recent DSM edition (DSM-5)[74] has deemphasized former ADHD

subtypes because of the recent literature on low stability rates of subtypes along time.[75,76]

Another possibility is that ADHD symptoms may be associated with an increased risk for ED with disturbances in body perception[77] as Fernandez-Aranda et al. 2013, demonstrated that problems in interoceptive awareness correlate with ADHD symptoms.

Interestingly, it has been suggested that attentional processes could dominate the physiological responses to self-image exposure in BN patients because of an abnormal arousal reaction with negative feelings when viewing their own bodies, probably because of an attentional bias.[78]

It is noteworthy that the risk for the association between ADHD with ED is more than the double that found between obesity and ADHD. In two recent reviews on the subject, the risk of obesity in people with ADHD ranged from[79] 1.37 up to[80] 1.55 in adults when compared to controls, whereas in children it ranged from[79] 1.13 to 1.22.[80] Obese people with ADHD differ from those without ADHD as they have a higher frequency of disturbed eating behaviors[5,25] and ED, and more psychiatric comorbidities,[25] suggesting that the mechanism underpinning this association is binge eating. Obesity has been found to be a long-term consequence of BED in epidemiological studies[81] and one study has demonstrated that LOC mediates BMI increments in ADHD children.[26] Further longitudinal studies tracking disordered eating and other confounding features such as medication from childhood into adult life and weight gain are of interest.

The Reward Deficiency Syndrome is a concept that links genetic abnormalities in dopaminergic genes to behavioral phenotypes. It is possible that this syndrome could be a transdiagnostic feature between ADHD,[82] ED, Obesity[83] and Substance Abuse Disorders.[84] As yet to our knowledge there are no genome wide association studies (GWAS) studies for BN and BED available to examine correlations in polygenic risk scores between these conditions. The analysis of specific genetic profiles may shed light to understanding the occurrence of diagnostic subgroups within a disorder.

In terms of functional magnetic resonance imaging studies an overlap in circuit anomalies in response to a variety of cognitive and emotional regulation tasks have been found by Seymour et al. 2015. Interestingly, a dissociation occurred regarding reward processing studies as ADHD participants demonstrated a weaker neural recruitment during reward anticipation and a higher than expected neural recruitment during reward receipt,[85] while, binge eaters had a hyper-responsivity to food-related stimuli in reward areas during anticipation and receipt.[86] There are still no studies demonstrating if the brain functioning of patients with ADHD + ED differs from patients with either of these disorders alone.

Although different studies found that ADHD + ED patients had higher impulsive traits measured by questionnaires than patients with either of those disorders alone,[20,22,24,25] these results were not replicated with the use of neuropsychological tests. The mediation between ADHD and binge eating was not explained by results from a Go/No-Go task.[20] Also, there were no significant differences when comparing bulimics with or without a childhood history of ADHD in tasks measuring executive functioning.[22]

The aforementioned explanations for the ADHD + ED comorbidity rely on single factors (e.g. impulsivity, genetic abnormalities) that do not account for the complexity of behaviors exhibited by both disorders. Hypothesis taking into account dual-process or even a three-level conceptualisation might convey a better understanding of this comorbidity. Strack and Deutsch[87] have proposed a dual process integrating reflective and impulsive functioning as determinants of habit. It could be possible that a distorted system of cognitions and beliefs (ED) would interact with an altered response to environmental stimuli (ADHD), leading to the activation of an altered behavioral schemata. Sergeant[88] conceptualized the cognitive energetic model for ADHD, with a first level of computational processing of attention depending on a second level of state factors (effort, arousal, and physiological activation), managed by a third level of executive functioning. Using this model as a basis, we suggest that not only ADHD neuropsychological functioning could alter information processing for food-related decision making but also changes in nutritional or emotional state promoted by ED could make ADHD individuals more prone to disinhibition.

Limitations

The number of relevant studies is limited. Among the 12 case-control of ADHD versus Controls studies exploring this comorbidity, five focused on paediatric populations with an age range from 10 up to 17 years. The definitions of ED in paediatric studies were broad, and included LOC,[26] disordered eating behaviors[51,54] in addition to DSM-5 ED syndromes. As the median age of treatment seeking for BN is 18 and for BED[89] is 22

it is probable that these paediatric cohorts will not have passed the age of maximum risk for ED. This might explain why these diagnoses were infrequent in paediatric populations and were absent in two studies.[51,52] Also, few studies explored ADHD in ED versus Controls, which limited us from exploring those results with a meta-regression. Given that recently lisdexamphetamine has been authorized to treat BED[40] it would be interesting to know if the prevalence of ED is reduced in the context of this treatment. However there was insufficient data on psychostimulant use to add it as a covariate in the meta-regression.

Conclusion

In the present meta-analysis, we have demonstrated evidence that ADHD individuals are at risk of disordered eating in childhood and ED (AN, BN, and BED) later in development. This research raises the question of whether children with ADHD should be screened for disordered eating and if so what form of intervention (psychological or pharmacological) might be used to moderate the risk.

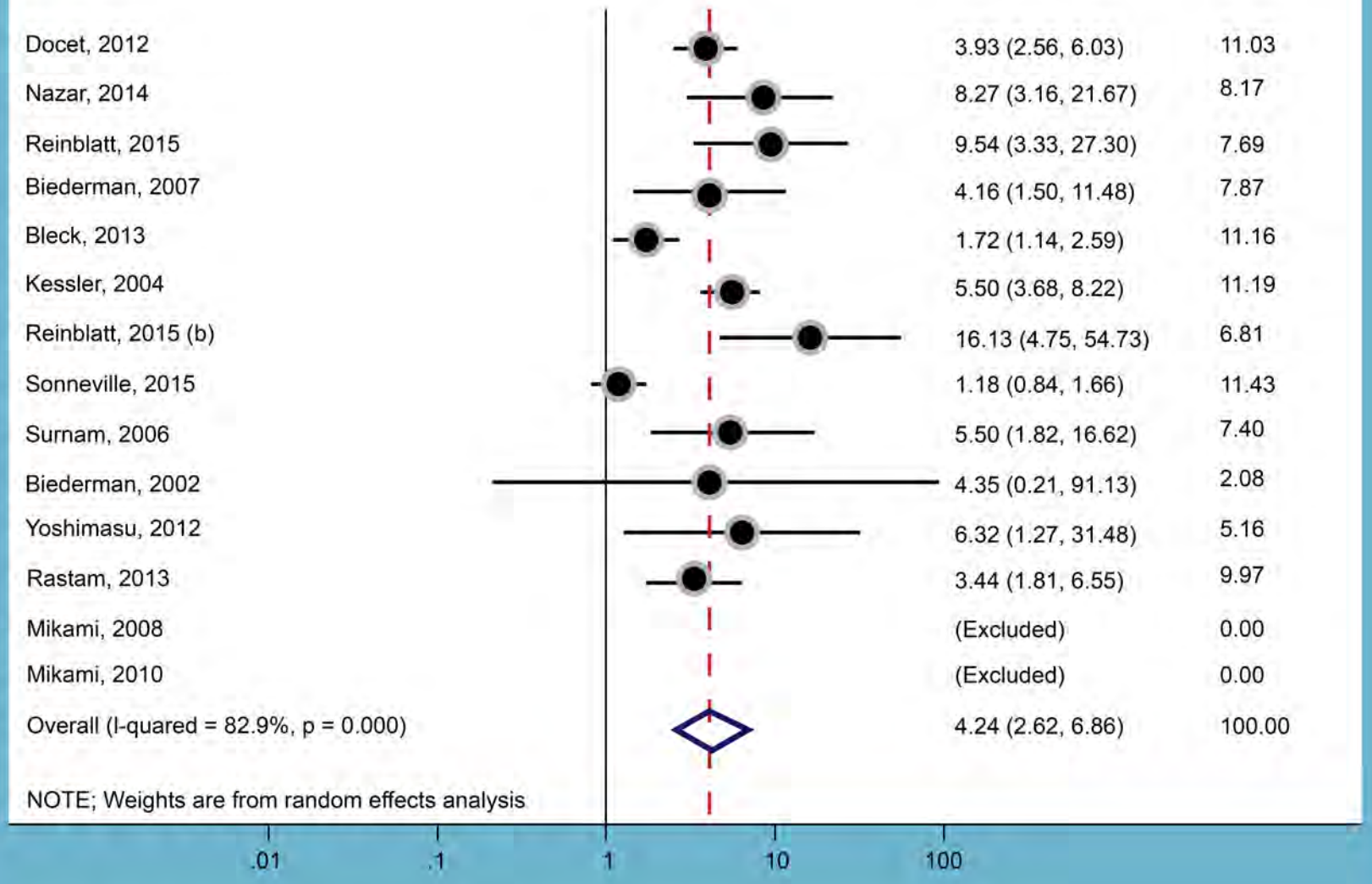
REFERENCES

1. McAleavey K. Ten years of treating eating disorders: what have we learned? A personal perspective on the application of 12-step and wellness programs. Adv Mind Body Med 2008;23:18–26.
2. Mischoulon D, Eddy KT, Keshaviah A, Dinescu D, Ross SL, Kass AE, et al. Depression and eating disorders: treatment and course. J Affect Disord 2011;130:470–477. 3
3. Westwood H, Eisler I, Mandy W, Leppanen J, Treasure J, Tchanturia K. Using the autism-spectrum quotient to measure autistic traits in anorexia nervosa: A systematic review and meta-analysis. J Autism Dev Disord 2016;46:964–977.
4. Wentz E, Lacey JH, Waller G, Råstam M, Turk J, Gillberg C. Childhood onset neuropsychiatric disorders in adult eating disorder patients. A pilot study. Eur Child Adolesc Psychiatry [Internet] 2005 ;14:431–437. [cited 2011 Jan 9]8Available from: http://www.ncbi.nlm.nih.gov/pubmed/16341499
5. Nazar BP, Pinna CMDS, Suwwan R, Duchesne M, Freitas SR, Sergeant J, et al. ADHD rate in Obese Women with Binge Eating and Bulimic Behaviours from a Weight Loss Clinic. J Atten Disord [Internet] 2012 ; [cited 2012 Aug 30]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22930790
6. Mattos P, Saboya E, Segenreich D, Duchesne M, Coutinho G. Comorbid eating disorders in a Brazilian Attention- Deficit/Hyperactivity Disorder adult clinical sample Transtornos alimentares comórbidos em uma amostra clínica de adultos com transtorno do déficit de atenção com hiperatividade. Eat Disord 2004;26:248–250.
7. Kooij JJS, Burger H, Boonstra AM, Van Der Linden PD, Kalma LE, Buitelaar JK. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychol Med [Internet] 2004;34:973–982.Available from: http://www.ncbi.nlm.nih.gov/pubmed/15554568
8. Agranat-Meged AN, Deitcher C, Goldzweig G, Leibenson L, Stein M, Galili-Weisstub E. Childhood obesity and attention deficit/hyperactivity disorder: A newly described comorbidity in obese hospitalized children. Int J Eat Disord [Internet] 2005 ;37:357–359. [cited 2010 Dec 18]4Available from: http://www.ncbi.nlm.nih.gov/pubmed/15856493
9. Surman CBH, Randall ET, Biederman J, Association between attention-deficit/hyperactivity disorder and bulimia nervosa: analysis of 4 case-control studies. J Clin Psychiatry [Internet] 2006 Mar;67:351. 34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16649819
10. Biederman J, Ball SW, Monuteaux MC, Surman CB, Johnson JL, Zeitlin S. Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study. J Dev Behav Pediatr [Internet] 2007 ;28:302–307. [cited 2010 Dec 18]4Available from: http://www.ncbi.nlm.nih.gov/pubmed/17700082
11. Sobanski E, Brüggemann D, Alm B, Kern S, Deschner M, Schubert T, et al. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci [Internet] 2007 ;257:371–377. [cited 2011 Feb 10]7Available from: http://www.ncbi.nlm.nih.gov/pubmed/17902010
12. Nazar BP, Pinna CMDS Coutinho G, Segenreich D, Duchesne M, Appolinario JC, et al. Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders. Rev Bras Psiquiatr [Internet] 2008;30:384–389. 4Available from: http://www.ncbi.nlm.nih.gov/pubmed/19142417
13. Fernández-Aranda F, Agüera Z, Castro R, Jiménez-Murcia S, Ramos-Quiroga JA, Bosch R, et al. ADHD symptomatology in eating disorders: a secondary psychopathological measure of severity?. BMC Psychiatry 2013;13:166.
14. Biederman J. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry [Internet] 2004 ;[cited 2011 Apr 3]65 Suppl 3:3–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15046528
15. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry [Internet] 2006 Apr;163:716–723. 4Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2859678&tool=pmcentrez&rendertype=abstract
16. Blinder BJ, Cumella EJ, Sanathara V. a. Psychiatric comorbidities of female inpatients with eating disorders. Psychosom Med [Internet] 2006 ;68:454–462. [cited 2011 Feb 7]3Available from: http://www.ncbi.nlm.nih.gov/pubmed/16738079
17. Hudson JI, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry [Internet] 2007;61:348–358. 3Available from: http://www.ncbi.nlm.nih.gov/pubmed/16815322
18. Stulz N, Hepp U, Gächter C, Martin-Soelch C, Spindler A, Milos G. The severity of ADHD and eating disorder symptoms: a correlational study. BMC Psychiatry 2013;13:44.
19. Cortese S, Isnard P, Frelut ML, Michel G, Quantin L, Guedeney A, et al. Association between symptoms of attention-deficit/hyperactivity disorder and bulimic behaviors in a clinical sample of severely obese adolescents. Int J Obes (Lond) [Internet] 2007 ;31:340–346. [cited 2010 Nov 14]2Available from: http://www.ncbi.nlm.nih.gov/pubmed/16733525
20. Steadman KM, Knouse LE. Is the Relationship Between ADHD Symptoms and Binge Eating Mediated by Impulsivity?. J Atten Disord 2014
21. Strimas R, Davis C, Patte K, Curtis C, Reid C, McCool C. Symptoms of attention-deficit/hyperactivity disorder, overeating, and body mass index in men. Eat Behav 2008;9:516–518. 4
22. Seitz J, Kahraman-Lanzerath B, Legenbauer T, Sarrar L, Herpertz S, Salbach-Andrae H, et al. The role of impulsivity, inattention and comorbid ADHD in patients with bulimia nervosa. Reif A, editor. PLoS One 2013 ;8: e63891.
23. Råstam M, Täljemark J, Tajnia A, Lundström S, Gustafsson P, Lichtenstein P, et al. Eating problems and overlap with ADHD and autism spectrum disorders in a nationwide twin study of 9- and 12-year-old children. Sci World J 2013;2013:1–7.
24. Nazar BP, de Sousa Pinna CM, Suwwan R, Duchesne M, Freitas SR, Sergeant J, et al. ADHD rate in obese women with binge eating and bulimic behaviors from a weight-loss clinic. J Atten Disord 2016;20:610–616.
25. Nazar BP, Suwwan R, de Sousa Pinna CM, Duchesne M, Freitas SR, Sergeant J, et al. Influence of attention-deficit/hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women. Compr Psychiatry [Internet] 2014 ;55:572–578. [cited 2014 Apr 12]Available from: http://www.ncbi.nlm.nih.gov/pubmed/24246603

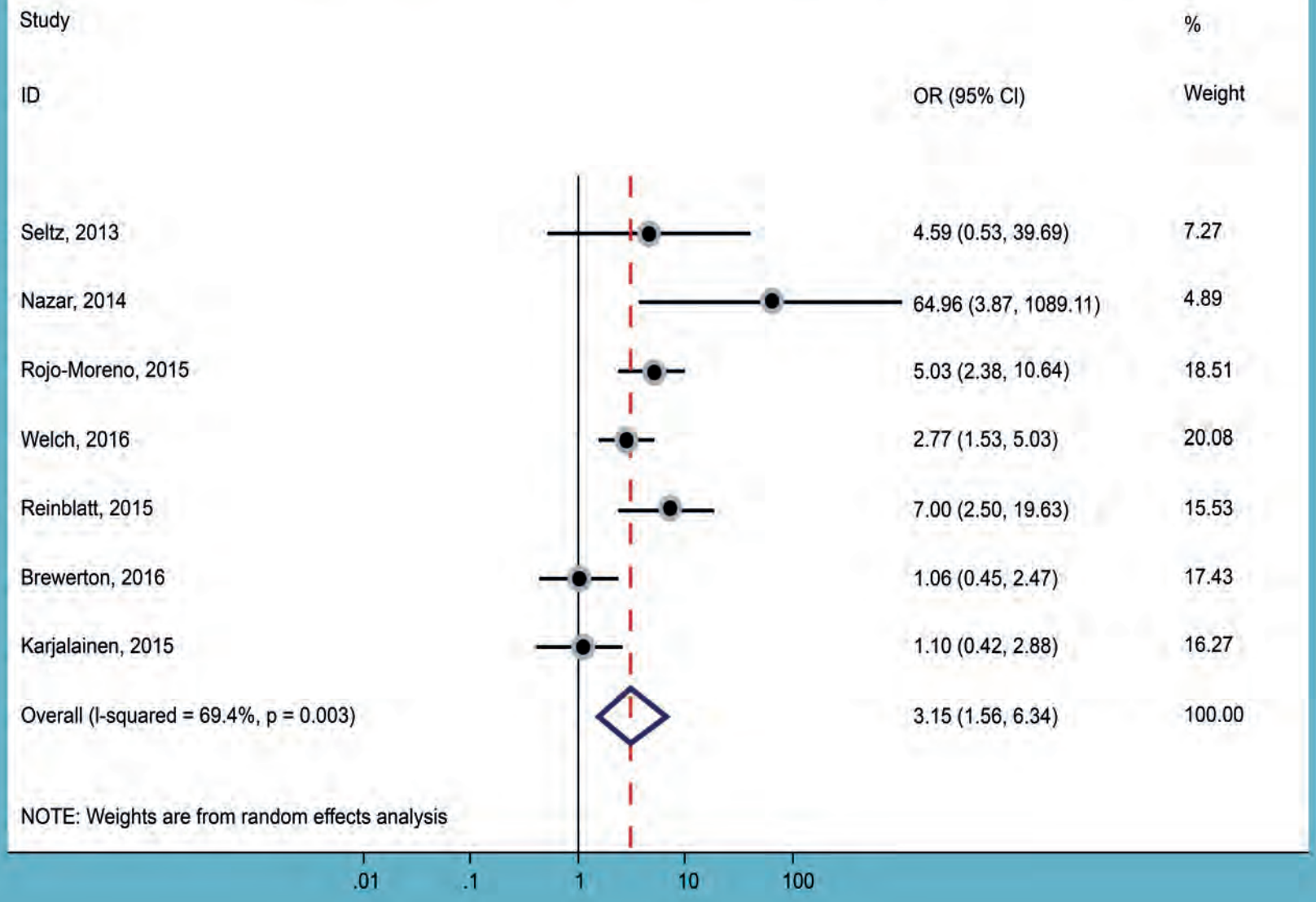
26. Reinblatt SP, Mahone EM, Tanofsky-Kraff M, Lee-Winn AE, Yenokyan G, Leoutsakos J-MS, et al. Pediatric loss of control eating syndrome: Association with attention-deficit/hyperactivity disorder and impulsivity. Int J Eat Disord 2015;48:580–588. 6
27. Duchesne M, Mattos P, Fontenelle LF, Veiga H, Appolinario C, Rizo L, et al. Neuropsychology of eating disorders: a systematic review of the literature. Rev Bras Psiquiatr Sao Paulo Brazil 1999 [Internet] 2004;26:107–117. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15517062
28. Porfirio MC, Lo-Castro A, Giana G, Giovinazzo S, Ouakil DP, Galasso C, et al. Attention-deficit hyperactivity disorder and binge eating disorder in a patient with 2q21.1–q22.2 deletion. Psychiatr Genet [Internet] 2012;22:202–205. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00041444-201208000-00008
29. Davis C, Patte K, Levitan RD, Carter J, Kaplan AS, Zai C, et al. A psychogenetic study of associations between the symptoms of binge eating disorder and those of attention deficit (hyperactivity) disorder. J Psychiatr Res 2009;43:687–696. 7
30. Yilmaz Z, Kaplan AS, Levitan RD, Zai CC, Kennedy JL. Possible association of the DRD4 gene with a history of attention-deficit/hyperactivity disorder in women with bulimia nervosa. Int J Eat Disord 2012;45:622–625.
31. Volkow ND, Swanson JM, Ph D. Clinical Practice: Adult Attention Deficit – Hyperactivity Disorder. N Engl J Med 2013;369:1935–1944.
32. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Prim 2015 ;15020.
33. Wonderlich S. a, Connolly KM, Stice E. Impulsivity as a risk factor for eating disorder behavior: assessment implications with adolescents. Int J Eat Disord [Internet] 2004 ;36:172–182. [cited 2011 Apr 5]Available from: http://www.ncbi.nlm.nih.gov/pubmed/15282687
34. Fischer S, Settles R, Collins B, Gunn R, Smith GT. The role of negative urgency and expectancies in problem drinking and disordered eating: testing a model of comorbidity in pathological and at-risk samples. Psychol Addict Behav 2012;26:112–123.
35. Svaldi J, Tuschen-Caffier B, Peyk P, Blechert J. Information processing of food pictures in binge eating disorder. Appetite [Internet] 2010 ;55:685–694. Elsevier Ltd; [cited 2012 Jul 13]Available from: http://www.ncbi.nlm.nih.gov/pubmed/20946926
36. Schmitz F, Naumann E, Trentowska M, Svaldi J. Attentional bias for food cues in binge eating disorder. Appetite 2014;80:70–80.
37. Renwick B, Campbell IC, Schmidt U. Review of attentional bias modification: A brain-directed treatment for eating disorders. Eur Eat Disord Rev 2013;21:464–474. 6
38. Boutelle KN, Monreal T, Strong DR, Amir N. An open trial evaluating an attention bias modification program for overweight adults who binge eat. J Behav Ther Exp Psychiatry 2016;52:138–146.
39. Lemiere J, Danckaerts M, Van Hecke W, Mehta MA, Peeters R, Sunaert S, et al. Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: an fMRI pilot study. Brain Res 2012;1450:57–66.
40. McElroy SL, Hudson JI, Mitchell JE, Wilfley D, Ferreira-Cornwell MC, Gao J, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry 2015;72:235–246.
41. Sokol MS, Gray NS, Goldstein a, Kaye WH. Methylphenidate treatment for bulimia nervosa associated with a cluster B personality disorder. Int J Eat Disord [Internet] 1999;25:233–237. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10065402
42. Schweickert LA, Strober M, Moskowitz A. Efficacy of methylphenidate in bulimia nervosa comorbid with attention-deficit hyperactivity disorder: a case report. Int J Eat Disord [Internet] 1997 ;21:299–301. [cited 2011 Jan 9]Available from: http://www.ncbi.nlm.nih.gov/pubmed/9097204
43. Drimmer EJ. Stimulant treatment of bulimia nervosa with and without attention-deficit disorder: three case reports. Nutrition [Internet] 2003;19:76–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12507648
44. Dukarm CP. Bulimia nervosa and attention deficit hyperactivity disorder: a possible role for stimulant medication. J Womens Health (Larchmt) [Internet] 2005 ;14:345–350. [cited 2011 Jan 9]Available from: http://www.ncbi.nlm.nih.gov/pubmed/15916509
45. Ioannidis K, Serfontein J, Müller U. Bulimia nervosa patient diagnosed with previously unsuspected ADHD in adulthood: clinical case report, literature review, and diagnostic challenges. Int J Eat Disord 2014;47:431–436.
46. Keshen A, Ivanova I. Reduction of bulimia nervosa symptoms after psychostimulant initiation in patients with comorbid ADHD: five case reports. Eat Disord 2013;21:360–369.
47. Kociancic T, Reed MD, Findling RL. Evaluation of risks associated with short- and long-term psychostimulant therapy for treatment of ADHD in children. Expert Opin Drug Saf 2004 Mar;3:93–100.
48. Pennell A, Couturier J, Grant C, Johnson N. Severe avoidant/restrictive food intake disorder and coexisting stimulant treated attention deficit hyperactivity disorder. Int J Eat Disord 2016
49. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J Am Acad Child Adolesc Psychiatry 2008;47:21–31.
50. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
51. Mikami AY, Hinshaw SP, Patterson KA, Lee JC. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. J Abnorm Psychol 2008;117:225–235.
52. Mikami AY, Hinshaw SP, Arnold LE, Hoza B, Hechtman L, Newcorn JH, et al. Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD. Int J Eat Disord [Internet] 2010;43:248–259. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19378318
53. Docet MF, Larrañaga A, Pérez Méndez LF, García-Mayor RV. Attention deficit hyperactivity disorder increases the risk of having abnormal eating behaviours in obese adults. Eat Weight Disord 2012;17:e132–e136.
54. Reinblatt SP, Leoutsakos J-MS, Mahone EM, Forrester S, Wilcox HC, Riddle MA. Association between binge eating and attention-deficit/hyperactivity disorder in two pediatric community mental health clinics. Int J Eat Disord 2015;48:505–511.
55. Rojo-Moreno L, Arribas P, Plumed J, Gimeno N, García-Blanco A, Vaz-Leal F, et al. Prevalence and comorbidity of eating disorders among a community sample of adolescents: 2-year follow-up. Psychiatry Res 2015;227:52–57.
56. Alegria M, Jackson JS, Kessler RC, Takeuchi D. Collaborative Psychiatric Epidemiology Survey (CPES). ICPSR20240-v8. [Internet]. Inter-university Consortium for Political and Social Research 2015-12-09. Ann Arbor, MI; Available from: http://doi.org/10.3886/ICPSR20240.v8
57. Fisher RA. Frequency Distribution of the Values of the Correlation Coefficient in Samples from an Indefinitely Large Population. Biometrika 1915;10:507.
58. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 ;327:557–560.
59. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006 ;25:3443–3457.
60. Wells G, Shia B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. [Internet]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
61. Sonneville KR, Calzo JP, Horton NJ, Field AE, Crosby RD, Solmi F, et al. Childhood hyperactivity/inattention and eating disturbances predict binge eating in adolescence. Psychol Med 2015 ;45:2511–2520.
62. Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry [Internet] 2002;159:36–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11772687
63. Bleck JR, DeBate RD, Olivardia R. The Comorbidity of ADHD and Eating Disorders in a Nationally Representative Sample. J Behav Health Serv Res [Internet] 2014 ;[cited 2015 Jan 27]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/25007864
64. Kessler RC, Merikangas KR. The National Comorbidity Survey Replication (NCS-R): background and aims. Int J Methods Psychiatr Res 2004;13:60–68.

65. Yoshimasu K, Barbaresi WJ, Colligan RC, Voigt RG, Killian JM, Weaver AL, et al. Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: a population-based birth cohort study. J Child Psychol Psychiatry 2012;53:1036–1043.
66. Mikami AY, Hinshaw SP, Patterson KA, Lee JC. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. J Abnorm Psychol [Internet] 2008;117:225–235. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18266500
67. Welch E, Jangmo A, Thornton LM, Norring C, von Hausswolff-Juhlin Y, Herman BK, et al. Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical course and psychiatric comorbidity. BMC Psychiatry 2016
68. Brewerton TD, Duncan AE. associations between attention deficit hyperactivity disorder and eating disorders by gender: Results from the national comorbidity survey replication. Eur Eat Disord Rev 2016 ;
69. Karjalainen L, Gillberg C, Råstam M, Wentz E. Eating disorders and eating pathology in young adult and adult patients with ESSENCE. Compr Psychiatry 2016;66:79–86.
70. Liao Y-T, Lee Y-C, Hung N-C, Lee S-H, Weng J-C, Chen VC-H. Association between Attention Deficit Hyperactivity Disorder Symptoms and Bulimia among College Students. Taiwan J Psychaitry. 2015;29:98–108.
71. Fischer M, Barkley RA. The persistence of ADHD into adulthood: (Once Again) It depends on whom you ask. ADHD Rep 2007;15:7–16.
72. Dias G, Mattos P, Coutinho G, Segenreich D, Saboya E, Ayrão V. Agreement rates between parent and self-report on past ADHD symptoms in an adult clinical sample. J Atten Disord 2008;12:70–75.
73. Murphy P, Schachar R. Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults. Am J Psychiatry 2000;157: 1156–1159.
74. American Psychiatric Association. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5. Arlington, VA: American Psychiatric Association; 2013.
75. Willcutt EG, Nigg JT, Pennington BF, Solanto MV, Rohde LA, Tannock R, et al. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. J Abnorm Psychol 2012;121:991–1010.
76. Wagner F, Martel MM, Cogo-Moreira H, Maia CRM, Pan PM, Rohde LA, et al. Attention-deficit/hyperactivity disorder dimensionality: the reliable "g" and the elusive "s" dimensions. Eur Child Adolesc Psychiatry 2016;25:83–90.
77. Williamson D, Johnston C. Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review. Clin Psychol Rev 2015;40: 15–27.
78. Ortega-Roldán B, Rodríguez-Ruiz S, Perakakis P, Fernández-Santaella MC, Vila J. The emotional and attentional impact of exposure to one's own body in bulimia nervosa: a physiological view. PLoS One 2014;9:e102595.
79. Nigg JT, Johnstone JM, Musser ED, Long HG, Willoughby MT, Shannon J. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. Clin Psychol Rev 2016;43:67–79.
80. Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association between ADHD and obesity: A systematic review and meta-analysis. Am J Psychiatry 2016;173:34–43.
81. Kessler RC, Berglund PA, Chiu WT, Deitz AC, Hudson JI, Shahly V, et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biol Psychiatry 2013;73: 90414. 9
82. Blum K, Chen AL-C, Braverman ER, Comings DE, Chen TJ, Arcuri V, et al. Attention-deficit-hyperactivity disorder and reward deficiency syndrome. Neuropsychiatr Dis Treat [Internet] 2008 ;4:893–918. [cited 2011 Apr 1] Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2626918&tool=pmcentrez&rendertype=abstract
83. Blum K, Chen TJH, Meshkin B, Downs BW, Gordon CA, Blum S, et al. Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant. Adv Ther [Internet] 2006 ;23:1040–1051. [cited 2011 Apr 1]6Available from: http://www.ncbi.nlm.nih.gov/pubmed/17276971
84. Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med [Internet] 1996 ;89:396–400. [cited 2011 Apr 1]7Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1295855&tool=pmcentrez&rendertype=abstract
85. Seymour KE, Reinblatt SP, Benson L, Carnell S. Overlapping neurobehavioral circuits in ADHD, obesity, and binge eating: evidence from neuroimaging research. CNS Spectr 2015;20:401–411. 4
86. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter a. Neuroimaging and obesity: current knowledge and future directions. Obes Rev [Internet] 2012 ; 13:43–56. [cited 2012 Jul 14]1Available from: http://www.ncbi.nlm.nih.gov/pubmed/21902800
87. Strack F, Deutsch R. Reflective and impulsive determinants of social behavior. Pers Soc Psychol Rev 2004;8:220–247. 3
88. Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neurosci Biobehav Rev 2000;24:7–12. 1
89. Micali N, Hagberg KW, Petersen I, Treasure JL. The incidence of eating disorders in the UK in 2000-2009: findings from the General Practice Research Database. BMJ Open 2013;3:5

Supplementary Materials 1 - Meta analysis of ED in ADHD individuals including outlier studies



Supplementary Material 2 - Meta analysis of ADHD in ED individuals including outlier studies



9.2 Artigo:

Influence of attention-deficit / hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women

Available online at www.sciencedirect.com

ScienceDirect

Comprehensive Psychiatry 55 (2014) 572–578

COMPREHENSIVE PSYCHIATRY

www.elsevier.com/locate/comppsych

Influence of attention-deficit/hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women

Bruno Palazzo Nazar[a,b,c,*], Raphael Suwwan[d], Camilla Moreira de Sousa Pinna[a,b,c], Monica Duchesne[c], Silvia Regina Freitas[c], Joseph Sergeant[e], Paulo Mattos[a]

[a]*Attention-Deficit Study Group (GEDA), Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*
[b]*Post-Graduate Program in Psychiatry and Mental Health, Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*
[c]*Group of Obesity and Eating Disorders (GOTA), State Intitute of Diabetes and Endocrinology (IEDE), Institute of Psychiatry (IPUB), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*
[d]*Child and Adolescent Psychiatry Unit (UPIA), Department of Psychiatry, Federal University of São Paulo (UNIFESP), São Paulo, Brasil*
[e]*Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, Amsterdam, The Netherlands*

Abstract

Objective: Previous studies have reported higher prevalence rates of attention-deficit/hyperactivity disorder (ADHD) both in eating disorders (ED) and in obese patients. We compared the psychiatric comorbidity profile of obese ADHD women with non-ADHD obese women and how ADHD symptoms impact in binge eating behaviors.
Design: Cross-sectional study of a clinical sample.
Subjects: 171 adult women were evaluated at a specialized clinic in obesity and ED.
Measurements: Participants complete a semi-structured interview and psychopathology rating scales. A hierarchical regression model was employed to predict binge eating behavior.
Results: Obese ADHD patients had a larger number of psychiatric comorbidities ($p < 0.001$), especially Substance Abuse Disorders, and higher scores on psychopathology rating scales ($p < 0.05$). The highest prediction for binge eating in the regression model was the presence of depressive symptoms, followed by ADHD inattention symptoms and trait-impulsivity.
Conclusion: ADHD should be routinely evaluated in obese since it is related with more severe psychopathology. Depressive symptoms can predict the presence of binge eating in obese patients.

1. Introduction

Although obesity is one of the most easily recognizable medical conditions, our understanding of this disorder is still limited, and success of available treatments even more [1]. Obesity is not only associated with the development of somatic medical conditions and psychiatric disorders. Obese patients have a 55% chance and an odds ratio (OR) of 1.5 of developing depression [2]. Recent studies ponder whether attention-deficit/hyperactivity disorder (ADHD) patients are more likely to become obese since, obese adults have a higher prevalence of ADHD than expected to normal weight subjects [3–5].

ADHD has a prevalence rate in the adult population of 4.4% [6]. Approximately 65% to 89% of adults with ADHD have one or more comorbid psychiatric disorders [7]. ADHD alone can impair social, marital, work and educational areas of functioning [8]. The presence of a comorbidity in ADHD patients leads to greater psychological distress and medical risk [9].

Independent of weight status, disrupted eating behaviors are thought to have a relation with ADHD. Two longitudinal studies addressed whether ADHD girls were at risk for Eating Disorders (ED). Mikami et al. (2008) conducted a 5-year longitudinal study of girls, who were 9-years old at baseline, and found that ADHD subjects developed more frequently eating disorder symptoms at puberty [10]. Biederman et al. evaluated the course of ADHD girls over

* Corresponding author at: Rua Lopes Quintas 100-apt 203/bloco 2-Rio de Janeiro-RJ-Brazil, ZIP-22460-010.
E-mail address: bruno.nazar@gmail.com (B.P. Nazar).

0010-440X/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.comppsych.2013.09.015

5-years up to late adolescence and reported that they exhibited 3.6 higher chance of meeting full criteria for ED at final assessment [11]. Three other longitudinal studies of ADHD patients found a higher risk for the occurrence of Bulimia Nervosa (BN) in girls [12,13] and in women [14]. The prevalence of ED is higher in ADHD individuals than in the general population, independent of Body Mass Index (BMI) [15]. Four studies evaluated ED prevalence in specialized ADHD centers and found an ED prevalence from 9% to 12% [9,16–18]. Three studies found Bulimia Nervosa (BN) as the most common ED [9,17,18]. Our group was the first to demonstrate Binge Eating Disorder (BED) to be the most frequent ED comorbidity with ADHD [16]. Two studies investigated the impact of ED in ADHD patients and suggested that patients with ADHD + ED have often other psychiatric comorbidities [16], particularly mood and anxiety disorders [11] than ADHD patients without ED.

Three studies evaluated ADHD in ED specialized centers, of which, two were conducted with inpatients [19,20], and one with a mixed sample of in- and outpatients [21]. These studies reported that ADHD was associated with binge/purge behaviors, but the analysis was performed as a single group, mixing together Anorexia Nervosa and BN subjects. Wentz [21] found a significantly higher prevalence of ADHD in ED samples (17%), whereas two other two studies found rates of 5.3% [20] and 6% [19]. It is noteworthy that, when studying only BN patients, the ADHD prevalence in the study by Blinder increased to 9% [19]. None of these previously cited studies evaluated obesity or BED in their samples.

BN and BED have in common the occurrence of binge eating episodes [22] but BN patients frequently engage in inadequate compensatory methods to lose weight (such as, purging, use of diet pills, laxatives or diuretics and fasting) [22]. The prevalence of BN in women in the general population is 1.5%, and for BED 3.5% [23]. In weight loss clinics, the incidence of BED in obese individuals is higher than would be expected from the general population, at about 29% [24]. Obesity is considered a general medical condition but not an ED, however it is strongly associated with disordered eating patterns and BED [24].

The objective of the present study was to evaluate the impact of ADHD in obese patients' psychopathology. Our first hypothesis was that ADHD impaired obese psychopathology and thus, would be associated with a greater number of comorbid psychiatric disorders and scores in rating scales, especially, of impulsivity measures [15,11,25]. A secondary hypothesis was that ADHD could influence the severity of binge eating and predict its severity.

2. Methods

2.1. Subjects

The sample was comprised of obese women seeking non-surgical treatment for obesity or eating disorders in the State Institute of Diabetes and Endocrinology, a public endocrinology hospital with an eating disorders and obesity clinic in Rio de Janeiro. Since our group is well known in Brazil to treat severe eating disorders we have a patient profile of eating disordered obese higher than other obesity clinics. Over a period of two years, a total of 171 patients aged 18 to 59 years old, with a BMI >25, were consecutively invited to participate in the study. BMI was calculated using the formula: weight (kg)/height^2 (m^2) [26]. Exclusion criteria consisted of less than five years of schooling/inability to read and complete forms and questionnaires; history of psychotic disorder; current treatment with psychoactive drugs; presence of uncontrolled medical disorders that interfere with weight, appetite and attention (such as history of traumatic brain injury or uncontrolled diabetes mellitus). Patients who were older than 60 years old were excluded because of the possible occurrence of normal age-related cognitive decline or pathological cognitive symptoms (e.g. mild cognitive impairment) that could mimic ADHD symptoms [22]. The majority of patients who sought treatment were female. Only 5 male patients were evaluated, and were excluded from the analyses because they were a small group.

A total of 132 patients were eligible to participate in the study and completed the protocol. Of the initial 171 patients, 39 (22.8% of the 171 evaluated) were excluded: 16 (9.3%) did not complete the protocol or pursued treatment, 9 were male subjects (5.2%), 8 patients were using psychoactive medication (4.6%), 5 patients were older than 60 years (2.9%), and 1 had schizophrenia (0.5%). Psychiatrists with expertise in both adult ADHD and eating disorders (BPN and CMSP) interviewed participants. Socieconomical status (SES) was evaluated according to the Brazilian Institute of Geography and Statistics criteria [27]

2.2. Eating Disorder Diagnosis

The eating disorder diagnosis was given using the Eating Disorders module of the SCID-P [28]. A patient was considered to have BN or BED, if she met all DSM-IV criteria for those disorders. Subclinical BED was diagnosed, if the patient had at least one binge-eating episode per week, and/or these occurred between three and six months.

2.3. Current and Childhood history of ADHD Symptoms

ADHD diagnosis was given using the Kiddie-*Schedule for Affective Disorders and Schizophrenia* (K-SADS) module for ADHD, adapted for adults [29]. ADHD was diagnosed, if the participant met DSM-IV criteria for at least 6 *current* inattention *or* hyperactivity/impulsivity symptoms, associated with at least 6 *past* inattention *or* hyperactivity/impulsivity symptoms, with onset before the age of 7 and occurring in at least 2 life-time domains with significant impairment. Patients with a positive diagnosis of ADHD were placed in the "Obese ADHD" group.

2.4. Psychiatric Comorbidity, Current Functioning and Mental Status

To evaluate the presence of psychiatric diagnosis, the Mini-International Neuropsychiatric Interview (MINI-Plus) was used [30]. We evaluated the presence of mood, anxiety, somatoform and substance use disorders.

All patients were asked to complete the Portuguese validated versions of the following self-reported questionnaires:

(1) *Beck Depression Inventory* (BDI) [31,32] developed for assessing depressive symptoms, it contains 21 questions, each answer being scored on a scale value of 0 to 3. The final score is a measure of symptom severity.
(2) *State–Trait Anxiety Inventory* (STAI) [33]: it is composed by two 20-item scales that measure trait and situational anxiety; in this study we used only the trait-anxiety scale.
(3) *Binge Eating Scale* (BES) [34]: a 16 self-report questionnaire used as a screening tool for binge-eating. It also evaluates the severity of binge eating as it assesses distorted cognitions and behavioural disinhibition towards food. The BES investigates the binge eating phenomenon in more depth than questionnaires for bulimia.
(4) *Barrat-Impusivity Scale* (BIS-11) [35,36]: This scale measures impulsivity in life situations and considers impulsivity in three domains: attentional (BIS-At), planning (BIS-Plan) and motor (BIS-Mot) impulsivity.

The study was approved by the hospital ethics committee. Written and oral information was provided to each individual before their participation in the study.

2.5. Statistical analysis

Demographic and clinical data (including age, weight, BMI, marital status, SES, Education and scores on questionnaires) were shown as means and *s.d.* or percentages. Analysis of variance (ANOVA) was performed on continuous variables of group comparisons, using *Bonferroni* test for *post-hoc* analysis, and *Pearson* Chi-Square test to study categorical data.

Our first hypothesis was that obese ADHD had a greater impairment in psychopathology than other obese, expressed by higher rate of psychiatric comorbidity and higher scores on rating scales. Patients were classified in three different groups for analysis of psychiatric comorbidity profile and rating scales scores, as follows: “Obese only” (when neither an ADHD nor an ED diagnosis was present), “Obese ED” (patients without ADHD but diagnosed with either BN, BED or subclinical BED, which have in common the occurrence of binge eating episodes), and “Obese ADHD” (when the patient had an ADHD diagnosis, independent of ED status). Obesity is a general medical condition and by itself is not considered an ED, not all obese patients have an ED. Obesity without ED is associated with higher rates of psychiatric comorbidity, justifying the use of an obese control group without ED [37].

Our second hypothesis was that ADHD symptoms could influence severity of binge eating behaviors. To test this hypothesis, a multiple linear regression was performed considering BES scores as the dependent variable and KSADS Inattention symptoms (K-SADS IN), KSADS Hyperactivity/Impulsivity symptoms (K-SADS HI), BDI, STAI and BIS-11 scores as independent variables. These scores were natural log transformed prior to statistical modeling to approximate a normal distribution and were entered into the model hierarchically according to their Pearson coefficient of correlation score.

A probability level of $p < .05$ was used to indicate statistical significance. All statistical analyses were performed using the SPSS v. 16.0 software for Windows package for personal computers (SPSS, Inc., Chicago, IL, USA).

3. Results

The demographic characteristics and results from self-report scales of the total sample and groups studied are given in Table 1. There were no statistically significant differences between the “Obese ADHD”, “Obese ED” and “Obese Only” groups with respect to demographic characteristics. The Obese ADHD group reported significantly more depressive, trait anxiety, binge eating and impulsivity symptoms (Table 1). The number and frequency of psychiatric comorbidities in the sample and for each group are presented in Table 2.

We performed a multiple regression in which we used the Natural Log transformed BES score as the dependent variable and entered in a stepwise regression the following variables as predictors: BDI, K-SADS IN, BIS-11, STAI and K-SADS HI. The results of this regression analysis are presented in Table 3. The overall variance explained by the five predictors was 30.6%. As can be seen from Table 3, the Beck Depression score gave the largest prediction (adjusted $R^2 = 20.4\%$) followed by a minor contribution from the KSADS IN (adjusted $R^2 = 7.8\%$) and BIS-11 (adjusted $R^2 = 2.1\%$), and no significant contribution by the STAI and the K-SADS HI to the BES score. The scatterplot of the BES by Beck prediction is given in Fig. 1.

4. Discussion

It should be noted that all subjects with ADHD were comorbid for ED. “Obese ADHD” patients had a significantly more severe Binge Eating pathology as measured by the BES than “Obese ED”. The ED profile, both BN and

Table 1
Demographic characteristics of participants and ratings on clinical scales.

	Total	Obese Only	Obese ED	Obese ADHD	F	Contrasts
Variable			Mean ± S.D.%			
N	132	42	50	40	–	–
Age (years)	38.28 [± 10.62]	40.53 [±10.43]	37.06 [±10.24]	37.47 [±11.29]	–	–
Body mass index (kg/m^2)	39.16 [± 7.35]	40.45 [±6.53]	39.61 [±8.43]	37.14 [±6.42]	–	–
Marital status%						
Currently married	51.5%	54.8%	53.5%	47.5%	–	–
Not currently married	48.5%	45.2%	46.9%	52.5%	–	–
Education						
College degree	77.3%	71.4%	77.6%	75%	–	–
No college degree	22.7%	28.6%	22.4%	25%	–	–
SES%						
Class A	4%	0%	2.1%	10.5%	–	–
Class B	39.7%	41%	31.3%	50%	–	–
Class C	55.6%	59%	66.7%	39.5%	–	–
Self-Report Rating Scales						
BES	25.488 [±10.37]	15.37 [±9.00]	27.34 [±7.04]	32.80 [±7.14]	50.83	1<2<3*
BDI	21.136 [±10.17]	15.67 [±9.14]	22.28 [±10.11]	25.21 [±8.29]	9.79	1<2<3*
STAI-T	53.375 [±12.05]	47.78 [±11.87]	53.45 [±11.06]	55.71 [±12.48]	3.87	1=2<3*
STAI-S	48.61 [±11.52]	44.01 [±10.59]	50.18 [±11.19]	50.25 [±11.69]	2.58	N.S
BIS-11 Total	70.68 [±10.17]	67.21 [±10.05]	68.70 [±7.73]	76.20 [±10.88]	9.73	1=2<3*
BIS-Attention subscale	20.42 [±3.16]	19.52 [±2.94]	19.93 [±2.93]	21.87 [±3.19]	6.65	1=2<3*
BIS-Planning subscale	27.14 [±5.53]	26.21 [±5.26]	26.17 [±5.14]	29.21 [±5.78]	4.13	1=2<3*
BIS-Motor subscale	22.89 [±4.76]	21.47 [±4.58]	22.04 [±4.01]	25.13 [±5.17]	6.92	1=2<3*

BES = Binge-Eating Scale; BDI = Beck Depressive Inventory; STAI-T = State–Trait Anxiety Inventory, Trait Subscale; STAI-S = State–Trait Anxiety Inventory, State Subscale; BIS-11 = Barratt Impulsiveness Scale; 1 = Obese Only Group; 2 = Obese ED Group; 3 = Obese ADHD Group; * = p-values ≤0.05; Contrast was performed using ANOVA (with Bonferroni test).

BED were significantly associated with ADHD diagnosis. Cortese et al. (2007) reported in a previous study increased bulimic behaviour in ADHD girls [38] but no association between more severe BN full syndrome and ADHD in women. Biederman [11] has found that childhood ADHD increases the risk of adolescent BN. We speculate that the presence of ADHD in obese women may increase their risk of presenting with ED and when that occurs, it is more severe.

With respect to comorbidity, previous reports indicate that patients with the comorbidity ADHD + ED have more psychiatric comorbidities, when compared to ADHD patients without ED [16], especially, Major Depressive Disorder (MDD) and Anxiety Disorders (AD) [11]. Both these studies compared ADHD + ED with ADHD patients, and since there was no ED control group, the question arises whether the results could be better explained by the ED status. We found that our "Obese ADHD" group was in fact an ADHD + ED set of patients and had significantly more psychiatric comorbidities, especially more AD and Substance Use Disorders (SUD) than the other two groups. "Obese ADHD" did not present increased rates of MDD, but had significantly higher scores on the BDI (Table 2).

Our findings show that patients with the comorbidity ADHD + ED have a higher frequency of SUD than ED patients (Table 2). Since we did not control for an ADHD group without ED, we are unable to determine here whether the increased risk of SUD is related to ADHD or to ED and this is a limitation of the current study. ADHD has been repeatedly associated with substance abuse with many studies showing a bidirectional overlap between these conditions [39]. Since the current study is cross-sectional we cannot suggest direction of causality between ADHD and ED-SUD.

A possible way of examining together obese ADHD + ED + SUD individuals is through the Reward Deficiency Syndrome (RDS) concept. RDS is characterized by genetic alterations associated with a hypodopaminergic state in brain systems linked to reward sensitivity [40]. It is expressed as a group of impulsive, compulsive or addictive behaviors. Evidence of RDS has been shown in obese [41], ADHD [42], and SUD patients [43]. Possibly, these "multi-impulsive" patients could in fact have specific genetic alterations in dopamine metabolism expressed by the RDS.

In the current sample, ADHD was associated with more severe binge eating episodes as measured by the BES. Further research is needed to investigate whether binge eating in ADHD has the same clinical characteristics and treatment-response as in non-ADHD patients. Levy [44], studied the treatment response of obese ADHD that failed to lose weight with standard weight-loss treatments. They achieved a significant weight-loss and binge eating control when initiating psychostimulant therapy. Binge eating is considered an impulsive feature in ED patients, but other psychological factors can trigger or be the basis of the binge eating phenomenon (*e.g.* depression, anxiety and fasting) [45]. We still do not know if other cognitive dysfunction(s) associated with ADHD rather than impulsivity might be

Table 2
Presence of DSM-IV Axis I disorders and their comorbidities.

Axis I Diagnoses	Total	Obese Only	Obese ED	Obese ADHD	Contrasts
N	132	42	50	40	
N° comorbidities	1.85	0.9 [±0.98]	1.86 [±1.1]	2.75 [±1.31]	1<2<3**
Any Mood disorders	68.2%	38.1%(16)	82%(41)	82.5%(33)	1<2=3*
Major depressive disorder	37.1%(49)	16.7%(7)	40%(20)	55%(22)	1<2=3*
Major depressive disorder (Past)	40.2%(53)	19%(8)	52%(26)	47.5%(19)	1<2=3*
Dysthymic disorder	5.3%(7)	2.4%(1)	6%(3)	7.5%(3)	N.S
Bipolar disorders	5.3%(7)	2.4%(1)	6%(3)	7.5%(3)	N.S
Any Anxiety disorder	61.4%(81)	40.5%(16)	62%(31)	82.5%(34)	1<2<3*
Panic disorders	9.1%(12)	4.8%(2)	10%(5)	12.5%(5)	1<2=3
Obsessive–compulsive disorder	3.8%(5)	0%(0)	0%(0)	12.5%(5)	1=2<3*
Posttraumatic stress disorder	4.5%(6)	0%(0)	4%(2)	10%(4)	N.S
Generalized anxiety disorder	45.5%(60)	19%(8)	48%(24)	70%(28)	1<2<3*
Social phobia	10.6%(14)	9.5%(4)	12%(6)	10%(4)	N.S
Specific phobia	15.2%(20)	11.9%(5)	16%(8)	17.5%(7)	N.S
Somatoform Disorder	2.2%(3)	0%(0)	2%(1)	5%(2)	N.S
Body Dysmorphic Disorder	3.1%(4)	2.4%(1)	2%(1)	5%(2)	N.S
Substance-related disorders	10.6%(14)	4.8%(2)	6%(3)	22.5%(9)	1<2<3**

1 = Obese Only Group; 2 = Obese ED Group; 3 = Obese ADHD Group. Contrasts performed using ANOVA. χ^2 test was used for categorical variables; *$p < .05$; **$p < .001$.

related to the pathophysiology of abnormal eating behaviors in obese ADHD patients.

The strongest predictor for binge eating in the current sample was depressive symptomatology. BED is associated with mood disorders, with higher rates of depression in this group of patients than what would be expected for the general population [45]. To date, there is not a clear explanation for the link between binge eating and depression. One possible hypothesis suggests that patients use binge eating to alleviate mood dysregulation and that this could be due to augmentation of tryptophan and serotonin release during binge episodes with high carbohydrate consumption [46]. Conversely, another possible explanation is an appetite increase induced by the depression in its atypical form, which could be a risk factor for the development of binge eating in vulnerable patients [45]. We may speculate that ADHD could be a mediator between binge eating and depressive symptoms in a subset of patients, since ADHD by itself is associated with development of depression [9,47].

Table 3
BES predicted by Beck depression inventory, K-SADS-IN, K-SADS-HI, BIS-11 and STAI CS in a forced entry regression model.

Variable	R^2	Adjusted R^2	Significance	Standardized B
BDI	.211	.204	**	.460
K-S IN	.294	.282	**	.305
BIS-11	.321	.303	*	.190
STAI CS	.329	.301	*N.S.*	.107
K-S HI	.331	.301	*N.S.*	−.565

Abbreviations: BDI = Beck Depression Inventory; K-S IN = Kiddie-SADS Inattention Symptoms; BIS-11 = Barratt Impulsiveness Scale 11; STAI CS = Spielberger Trait–State Anxiety Inventory Composite Score; K-S HI = Kiddie-SADS Hyperactivity–Impulsivity Symptoms ** = $p < 0.001$; * = $p < 0.05$; *N.S.* = Non-Significant.

Current attentional deficits and impulsivity were predictors of binge eating. Patients with BED describe difficulties shifting their focus to environment from food cues until they obtain it for consumption. This behavior is in line with functional MRI studies that suggest binge eaters have higher activation of areas related to reward anticipation and emotional salience of stimuli (*e.g.* striatum, hippocampus, amygdala), and hypoactivation of areas relating with planning, attention and executive functions (*e.g.* anterior cingulate cortex, dorsolateral prefrontal cortex and orbitofrontal cortex) [48]. Since we did not perform a neuropsychological evaluation of attention, we cannot infer which feature of this cognitive process may be affected. The results reported here suggest that neuropsychological factor(s) may be involved in binge eating behaviour. We note that there is evidence of executive functions difficulties in these patients [49]. Specifically, we propose future studies should be aimed at determining their attentional control and ability to plan and suppress behaviour.

Studies investigating the relation of ADHD symptoms, impulsivity and BMI are conflicting [15,50–53]. Females with a childhood history of ADHD symptoms evaluated by the Wender Utah Rating Scale (WURS) have been associated with higher BMI [52] but results from a previous study by our group [53], using a semi structured ADHD interview, do not support this association. Childhood ADHD symptoms and the presence of a variant of the GABRA2 gene (encoding a subunit of the GABA A receptor) may represent an endophenotype of impulsivity associated with higher BMI in women with SUD. Our results corroborate an association between ADHD comorbid with Eating Disorders and SUD in obese women but we could not test for genetic markers.

Two limitations in our study are the lack of an obese ADHD group without ED and the lack of a substantial

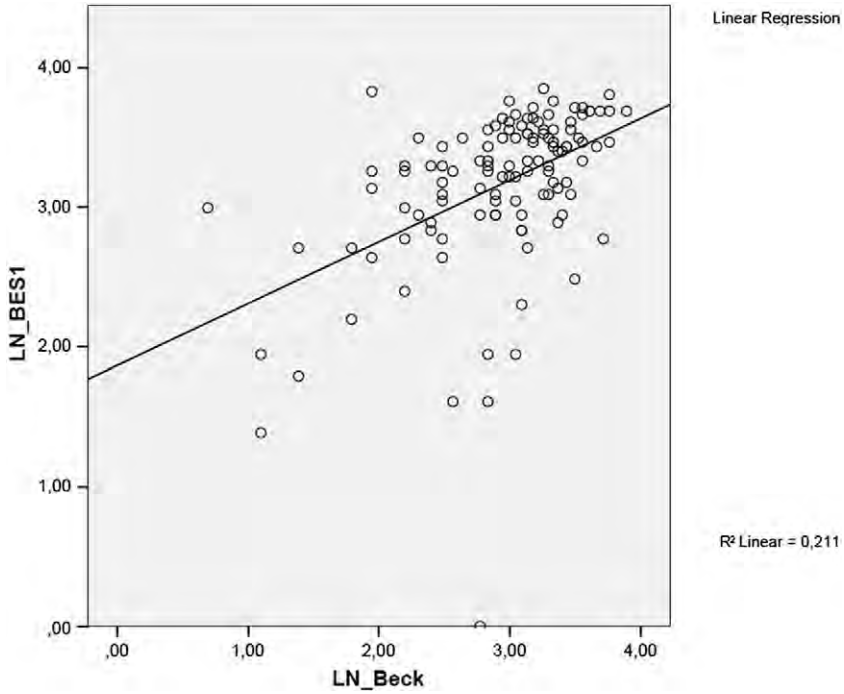


Fig. 1. BES (transformed Natural Log score) predicted by BDI (transformed Natural Log score). Higher Beck scores predicted greater BES scores.

number of male patients to generalize results concerning possible gender effects. However, these limitations would not likely explain our findings.

5. Conclusion

This study suggests that obese women should be routinely evaluated for ADHD. When ADHD is present in obese women, a thorough evaluation for ED should be performed as our findings suggest a high association between ADHD and ED. ADHD in obese women is associated with the occurrence of other psychiatric comorbidities, especially AD and SUD [7,11]. The presence of depressive symptoms and inattention can predict the presence of binge eating in obese women.

References

[1] Devlin MJ, Yanovski SZ, Wilson GT. Reviews and overviews obesity: what mental health professionals need to know. Psychiatry: Interpersonal and Biol Process 2000:854-66.

[2] Luppino FS, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220-9.

[3] Pagoto SL, et al. Association between adult attention deficit/hyperactivity disorder and obesity in the US population. Obesity (Silver Spring) 2009;17:539-44.

[4] Altfas JR. Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. BMC Psychiatry 2002;2:9.

[5] van Egmond-Fröhlich AWA, Widhalm K, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with childhood overweight adjusted for confounding parental variables. Int J Obes 2012;36:963-8.

[6] Kessler RC, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716-23.

[7] Sobanski E. Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2006;256(Suppl):i26-31.

[8] Bernfort L, Nordfeldt S, Persson J. ADHD from a socio-economic perspective. Acta Paediatr (Oslo, Norway: 1992) 2008;97:239-45.

[9] Sobanski E, et al. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2007;257:371-7.

[10] Mikami AY, Hinshaw SP, Patterson KA, Lee JC. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. J Abnorm Psychol 2008;117:225-35.

[11] Biederman J, et al. Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study. J Dev Behav Pediatr: JDBP 2007;28:302-7.

[12] Hinshaw SP, Owens EB, Sami N, Fargeon S. Prospective follow-up of girls with attention-deficit/hyperactivity disorder into adolescence: evidence for continuing cross-domain impairment. J Consult Clin Psychol 2006;74:489-99.

[13] Biederman J, Petty CR, Monuteaux MC, et al. Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case–control study. Am J Psychiatry 2010;167:409-17.

[14] Biederman J, Faraone SV, Monuteaux MC, Bober M, Cadogen E. Gender effects on attention-deficit/hyperactivity disorder in adults, revisited. Biol Psychiatry 2004;55:692-700.

[15] Nazar BP, et al. Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders. Rev Bras Psiquiatr 2008;30:384-9.

[16] Mattos P, et al. Comorbid eating disorders in a Brazilian attention-deficit/hyperactivity disorder adult clinical sample. Rev Bras Psiquiatr (São Paulo, Brazil: 1999) 2004;26:248-50.

[17] Kooij JJS, et al. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-

controlled double-blind cross-over trial. Psychol Med 2004; 34:973-82.

[18] Surman CBH, Randall ET, Biederman J. Association between attention-deficit/hyperactivity disorder and bulimia nervosa: analysis of 4 case–control studies. J Clin Psychiatry 2006;67:351-4.

[19] Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with eating disorders. Psychosom Med 2006;68:454-62.

[20] Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity symptoms and disorder in eating disorder inpatients. Int J Eat Disord 2009;42:375-8.

[21] Wentz E, et al. Childhood onset neuropsychiatric disorders in adult eating disorder patients. A pilot study. Eur Child Adolesc Psychiatry 2005;14:431-7.

[22] American Psychiatric Association *Diagnostic and statistical manual of mental disorders*. Text revision (DSM-IV-TR), 1. Arlington, VA: American Psychiatric Association; 2000.

[23] Hudson JI, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;61:348-58.

[24] Treasure J, Claudino AM, Zucker N. Eating disorders. Lancet 2010;375:583-93.

[25] Rosval L, et al. Impulsivity in women with eating disorders: problem of response inhibition, planning, or attention? Int J Eat Disord 2006;3–6 doi:10.1002/eat.

[26] Centers for Disease Control and Prevention. Adult BMI; 2009. at <http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm>.

[27] IBGE, I. B. de G. e E. Censo Demográfico 2000; 2002. at <http://www.ibge.gov.br>.

[28] Tavares M. Psicodiagnóstico V: *Entrevista Clínica Estruturada para o DSM-IV. Transtornos do eixo I (Versão 2.0)*. Projeto Brasil. Instituto de Psicologia-Universidade de Brasília. Porto Alegre: Artes Médicas; 2000.

[29] Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837-44.

[30] Amorim P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. Rev Bras Psiquiatr 2000;22.

[31] Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatr 1974;7:151-69.

[32] Gorenstein C, Andrade L, Vieira Filho AH, Tung TC, Artes R. Psychometric properties of the Portuguese version of the Beck Depression Inventory on Brazilian college students. J Clin Psychol 1999;55:553-62.

[33] Andrade L, Gorenstein C, Vieira Filho AH, Tung TC, Artes R. Psychometric properties of the Portuguese version of the State–Trait Anxiety Inventory applied to college students: factor analysis and relation to the Beck Depression Inventory. Revista brasileira de pesquisas médicas e biológicas/Sociedade Brasileira de Biofísica … [et al] 2001;34:367-74.

[34] Freitas S, Lopes CS, Coutinho W, Appolinario JC. Tradução e adaptação para o português da Escala de Compulsão Alimentar Periódica Translation and adaptation into Portuguese of the Binge-Eating Scale. Rev Bras Psiquiatr 2001;23:215-20.

[35] Malloy-diniz LF, et al. Tradução e adaptação cultural da Barratt Impulsiveness Scale (BIS-11) para aplicação em adultos brasileiros. J Bras Psiquiatr 2010;59:99-105.

[36] Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995;51:768-74.

[37] Mustillo S, et al. Obesity and psychiatric disorder: developmental trajectories. Pediatrics 2003;111:851-9.

[38] Cortese S, et al. Association between symptoms of attention-deficit/hyperactivity disorder and bulimic behaviors in a clinical sample of severely obese adolescents. Int J Obes 2007;31:340-6.

[39] Wilens TE. Attention-deficit/hyperactivity disorder and the substance use disorders: the nature of the relationship, subtypes at risk, and treatment issues. Psychiatr Clin N Am 2004;27:283-301.

[40] Blum K, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;89:396-400.

[41] Davis C, et al. Dopamine transporter gene (DAT1) associated with appetite suppression to methylphenidate in a case-control study of binge eating disorder. Neuropsychopharm: Off Publ Am Coll Neuropsychopharmacol 2007;32:2199-206.

[42] Blum K, et al. Attention-deficit-hyperactivity disorder and reward deficiency syndrome. Neuropsychiatr Dis Treat 2008;4:893-918.

[43] Kamarajan C, et al. Dysfunctional reward processing in male alcoholics: an ERP study during a gambling task. J Psychiatr Res 2010;44:576-90.

[44] Levy LD, Fleming JP, Klar D. Treatment of refractory obesity in severely obese adults following management of newly diagnosed attention deficit hyperactivity disorder. Int J Obes 2009;33:326-34.

[45] Dingemans AE, van Furth EF. Binge eating disorder psychopathology in normal weight and obese individuals. Int J Eat Disord 2012;45:135-8.

[46] Harrold J, Harrold JA, Dovey TM, Blundell JE, Halford JC. CNS regulation of appetite. Neuropharmacology 2012;63:3-17.

[47] Blomquist KK, Masheb RM, White MA, Grilo CM. Parental substance use history of overweight men and women with binge eating disorder is associated with distinct developmental trajectories and comorbid mood disorder. Compr Psychiatry 2011;52:693-700.

[48] Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev: Off J Int Assoc study Obes 2012;13:43-56.

[49] Galioto R, et al. Cognitive function in morbidly obese individuals with and without binge eating disorder. Compr Psychiatry 2012;53:490-5.

[50] Mobbs O, Crépin C, Thiéry C, Golay A, Van der Linden M. Obesity and the four facets of impulsivity. Patient Educ Couns 2010;79:372-7.

[51] Fleming JP, Levy LD, Levitan RD. Symptoms of attention deficit hyperactivity disorder in severely obese women. Eat Weight Disord: EWD 2005;10:e10-3.

[52] Bauer LO, Yang B-Z, Houston RJ, Kranzler HR, Gelernter J. GABRA2 genotype, impulsivity, and body mass. Am J Addict Am Acad Psychiatr Alcohol Addict 2012;21:404-10.

[53] Nazar BP, et al. ADHD rate in obese women with binge eating and bulimic behaviours from a weight loss clinic. J Atten Disord 2012 Aug 28. [Epub ahead of print].

9.3 Artigo:

Can a Continuous Perfoemance Test help to assign innatention when mood and ADHD symptoms coexist?

Psychiatry Research xxx (2016) xxx-xxx

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com

How can Continuous Performance Test help to assess inattention when mood and ADHD symptoms coexist?

Cintia Mesquita [a], Bruno P. Nazar [a, b, *], Camilla M.S. Pinna [a], Beatriz Rabelo [a], Maria Antonia Serra-Pinheiro [a], Joseph Sergeant [c], Paulo Mattos [a, d]

[a] Department of Psychiatry and Mental Health, Federal University of Rio de Janeiro Institute of Psychiatry, Rio de Janeiro - Brazil
[b] Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IOPPN) – King's College London, London, United Kingdom
[c] Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, Netherlands
[d] D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil

ARTICLE INFO

Article history:
Received 10 September 2015
Received in revised form 28 June 2016
Accepted 29 June 2016
Available online xxx

Keywords:
A
ttention Deficit Disorder with Hyperac-
tivityDepression
Neuropsychology
Comorbidity
University students
Differential diagnosis
Neuropsychology

ABSTRACT

Depression and attention-deficit/hyperactivity disorder (ADHD) are prevalent, and often comorbid, disorders, with varying severity levels among patients. Inattention is a symptom present in both disorders, which often makes their differential diagnosis difficult in clinical practice (depression only versus comorbidity). This study aimed to investigate the influence of depressive symptoms on attention performance using one of the most common tasks in clinical practice, the continuous performance test (CPT). Ninety-three college students (60 men, 33 women) with a mean age of 24 years old were investigated with self-reports and semi-structured interviews for ADHD; the Beck Depression Inventory (BDI) was used for depression ratings. Attention measures were derived from the CPT. There was no correlation between depression and ADHD symptoms; in addition, depression was not correlated with any of the CPT scores; ADHD symptomatology was the only predictor of changes in those CPT variables (commission and omission errors and d prime). ADHD-associated impairment on the CPT was not augmented by the presence of depressive symptoms, making neuropsychological results on this test helpful for the differential diagnosis. When attention deficits are observed in individuals with mild or moderate depression, they are most likely not attributed to depression.

1. Introduction

Depression and Attention-Deficit/Hyperactivity Disorder (ADHD) are highly prevalent disorders, often comorbid with each other (Kessler et al., 2005b), with varying severity in the population (Kooij et al., 2001; McGough et al., 2005; Murphy and Barkley, 1996). Both disorders are heritable, sharing familial pathophysiological and genetic risk factors (Biederman et al., 1993; Rommelse et al., 2008). The presence of comorbidities, like depression, may obscure an ADHD diagnosis (Adler, 2004). On the other hand, comorbid depression augments the impact of ADHD (Biederman, 2004; Secnik et al., 2005). Since both disorders comprise inattention as part of their clinical picture (American Psychiatric Association, 2013), differentiating among these diagnoses may be difficult in clinical practice. Another challenge seen by clinicians is to either make a differential diagnosis of depression or ADHD only versus that of depression with comorbid ADHD).

Severely depressed patients are seldomly referred to neuropsychological testing because depression can seriously compromise their performance, thus complicating interpretation of results (Lezak et al., 2012). Contrastingly, less severe cases are often referred to a neuropsychologist in order to help disentangle the cause of inattention reported by the patient. This latter scenario demands a more thorough clinical investigation since both ADHD and depression may contribute to impairments on attentional tests. In fact, some authors (Groth-Marnat, 2000; Sweet et al., 1992) suggest caution when interpreting attentional deficits when mood symptoms are present.

For many decades, neuropsychologists have attempted to understand the neuropsychological dysfunction in depression. Beblo et al. (2011) have summarized several clinical and demographic factors, which potentially influence the profile and the severity of neuropsychological deficits of patients with mood disorders. Additionally, they have demonstrated that although those deficits are present mainly on attention, they are also manifest across a wide range of cognitive domains as executive functions and memory.

A large number of studies have been conducted in middle-aged and elderly depressed patients with mixed clinical variables that could account for the discrepant findings in the literature (Groth-Marnat, 2000). The type of mood disorder, its course, number of episodes and residual symptoms are some of such variables. Most studies commonly included only the more severe form of the disorder, Major Depressive Disorder (MDD) and also patients under medication, which might affect cognition, specially benzodiazepines and antidepressants with anticholinergic properties (Fossati et al., 2002). Thus, it is not clear if those results can be generalized to less severe depressive cases. Also, many studies comprised small samples and provided no data regarding depression severity or comorbidity (Westheide et al., 2007). Patients with Bipolar Disorder also have

* Correspondence to: Rua Visconde de Pirajá 547 – sala 610 – CEP: 22410-900.
Email address: bruno.nazar@kcl.ac.uk, bruno.nazar@gmail.com (B.P. Nazar)

http://dx.doi.org/10.1016/j.psychres.2016.06.054
0165-1781/

Psychiatry Research xxx (2016) xxx-xxx

demonstrated impaired performance in Continuous Performance Tests (CPT) when compared to controls (Najt et al., 2005).

Fischer et al. (2005) demonstrated that depression did not contribute to impairments on the CPT of a clinical sample of young adults. In contrast, Larochette et al. (2011), reported that depressive symptoms significantly impaired the neurocognitive performance of young adults with ADHD comorbid with severe depression. However, this experiment attention was inferred through indirect indexes from the Wechsler Intelligence Scale and the Wechsler Memory Scale, rather than using attention tests. The use of tests tailored for attention assessment could document more specific deficits and contribute to a better understanding of the relation between mood symptoms and performance.

There are different CPT versions available for research use and relatively few studies using them on adult ADHD population (Mowinckel et al., 2015). Variability among different CPTs may affect their sensitivity and generalization of data on performance must be regarded with caution (Maoz et al., 2015). A meta-analysis including measures from different CPT versions demonstrated that the attentional and decision-making deficits of ADHD adults are of a similar magnitude when compared to controls (Mowinckel et al., 2015). Interestingly, such results contrast with those found in pediatric ADHD studies (Rossi et al., 2015) where their attentional profile is characterized by more variable performance, difficulty in rapidly adapting performance, slower processing speed, less efficient responses and reduced duration of the engagement of focus on tasks. Furthermore, ADHD patients with comorbid Borderline Personality Disorder (BPD) present changes in CPT response style with more widespread inhibition deficiencies (van Dijk et al., 2014).

Hill et al. (2008) investigated 161 adult patients of normal intelligence quotients (IQ) and found that self-reported depressive symptoms using the Beck Depression Inventory (BDI) minimally affected attention performance on the CPT (less than 1.5% of unique variance on all measures). This finding suggests that attention deficits within this population were most likely indicative of primary attention problems rather than functional impairment secondary to depression. In concert with this, some studies (Fischer et al., 2005; Morasco et al., 2006) also found that self-reported mood symptoms exerted minimal or equivocal influence on cognitive performance. Although there is evidence of a positive relationship between attention and depression (Watari et al., 2006) other studies failed to replicate such relationship (Rohling et al., 2002; Tsushima et al., 2005).

The aim of this study was to investigate how depressive and ADHD symptoms influenced changes on CPT performance. We have chosen to investigate college students because a relatively large number of college students (up to 8%) report clinically significant levels of ADHD symptomatology and at least 25% of those with disabilities receive an ADHD diagnosis (DuPaul et al., 2009). In addition, college students belong to an age group considered to be at risk for the emergence of depression (Kessler et al., 2005a; Sweet et al., 1992). In particular, medical students present high prevalence rates of depression (Goldman et al., 2015).

Our hypothesis was that CPT measures were indicative of primary inattention deficits and not secondary to depressive symptomatology. We tested this hypothesis investigating the performance on CPT by a sample of young adults controlling for both ADHD and depression symptoms in a dimensional way (number of symptoms), which might provide more reliable data (Larsson et al., 2012). For the purposes of this study, Major Depression was an exclusionary criterion.

2. Methods

2.1. Subjects

The initial sample consisted of 143 medical students from a public university in Rio de Janeiro, Brazil, which volunteered for this study. Ninety-three students completed protocol while 50 had some of the main variables of interest (ADHD, depressive symptoms or CPT) incomplete (2 students missed all three variables and 52 students had any combination of 2 variables missing). There was no statistical significant difference between the socio demographic profile of completers and non-completers. The complete sample consisted of 60 (64.5%) women and 33 (35.5%) men with a mean age of 24 years old.

2.2. Procedures

Evaluation of all participants consisted of the ASRS - Adult Self Rating Scale (Mattos et al., 2006) and a semi-structured interview using DSM-IV criteria (K-SADS for ADHD (Kaufman et al., 1997)) by board certified psychiatrists with more than 10 years of experience in adult ADHD (BPN and PM); diagnoses were made upon discussion of cases (history, self-report and semi-structured interview). Since there is some evidence that self-report of ADHD symptoms may be somewhat unreliable (Sibley et al., 2012) ADHD symptomatology was assessed not only by self-report (ASRS) but also the semi-structured interview (K-SADS). All ADHD assessments were done blind to the screening status and all students with more than 5 current symptoms of inattention or hyperactivity/impulsivity were discussed with the other rater. Participants completed the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). Individuals with current Depressive Episode were not included for the purposes of this study; other exclusion criteria were psychosis, epilepsy and current use of benzodiazepines or antidepressants. All participants signed an informed consent; the local Ethics Committee approved this study.

Neuropsychological evaluation comprised CPT and IQ, calculated with the Four- Subtest Form of the Wechsler Abbreviated Intelligence Scale (WASI) (Beck et al., 2009), from which the blocks, vocabulary, matrix and similarities were administered. The Conner's Continuous Performance Task II (CPT) (Conners, 2004) is the most commonly used attention task in clinical practice (Rabin, Barr, & Burton, 2005) giving the opportunity to evaluate the ability of a subject to maintain consistent responding (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) it primarily measures sustained attention, distractibility and response inhibition through errors (omissions and commissions), reaction time (RT) and RT variability. Variables of interest in the present study were: Number of Omission errors (OMI), Commission errors (COM), Hit Reaction Time (HRT), HRT Block Change (HRT BL CHANGE), Reaction Time by Inter-Stimulus Interval (Hit RT ISI Change) and Attentiveness (d'). OMI occur when subjects fail to respond on trials containing target letters (all non-"X" letters), COM occur when they respond on trials with letters "X". HRT is the mean response time for all non-X responses over all six-time blocks and represents the subject's easier discrimination of the target. HRT BL CHANGE (a vigilance measure) is the slope of change in the reaction time over the six time blocks; a positive slope indicates a slowing RT and a negative slope indicates quicker RT as the test progresses. Hit RT ISI CHANGE (capacity to adjust to presentation speed) is calculated by computing the slope of change in RT over the three ISIs (1, 2, and 4 s). The ISIs are block-randomized so that all three ISI conditions would occur every block but in a dif-

Psychiatry Research xxx (2016) xxx-xxx

ferent order; by varying the inter-stimulus intervals (1, 2 and 4 s) it is possible to assess the ability to adjust to changing tempo and task demand. The index d′ reflects the subject's perceptual sensitivity to targets, in other words, it is a measure of how well the individual discriminates between targets (signals) from non-targets (noise). Higher d′ values indicate greater sensitivity and better discrimination between targets and non-targets.

2.3. Statistical analysis

First, we investigated the correlation between depression and ADHD symptoms, either measured by self-report (ASRS) or semi-structured interview (K-SADS). Statistical tests were then performed to verify the significance of the correlation of CPT scores with the number of inattentive and hyperactive symptoms (defined by K-SADS scores) and the depressive symptoms (defined by BDI total scores). A K-SADS composite score was calculated with the total number of symptoms (inattention and hyperactivity/impulsivity); a second composite score was calculated using this first composite score multiplied by BDI score. Except for d', all distributions of the scores were not normal, and Spearman correlation was used in the analysis. Correlations (Spearman) were made among OMI, COM, d′, HRT, HRT BL and HRT ISI CHANGE results and the BDI, ASRS and KSADS values in order to identify initially the association of the studied variables. Afterwards, we performed multiple linear regressions to test our hypothesis, considering the CPT measures as the dependent variables in each regression, and KSADS composite score, BDI score, and KSADS CompxBDI, as independent variables. These scores were natural log transformed prior to statistical modeling to approximate a normal distribution. A probability level of $p<0.05$ was used; correlations above 0.3 were considered significant.

3. Results

The sample had a mean IQ of 115 (high average). There was no significant interaction between IQ, gender, ADHD symptoms and CPT measures. Regarding ADHD symptoms, 31% had at least 6 current inattention symptoms and 9% had at least 6 current hyperactivity-impulsivity symptoms; formal diagnosis using DSM-IV criteria in this sample was 4.57%.

Depression was absent in 72.5% of the sample; 17.5% had mild depressive symptoms and 10% had moderate depressive symptoms according to the BDI classification. There was no correlation between depression and ADHD symptoms, either measured by self-report (ASRS scores) or semi-structured interview. Depression was not significantly correlated either with inattention (ρ =0.12) or hyperactivity-impulsivity (ρ =−0.03). Also, additional analysis demonstrated that ASRS items were not correlated with the BDI total score.

Multiple regression analysis is presented in Table 1. The only variable that significantly predicted changes in CPT was the KSADS Comp Score, with a standardized B of 0.186 for CPT Omission; 0.291 for CPT Commission and −0.226 for CPTd′. The scatterplot of the CPT Omission, CPT Commission and CPT D Prime by KSADS CS prediction is given, respectively, in Figs. 1–3.

Table 1
Multiple linear regressions with CPT factors as independent variables.

	R^2	Adjusted R^2	Standardized B	Significance
		CPT Omission		
KSADS CS	0.35	0.025	0.186	<0.05
BDI	0.35	0.17	0.025	N. S.
KSADSCSxBDI	0.35	0.07	−0.011	N. S.
		CPT Comission		
KSADS CS	0.085	0.076	0.291	<0.05
BDI	0.105	0.088	0.144	N. S.
KSADSCSxBDI	0.106	0.8	−0.65	N. S.
		CPT HRT		
KSADS CS	0.001	−0.011	−0.028	N. S.
BDI	0.016	−0.007	−0.124	N. S.
KSADSCSxBDI	0.016	−0.019	0.024	N. S.
		CPT St Error		
KSADS CS	0.001	−.01	−0.038	N. S.
BDI	0.011	−0.13	−0.098	N. S.
KSADSCSxBDI	0.013	−0.022	−0.106	N. S.
		CPT D Prime		
KSADS CS	0.051	0.04	−0.226	<0.05
BDI	0.078	0.56	−0.0164	N. S.
KSADSCSxBDI	0.087	0.054	0.197	N. S.
		CPT HRT BL Change		
KSADS CS	0.028	0.016	−0.166	N. S.
BDI	0.046	0.023	0.135	N. S.
KSADSCSxBDI	0.013	−0.022	−0.106	N. S.
		CPT HRT ISI Change		
KSADS CS	0.002	−0.009	0.047	N. S.
BDI	0.005	−0.019	−0.052	N. S.
KSADSCSx DI	0.011	−0.024	0.170	N. S.

$p<0.05$; N.S. = Non-Significant; KSADS CS = KSADS Composite Score (Inattention+Hyperactivity/Impulsivity symptoms); BDI = Beck Depression Inventory; KSADSCS x BDI = KSADS Composite Score x Beck Depression Inventory

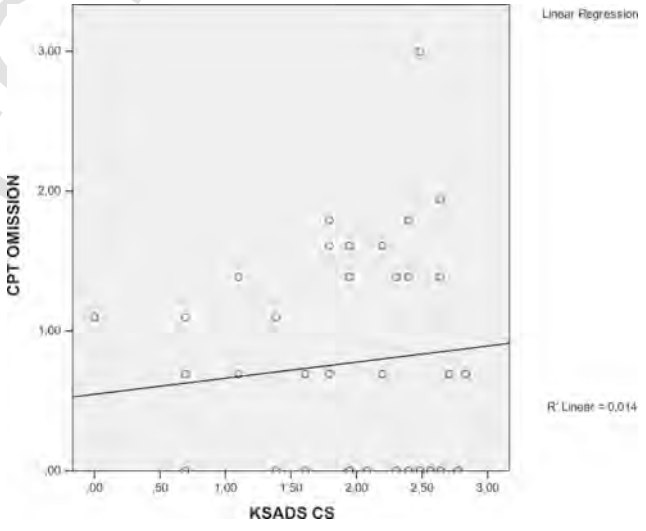


Fig. 1. Linear regression scatterplot CPT omission (dependent variable) And KSADS composite score (independent variable).

4. Discussion

This study aimed to investigate the influence of depressive and ADHD symptoms on attention performance using one of the most common tasks in clinical practice, the CPT. Both ADHD and depression can be measured dimensionally and comprise inattention as part of the clinical picture. Individuals presenting both depressive symptoms and inattention are often referred to neuropsychological evaluation, where CPT is commonly considered the main task addressing attentional skills. Of note, regularly the patient's referral has different diagnostic purposes. In this study, ADHD symptoms were neither correlated with nor predicted by BDI scores suggesting that an increasing number of ADHD symptoms were not associated with more depressive symptoms. Also, depression was not correlated with any of the CPT scores suggesting a lack of impact on attentional performance in this sample. We suggest that ADHD associated impairment on the CPT is not augmented by the presence of mild depressive

Psychiatry Research xxx (2016) xxx-xxx

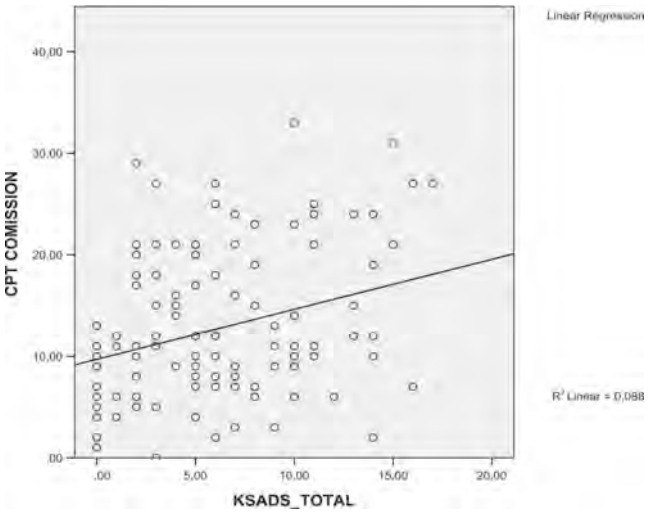


Fig. 2. :Linear regression scatterplot CPT comission (dependent variable) and KSADS composite score (independent variable).

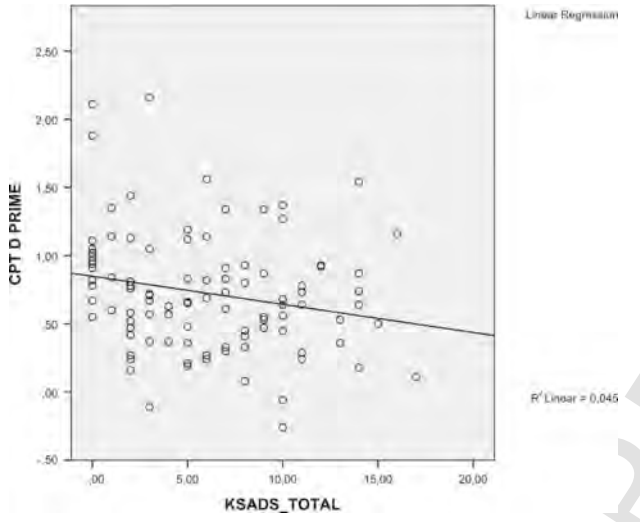


Fig. 3. : Linear regression scatterplot CPT D prime (dependent variable and KSADS_-TOTAL = composite score (independent variable).

symptoms because of a ceiling effect. Furthermore, mild depressive symptoms do not add extra impairment to that which is already present and associated with ADHD symptoms.

In our sample, OMI and COM, as well as d′ were correlated to ADHD symptoms (K-SADS composite score); the percentage of prediction for COM was higher than for OMI. An impaired capacity to inhibit a pre-potent motoric response (Barkley, 1997) could explain higher COM errors (Rivenes et al., 2009) and a lack of effort necessary to meet task demands (Luman et al., 2009) could explain both OM and COM errors in CPT, even when primary monitoring functions are intact (Barkley, 1997). Also, ADHD symptomatology was the only predictor of changes in those CPT variables and such measures may help in the differential diagnosis (Depression only versus Depression comorbid with ADHD). These findings are in accordance to those of the only other somewhat similar study in our country (Malloy-Diniz et al., 2007).

There are several theoretical models explaining neuropsychological deficits in ADHD, which could explain higher OMI and COM errors in CPT. Using a different methodology, our results are in accordance with Hill et al., (2008), who suggested that when attention deficits are observed they are more likely not accounted for depression. This finding is particularly helpful for the neuropsychologist who must conclude on the nature of attention deficits when both ADHD and depressive symptoms are present. Whenever depression is considered to cause inattention, clinicians tend to either postpone or discard ADHD diagnosis and invest in depression treatment. If ADHD symptoms were considered as the source of attention complaints, clinicians would consider an ADHD diagnosis in the first place, even if depressive symptoms merited a parallel treatment. Our results suggest that CPT measures demonstrating inattention correlates to ADHD symptomatology even if another potential contributing factor, as depression is present.

5. Limitations

It should be noted that individuals with major depression were not included for the purposes of this study; our sample mirrors the proportion of depression described in similar studies (Murphy et al., 2002), we intended to evaluate individuals with milder depressive symptomatology whose neuropsychological testing results must be interpreted either as indicative of a primary attention deficit or secondary to depression.

Additional analyses of potential contributing factors for CPT performance, which are beyond the scope of this study, like executive functions measures, should also be investigated in future studies. We have evaluated a sample of young university students and it should be noted that our results might not be generalized to other different samples.

Conflicts of interest

Paulo Mattos was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, and Shire in the previous years; he received travel awards to participate in scientific meetings from those companies. The ADHD outpatient program (Grupo de Estudos do Déficit de Atenção/Institute of Psychiatry) chaired by Dr. Mattos has also received research support from Novartis and Shire.

Joseph A. Sergeant has served on the advisory boards of Lilly and Shire, and received grants from Lilly. He has also received speaker's fees from Shire, Lilly, Janssen- Cillag, and Novartis. The other authors do not state any conflict of interests.

Acknowledgment

None.

References

Adler, L.A., 2004. Clinical presentation of adult patients with ADHD. J. Clin. Psychiatry 65 (Suppl 3), 8–11.

American Psychiatric Association, 2013. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Arlington, VA.

Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol. Bull. 121, 65–94.

Beck, A.T., Beamesderfer, A., 1974. Assessment of depression: the depression inventory. Mod. Probl. Pharm. 7, 151–169.

Biederman, J., 2004. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. J. Clin. Psychiatry 65 (Suppl 3), 3–7.

Biederman, J., Faraone, S.V., Spencer, T., Wilens, T., Norman, D., Lapey, K.A., Mick, E., Lehman, B.K., Doyle, A., 1993. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am. J. Psychiatry 150, 1792–1798.

DuPaul, G.J., Weyandt, L.L., O'Dell, S.M., Varejao, M., 2009. College students with ADHD: current status and future directions. J. Atten. Disord. 13, 234–250.

Fischer, M., Barkley, R.A., Smallish, L., Fletcher, K., 2005. Executive functioning in hyperactive children as young adults: attention, inhibition, response perseveration, and the impact of comorbidity. Dev. Neuropsychol. 27, 107–133.

Fossati, P., Coyette, F., Ergis, A.-M., Allilaire, J.-F., 2002. Influence of age and executive functioning on verbal memory of inpatients with depression. J. Affect. Disord. 68, 261–271.

Goldman, M.L., Shah, R.N., Bernstein, C.A., 2015. Depression and suicide among physician trainees: recommendations for a national response. JAMA Psychiatry 72, 411–412.

Groth-Marnat, G. (Ed.), 2000. Neuropsychological Assessment in Clinical Practice: A Guide to Test Interpretation and Integration, 1st ed., Hoboken: NJ . John Wiley & Sons.

Hill, B.D., Smitherman, T.A., Pella, R.D., O'Jile, J.R., Gouvier, W.D., 2008. The relation of depression and anxiety to measures of attention in young adults seeking psychoeducational evaluation. Arch. Clin. Neuropsychol. 23, 823–830.

Kessler, R.C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., Howes, M.J., Jin, R., Secnik, K., Spencer, T., Ustun, T.B., Walters, E.E., 2005. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol. Med. 35, 245–256.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62, 593–602.

Kooij, J.J., Aeckerlin, L.P., Buitelaar, J.K., 2001. Functioning, comorbidity and treatment of 141 adults with attention deficit hyperactivity disorder (ADHD) at a psychiatric outpatient department. Ned. Tijdschr. Geneeskd. 145, 1498–1501.

Larochette, A.-C., Harrison, A.G., Rosenblum, Y., Bowie, C.R., 2011. Additive neurocognitive deficits in adults with attention-deficit/hyperactivity disorder and depressive symptoms. Arch. Clin. Neuropsychol. 26, 385–395.

Larsson, H., Anckarsater, H., Råstam, M., Chang, Z., Lichtenstein, P., 2012. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8500 twin pairs. J. Child. Psychol. Psychiatry 53, 73–80.

Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D., 2012. Neuropsychological Assessment, Fifth Edition. Oxford.

Luman, M., Van Meel, C.S., Oosterlaan, J., Sergeant, J. a, Geurts, H.M., 2009. Does reward frequency or magnitude drive reinforcement-learning in attention-deficit/hyperactivity disorder?. Psychiatry Res. 168, 222–229.

Malloy-Diniz, L., Fuentes, D., Leite, W.B., Correa, H., Bechara, A., 2007. Impulsive behavior in adults with attention deficit/ hyperactivity disorder: characterization of attentional, motor and cognitive impulsiveness. J. Int. Neuropsychol. Soc. 13, 693–698.

H., Maoz, S., Aviram, U., Nitzan, A., Segev, Y., Bloch, 2015. Association Between Continuous Performance and Response Inhibition Tests in Adults With ADHD. J. Atten. Disord.

McGough, J.J., Smalley, S.L., McCracken, J.T., Yang, M., Del'Homme, M., Lynn, D.E., Loo, S., 2005. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. Am. J. Psychiatry 162, 1621–1627.

Morasco, B.J., Gfeller, J.D., Chibnall, J.T., 2006. The relationship between measures of psychopathology, intelligence, and memory among adults seen for psychoeducational assessment. Arch. Clin. Neuropsychol. 21, 297–301.

Mowinckel, A.M., Pedersen, M.L., Eilertsen, E., Biele, G., 2015. A meta-analysis of decision-making and attention in adults with ADHD. J. Atten. Disord. 19, 355–367.

Murphy, K., Barkley, R.A., 1996. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr. Psychiatry 37, 393–401.

Murphy, K.R., Barkley, R.A., Bush, T., 2002. Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. J. Nerv. Ment. Dis. 190, 147–157.

Najt, P., Glahn, D., Bearden, C.E., Hatch, J.P., Monkul, E.S., Kaur, S., Villarreal, V., Bowden, C., Soares, J.C., 2005. Attention deficits in bipolar disorder: a comparison based on the continuous performance test. Neurosci. Lett. 379, 122–126.

Rivenes, A.C., Harvey, S.B., Mykletun, A., 2009. The relationship between abdominal fat, obesity, and common mental disorders: results from the HUNT study. J. Psychosom. Res. 66, 269–275.

Rohling, M.L., Green, P., Allen, L.M., Iverson, G.L., 2002. Depressive symptoms and neurocognitive test scores in patients passing symptom validity tests. Arch. Clin. Neuropsychol. 17, 205–222.

Rommelse, N.N., Altink, M.E., Martin, N.C., Buschgens, C.J., Faraone, S.V., Buitelaar, J.K., Sergeant, J. a, Oosterlaan, J., 2008. Relationship between endophenotype and phenotype in ADHD. Behav. Brain Funct. 4, 4.

Rossi, A.S.U., de Moura, L.M., de Mello, C.B., de Souza, A.A.L., Muszkat, M., Bueno, O.F.A., 2015. Attentional profiles and white matter correlates in attention-deficit/hyperactivity disorder predominantly inattentive type. Front. Psychiatry 6, 122.

Secnik, K., Swensen, A., Lage, M.J., 2005. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. Pharmacoeconomics 23, 93–102.

Sweet, J., Newman, P., Bell, B., 1992. Significance of depression in clinical neuropsychological assessment. Clin. Psychol. Rev. 12, 21–24.

Tsushima, W.T., Johnson, D.B., Lee, J.D., Matsukawa, J.M., Fast, K.M.S., 2005. Depression, anxiety and neuropsychological test scores of candidates for coronary artery bypass graft surgery. Arch. Clin. Neuropsychol. 20, 667–673.

van Dijk, F., Schellekens, A., van den Broek, P., Kan, C., Verkes, R.-J., Buitelaar, J., 2014. Do cognitive measures of response inhibition differentiate between attention deficit/hyperactivity disorder and borderline personality disorder?. Psychiatry Res. 215, 733–739.

Watari, K., Letamendi, A., Elderkin-Thompson, V., Haroon, E., Miller, J., Darwin, C., Kumar, A., 2006. Cognitive function in adults with type 2 diabetes and major depression. Arch. Clin. Neuropsychol. 21, 787–796.

Westheide, J., Wagner, M., Quednow, B.B., Hoppe, C., Cooper-Mahkorn, D., Strater, B., Maier, W., Kuhn, K.-U., 2007. Neuropsychological performance in partly remitted unipolar depressive patients: focus on executive functioning. Eur. Arch. Psychiatry Clin. Neurosci. 257, 389–395.

9.4 Artigo:

Early Response in Eating Disorders Treatment:

A Systematic Review and

Diagnostic Test Accuracy Meta-Analysis

REVIEW

Early Response to treatment in Eating Disorders: A Systematic Review and a Diagnostic Test Accuracy Meta-Analysis

Bruno Palazzo Nazar[1,2]*, Louise Kathrine Gregor[1], Gaia Albano[1,3], Angelo Marchica[3], Gianluca Lo Coco[3], Valentina Cardi & Janet Treasure[1†]

[1]Department of Psychological Medicine, King's College London, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), London, UK
[2]Federal University of Rio de Janeiro, Institute of Psychiatry (IPUB-UFRJ), Brazil
[3]University of Palermo, Department of Psychology and Educational Sciences, Palermo, Italy

Abstract

Objective: Early response to eating disorders treatment is thought to predict a later favourable outcome. A systematic review of the literature and meta-analyses examined the robustness of this concept.
Method: The criteria used across studies to define early response were summarised following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Diagnostic Test Accuracy methodology was used to estimate the size of the effect.
Results: Findings from 24 studies were synthesized and data from 14 studies were included in the meta-analysis. In Anorexia Nervosa, the odds ratio of early response predicting remission was 4.85(95%CI: 2.94–8.01) and the summary Area Under the Curve (AUC) = .77. In Bulimia Nervosa, the odds ratio was 2.75(95%CI:1.24–6.09) and AUC = .67. For Binge Eating Disorder, the odds ratio was 5.01(95%CI: 3.38–7.42) and AUC = .71.
Conclusion: Early behaviour change accurately predicts later symptom remission for Anorexia Nervosa and Binge Eating Disorder but there is less predictive accuracy for Bulimia Nervosa.

Received 19 August 2016; Revised 21 October 2016; Accepted 10 November 2016

Keywords
early response; eating disorders; Anorexia Nervosa; Bulimia Nervosa; binge eating disorder; family therapy; cognitive behavioural therapy

***Correspondence** Dr Bruno Palazzo Nazar, Psychological Medicine, King's College London, Rua Lopes Quintas 100, apt 203 bl2, 22460-010 Rio de Janeiro, Brazil. Tel: +55 21 3647 3649.
Email:
†Joint last authors

Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/erv.2495

Introduction

Time is of the essence in the treatment of eating disorders, as the longer the duration of untreated illness, the worse the prognosis, particularly for Anorexia Nervosa (AN) (Treasure & Russell, 2011). The response to treatment is greatest in the initial stages of the illness, and it diminishes the longer the disorder persists (Treasure, Stein, & Maguire, 2015).

The management of chronic diseases can be enhanced by treatment strategies where the treatment plan is modified according to the patient's history, clinical or psychopathological features and/or their response to previous treatments (Lavori & Dawson, 2008). This is of great interest for clinicians, as it can offer an opportunity to personalise therapy in order to optimise outcome (Wilson, Vitousek, & Loeb, 2000). Early and intermediate markers of treatment response can be used in this individualised medicine approach.

Early response to eating disorders treatment generally refers to a clinically meaningful improvement in behavioural symptoms within the first weeks of treatment (e.g. early binge eating and purging reduction; early weight gain in AN; early changes to dietary restriction). This concept is also referred to as 'rapid' response (MacDonald, Trottier, McFarlane, & Olmsted, 2015). An early response to treatment was one of the strongest predictors found in a recent meta-analysis of remission at the end of treatment and follow-up (Vall & Wade, 2015). Differentiating responders from non-responders early in treatment allows for the possibility of adding potential augmentations to improve outcome in those less likely to remit (Madden et al., 2015). This type of design has been introduced in response to family-based treatment (FBT) in adolescent AN (Doyle, Le Grange, Loeb, Doyle, & Crosby, 2010; Lock et al., 2015).

Interestingly, it seems that early change may predict remission across a variety of treatments, regardless of their duration or modality (Fernández-Aranda et al., 2009; Fernàndez-Aranda et al., 2009).

One limitation of the current literature is the use of many different definitions of early response. For example, Bulik, Sullivan, Carter, McIntosh, and Joyce (1999) defined early response to Bulimia Nervosa (BN) treatment as attainment of remission

status at the end of treatment. This is in contrast to many other studies, which have used strategies with statistical modeling to find symptom reduction and treatment duration cut-offs. Moreover, the definitions for remission often vary (Agüera et al., 2013). As yet there are no absolute criteria for either the timing considered as 'early' or the amount of symptom change used to demarcate an early response. Also, these criteria may vary depending on the population studied, treatment plan and setting.

A recent review and meta-analysis of 34 articles on the rapid response to eating disorder treatment (Linardon, Brennan, & de la Piedad Garcia, 2016) synthesized the size of the effect of various definitions of 'early response' to predict remission (Linardon et al., 2016). They defined early response in terms of any change in eating disorder symptomatology within the first half of the treatment delivered. The authors found that early response was associated with sustained end of treatment and follow-up improvements in eating disorder symptoms, with no moderator effects such as type of eating disorder diagnosis, treatment modality and the criteria used to define an early response. The definition of 'early' and the length of treatment were not examined because of large variability. Also, they did not provide a quantitative synthesis of early weight gain in AN or a qualitative synthesis of BN and BED results. Thus, the concept of early response still requires further investigation and clarification. One method to do this may be to calculate diagnostic test accuracy measures for each eating disorder syndrome.

Diagnostic test accuracy methodology is routinely used to determine reliable cut-off points to predict a disease state (Macaskill, Gatsonis, Deeks, Harbord, & Takwoingi, 2010). In mental health studies (Takwoingi, Riley, & Deeks, 2015), it has been used to establish the reliability of screening and diagnostic measures (Mitchell, Shukla, Ajumal, Stubbs, & Tahir, 2014; Manea, Gilbody, & McMillan, 2015). We have employed this methodology to determine the accuracy of predicting end of treatment remission status from the early response to treatment for AN, BN and Binge Eating Disorder (BED).

The aim of this systematic review is to collate the literature relating to the early response to treatment in eating disorders and conduct a meta-analysis using diagnostic test accuracy methodology to examine the robustness of the early response concept as a predictor of outcome.

Methods

Systematic review

We performed a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) using the PubMed, PsychInfo, Embase, Scopus and Web of Knowledge databases, with the following search terms: ('earl* response' OR 'short-term response' OR 'rapid response') AND ('Eating disorder' OR 'Anorexia Nervosa' OR 'Bulimia Nervosa' OR 'Binge Eating' OR 'EDNOS'). Subsequently, a hand-search of the reference lists from selected papers was analysed, and authors were contacted when further information was not reported in the manuscript.

Articles were considered eligible for inclusion in the review if they were published any time before August 2016 (week 4); if they were published in English, Spanish, Portuguese, French or German languages; if they described criteria used to define early response and remission status. The study selection for screening was performed independently by two different authors (GA, AM) and later discussed with two other authors (BPN, VC). Two authors (GA, LG) extracted data under the supervision of the first author (BPN). All selection procedures are demonstrated in **Figure** 1.

Meta-analysis

The statistical methods developed for meta-analysis of diagnostic test accuracy were employed in order to test the predictive validity of the early response/remission paradigm. A participant was considered positive if remission was achieved. In line with this, early response subjects achieving remission were considered true positives; non-early responders that achieved remission were the false positives; non-early responders that did not achieve remission were the true negatives and the early response subjects that did not remit were the false negatives.

The accuracy measures reported by a diagnostic test accuracy meta-analysis include sensitivity, specificity, positive likelihood ratios and negative likelihood ratios. Sensitivity refers to how well a test can predict a given outcome when this is present (e.g. presence of disease), while specificity points to the capacity of a test to rule out an outcome when it is really absent. The likelihood ratios are used to indicate the probability of a diagnosis using the presence of a marker (Cochrane handbook for DTA reviews, 2010). Likelihood ratios range from zero to infinity, with larger ratios demonstrating increased probability that a sign or test indicates a positive diagnosis; ratios equal to 1 lack any diagnostic value and ratios from 0 to 1 indicate absence of the diagnosis (Attia, 2003). There is a greater chance of obtaining the investigated outcome as the positive likelihood ratio increases. Conversely, it is less likely to find the outcome as the negative likelihood ratio decreases. The last accuracy measure is the Diagnostic Odds Ratio (DOR), which is an indicator of test performance providing a measure of the strength of association between a test and an outcome.

Additionally, the diagnostic test accuracy meta-analysis can combine the different Receiver Operating Characteristic (ROC) curves from each study to produce a synthetic curve, named Summary Receiver Operating Characteristic (SROC). Using the SROC curve, it is possible to produce a summary Area Under the Curve (AUC) measure. This method takes into account the rate of false positives and true positives at different cut-off values, produced by sensitivity and specificity of a test for an outcome. The best test has an AUC of 1, while a poor test has an AUC of 0.5 (Lalkhen & McCluskey, 2008).

In order to include papers in the meta-analysis, we needed data on the true positives, false positives, true negatives and false negatives for any given categorisation of early response and the number of patients achieving remission. Thus, we only included studies that provided information about the number of participants that achieved remission in the early response and non-early response groups, as well as the total number of participants classified as early responders and the number of participants that achieved remission. The accuracy measures were calculated from the pooled values for sensitivity, specificity, positive and negative likelihood ratios and DOR, all obtained using the *Meta-Disc* package (Zamora, Abraira, Muriel, Khan, & Coomarasamy, 2006).

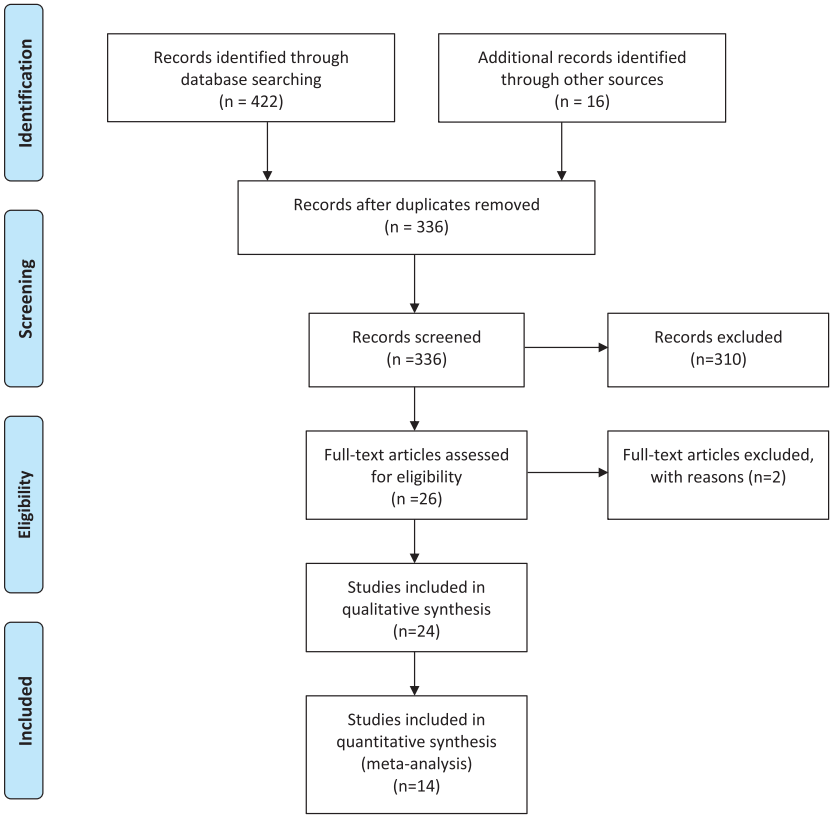


Figure 1. Search flow diagram for research about Early Response in the treatment of eating disorders

Further information, not reported in the published manuscript, was kindly obtained directly from the main authors of Schlup, Meyer, and Munsch (2010), Vaz, Conceição, and Machado (2014), Le Grange, Accurso, Lock, Agras, and Bryson (2014) and MacDonald, Trottier, McFarlane, and Olmsted (2015) in order to complete the meta-analysis.

Publication bias

Risk of bias across studies was examined with Q and I^2 statistics, but because they do not account for specific diagnostic test accuracy biases, such as threshold effects, a scatterplot of studies in the SROC graphic, was examined (Macaskill et al., 2010). Each individual study is represented as a point in space across the SROC graphic, and bias can be analysed through visual inspection.

Results

The search resulted in a final selection of 24 articles for the qualitative synthesis. For the meta-analysis of AN results, only three studies (Le Grange et al., 2014; Madden et al., 2015; Wales et al., 2016) had the variables of interest. Two of these studies (Le Grange et al., 2014; Madden et al., 2015) performed two separate analyses using different definitions of early response, which were both examined. For BN, four studies (MacDonald et al., 2015; Raykos et al., 2014; Thompson-Brenner, Shingleton, Sauer-Zavala, Richards, & Pratt, 2015; Vaz et al., 2014) had information available for synthesis, while seven studies (Grilo, White, Wilson, Gueorguieva, & Masheb, 2012; Grilo, Masheb, & Wilson, 2006; Grilo & Masheb, 2007; Grilo, White, Masheb, & Gueorguieva, 2015; Masheb & Grilo, 2007; Safer & Joyce, 2011; Schlup et al., 2010) were included in the BED meta-analysis.

The demographic characteristics of participants, study design and treatment administered during the original trials are presented in **Table** 1. The definition of early response varied primarily according to the eating disorder diagnosis of interest. The main outcome for AN was the attainment of 95% of Ideal Body Weight (IBW), whereas for BN, it was a percentage reduction in bingeing and/or purging over a variable time period. For BED it was a percentage reduction in bingeing over a period of time, and in some studies weight loss was also included as an outcome. The IBW measure used across studies was based on Center for Disease Control growth charts that are routinely used in clinical settings, with cut-offs defined through epidemiological studies (Kuczmarski et al., 2000). The only study that did not state how they defined the percentage of IBW was Lock, Couturier, Bryson, and Agras, 2006. Some studies required improvements in psychopathology, measured by the EDE-Q, to fall within 1 (Doyle et al., 2010; Le Grange et al., 2014; Madden et al., 2015) or 2 (Lock et al., 2006) standard deviations of community norms in combination with weight gain to define AN remission,

The studies either employed a hypothesis generating approach, where they selected the time point for defining early response from their statistical analysis, or used a hypothesis testing approach, whereby criteria used in previous studies were used to

Table 1 Summary of demographic and clinical characteristics of included studies about Early Response in the treatment of Eating Disorders

Author	Year	Sample size	Sex	Mean age of total sample (SD)	Mean BMI of total sample at baseline (SD)	Diagnoses of sample	Study design	Duration of intervention	Treatment	Control condition
Agras et al.	2000	194	194 F	28.1 (±7.9)	N.R.	BN	Observational before-after study	18 sessions over 16 weeks (twice weekly for the first 2 weeks, weekly thereafter)	Cognitive Behavioural Therapy	N.A.
Doyle et al.	2010	65	58 F 7 M	14.9 (±2.1)	17.0 (±1.7)	AN	Observational before-after study	20 sessions over 12 months	Family-Based Treatment	N.A
Fairburn et al.	2004	220	220 F	N.R.	N.R.	BN	Randomised controlled trial	19 sessions over a period of 20 weeks	Cognitive Behavioural Therapy	Interpersonal Psychotherapy
Grilo et al.	2014	104	73 F 31 M	43.9 (±11.2)	38.3 (±5.6)	BED	Randomised controlled trial	16 weeks (sessions per week N.R.)	Self-Help Cognitive Behavioural Treatment + Sibutramine	Sibutramine Placebo Self-Help Cognitive Behavioural Therapy + Placebo
Grilo et al.	2012	90	56 F34 M	44.89(±9.48)	38.65(±5.70)	BED	Randomised controlled trial	16 group sessions over 24 weeks	Cognitive Behavioural Therapy	Behavioural Weight Loss
Grilo et al.	2007	50	44 F6 M	47.0 (±7.0)	36.0 (±4.7)	BED	Randomised controlled trial	6 sessions over 12 weeks	Cognitive Behavioural Therapy Guided Self-Help + Orlistat	Cognitive Behavioural Therapy Guided Self-Help + Placebo
Grilo et al.	2006	108	84 F24 M	44.0(±8.6)	36.3 (±7.9)	BED	Randomised controlled trial	16 sessions over 16 weeks	Cognitive Behavioural Therapy + Fluoxetine	Cognitive Behavioural Therapy + Placebo
Hartmann et al.	2007	85	N.R.	25.05(±6.51)	13.88 (±1.34)	AN	Observational before-after study	N.R.	Inpatient Treatment	N.A.
Hilbert et al.	2015	205	N.R.	N.R.	N.R.	BED	Randomised controlled trial	16 sessions over 16 weeks followed by 4 fortnightly sessions	Interpersonal Psychotherapy	Self-Help Cognitive Behavioural Therapy Behavioural Weight Loss
Le Grange et al.	2014	121	110 F11 M	14.4 (±1.6)	16.1 (±1.1)	AN	Randomised controlled trial	24 sessions over 12 months	Family-Based Treatment	Adolescent Focused Therapy
Le Grange et al.	2008	80	78 F2 M	16.1(±1.6)	22.1 (±3.0)	BN	Randomised controlled trial	20 sessions over 6 months	Family-Based Therapy	Individual Supportive Psychotherapy
Lock et al.	2006	86	78 F8 M	15.2 (±1.7) long-term family-based therapy ($n = 42$) 15.2 (±1.6) short-term family-based therapy ($n = 44$)	16.0 (±1.6) at identification 17.1 (±1.4) at randomisation	AN	Randomised controlled trial	10 sessions over 6 months (short-term) or 20 sessions over 12 months (long-term)	Family-Based Therapy Short-term	Family-Based Therapy Long-term (20 sessions 12 months)
MacDonald et al.	2015	158	152 F6 M	27.1 (±8.8)	23.2 (±4.4)	BN	Observational before-after study	Open agenda; up to 35–40 h per week (sessions per week N.A. as continuous)	Day Hospital Treatment	N.A.
Madden et al.	2015	82	78F4M	14.67 (±1.41)	N.R.	AN	Randomised controlled trial	20 sessions outpatient FBT	Long-stay Hospitalisation for Weight restoration	Short-stay Hospitalisation for Medical Stabilisation
Marrone et al.	2009	116	114 F2 M	N.R.	N.R.	BN	Randomised controlled trial		Telemedicine Cognitive Behavioural Therapy	Face-to-Face Cognitive Behavioural Therapy

Continues

Table 1. (Continued)

Author	Year	Sample size	Sex	Mean age of total sample (SD)	Mean BMI of total sample at baseline (SD)	Diagnoses of sample	Study design	Duration of intervention	Treatment	Control condition
								20 sessions over 16 weeks (twice weekly for first fortnight, weekly thereafter)		
Masheb et al.	2007	75	61 F14 M	46.0 (±9.1)	35.3 (±6.9)	BED	Randomised controlled trial	6 sessions over 12 weeks + self-help	Cognitive Behavioural Therapy Guided Self-Help	Behavioural Weight Loss Guided Self-Help
McFarlane et al.	2008	58	58 F	29.8 (±9.4)	23.2 (±7.3)	18 = AN16 = BN 24 = EDNOS	Observational before-after study	N.R.	Day Hospital Treatment	N.A.
Raykos et al.	2013	105	N.R.	25.9 (±8.9)	N.R.	17 = AN50 = BN 38 = EDNOS	Observational before-after study	20 sessions over 20 weeks	Enhanced Cognitive Behavioural Therapy	N.A.
Safer et al.	2011	101	86 F15 M	52.1 (±10.6)	N.R.	BED	Randomised controlled trial	20 sessions over 20 weeks	Dialectical Behaviour Therapy	Active Comparison Group Therapy
Schlup et al.	2010	76	76 F	44.5(±10.7)	33.2 (±5.6)	BED	Non-randomized controlled trial	16 sessions over 16 weeks then 6 sessions over 6 months (long-term) or 8 sessions over 8 weeks then 5 sessions over 12 months (short-term)	Cognitive Behavioural Therapy Long-term and Short-term	Cognitive Behavioural Therapy Short-term (8 sessions)
Thompson-Brenner et al.	2015	43	43 F	25.7 (±8.4)	23.5 (±3.5)	BN	Randomised controlled trial	2 sessions per week over 4 weeks	Enhanced Cognitive Behavioural Therapy	N.A.
Vaz et al.	2014	42	42 F	26.3(±7.02)	22.7 (±4.0)	BN	Observational before-after study	1 fortnightly session over 16 weeks	Self-Help Cognitive Behavioural Therapy + Group Meetings	N.A.
Wales et al.	2015	102	82F20M	26.56 (±8.95)	13.07 (±1.42)	AN	Observational before-after study	Open agenda, (sessions per week N.A. as continuous)	Inpatient Treatment, Weight Restoration + Cognitive Behavioural Therapy + Group Therapy	N.A.
Zunker et al.	2010	179	161 F18 M	46.5(±10.2)	39.25 (N.R.)	BED	Randomised controlled trial	15 sessions over 20 weeks	Self-Help Cognitive Behavioural Therapy + Group Meetings	Therapist-led Cognitive Behavioural Therapy Therapist-assisted Cognitive Behavioural Therapy

Legend: N.A. = not applicable; N.R. = not reported; F = female; M = male.

Table 2 Summary of statistical modeling and definitions of Early Response and Remission in the included studies

Author, year	Patient group	Statistical modelling for defining ER	ER measure and time point	Patients within ER category (percentage and number)	Definition of Remission (percentage and number of remitted patients)
Doyle, 2010	Adolescent outpatient	ROC curve and AUC analysis	Weight gain of 1.61% at session 3 and 2.68% at session 4 predicts weight gain at EOT	(% and n N.R.)	Achieving 95% of IBW at EOT 47.7% ($n = 31$) of patients achieved remission
Hartmann, 2007	Adolescent inpatient	Growth curve analysis; non-linear regression; ROC curves	Weight gain of 0.46 BMI points in weeks 1–2 and 0.38 BMI points in weeks 3–4 predicts remission at EOT	(% and n N.R.)	Achieving BMI of 17.5 kg/m^2 or gaining 2 kg (% and n N.R.)
Le Grange, 2014	Adolescent outpatient	ROC curves and AUC analysis; *t*-test and Chi-square tests	Weight gain on any session from 3 to 8 in FBT or 4 to 6 in AFT predicts weight gain at EOT	13.1% ($n = 7$) of patients at the strongest predictor of FBT (session 8) and 35% ($n = 19$) of patients at the strongest predictor of AFT (session 5) showed ER.	Achieving 95% of IBW at EOT + EDE-Q within 1 S.D. of norm 42% ($n = 21$) of patients in FBT and 23% ($n = 12$) of patients in AFT achieved remission
Lock, 2006	Adolescent outpatient	Intention-to-treat analysis; ROC curves and AUC analysis; logistic regression	Weight gain of 2.3 ($\pm$1.9) kg by session 2 4 ($\pm$3.0) kg by session 9; 4.35 ($\pm$2.8) kg by session 10 predicts weight gain at EOT	(% and n N.R.)	Achieving 95% of IBW + EDE-Q within 2 S.D. of norm at EOT 62% ($n = 42$) of patients achieved remission
Madden, 2015	Adolescent outpatient and inpatient	ROC curve analysis; *t*-test and Chi-square tests; logistic regression	Weight gain of 1.8 kg at session 4 predicts remission at EOT	35% ($n = 24$) of patients showed ER	Strict definition: Achieving 95% of IBW at EOT + EDE-Q within 1 S.D. of norm 18.5% ($n = 16$) of patients achieved strict remission Broad definition: 95% EBW at EOT + EDE-Q within 2 S.D. of norm
McFarlane, 2008	Adult outpatient	Kaplan–Meier survival analysis	90% adherence to prescribed meal plan for at least 2 weeks within first 3 weeks	69% of entire Transdiagnostic sample showed ER. ER N.R. by diagnostic category	Partial remission definition: no more than 2 bingeing and/or purging episodes per month for 2 months, achieving and maintain a BMI of 19.5 or higher for two months, and adhering to a prescribed normalised meal plan for two months 48% ($n = 8$) of AN sample achieved remission
Raykos, 2013	Adolescent and adult outpatient	Chi-square tests; ANOVA	A reduction on the EDE-Q global by at least 1.52 points in the first 3–6 weeks	11% ($n = 4$) of patients showed ER	A post-treatment BMI >18.5 A global EDE-Q score within 1 S.D. of norm Abstinence from binge eating and purging for 28 days prior to the end of treatment 41% ($n = 7$) of patients achieved full remission; 29% ($n = 5$) of patients achieved partial remission
Wales, 2015	Adult inpatient	Logistic regression analysis			

Continues

Table 2. (Continued)

Author, year	Patient group	Statistical modelling for defining ER	ER measure and time point	Patients within ER category (percentage and number)	Definition of Remission (percentage and number of remitted patients)
			Weight gain of 0.5—1 kg per week during first 6 weeks predicts remission at EOT	51.7% ($n = 45$) of patients showed ER	Achieving a BMI of 17.5 kg/m^2 82.2% ($n = 37$) of ER and 35.7% ($n = 15$) of NER achieved remission
Fairburn, 2004	Adult outpatient	Results by Agras et al. (2000) to define ER as same group	Reduction of >49% in purging after 4 weeks (session 6) predicts remission	(% and n N.R.)	Abstinence from bingeing and purging in last 28 days prior to EOT 17.7% ($n = 39$) of patients achieved remission
Le Grange, 2008	Adolescent outpatient	ROC curves and AUC analysis	Reduction of >85% in bingeing and purging after 6 weeks (session 6) predicts remission	(% and n N.R.)	Abstinence from bingeing and purging at EOT (% and n N.R.)
MacDonald, 2015	Adult day hospital	ROC curves and AUC analysis	Using frequency criteria: <3 in the first 4 weeks or <1 in the first 2 weeks Using percentage criteria: >99.7% in the first 4 weeks or >95.7% in the first 2 weeks	Using frequency criteria: 65.8% and 61.4% Using percentage criteria: 32.3% and 51.9%	< 1 bingeing and/or purging episode in the last 2 weeks of Day Hospital and < 1 episode in the 1st month after Day Hospital ended 79% ($n = 76$) of patients with ER achieved remission; 41.6% ($n = 25$) of patients with NER achieved remission
Marrone, 2009	Adult outpatient	ROC curves and AUC analysis	44.51% reduction in bingeing at week 6 for telemedicine CBT and 87.21% reduction in bingeing at week 8 for face-to-face CBT	(% and n N.R.)	Abstinence from bingeing and purging in the last 28 days prior EOT 38.8% ($n = 45$) of patients achieved remission
McFarlane, 2008	Adult outpatient	Kaplan–Meier survival analysis	90% adherence to prescribed meal plan for at least two weeks within the first three weeks of treatment	69% of entire transdiagnostic sample – not clear how many of this had BN	Partial remission definition: no more than 2 bingeing and/or purging episodes per month for 2 months, achieving and maintain a BMI of 19.5 or higher for two months, and adhering to a prescribed normalised meal plan for two months 59% ($n = 11$) of BN sample achieved remission
Thompson-Brenner, 2015	Adult outpatient	ROC curves and AUC analysis	65% reduction in purging or 25% reduction of BDI by week 4	For purging, 44.2% ($n = 19$) of patients showed ER. For BDI, 53.4% ($n = 23$) of patients showed ER	Abstinence from bingeing and purging at EOT 44.2% ($n = 19$) of patients achieved remission 79% ($n = 15$) of patients with ER and 29% ($n = 7$) of patients with NER achieved remission
Vaz, 2014	Adult outpatient	Intention-to-treat analysis; logistic regression; survival analysis	Arbitrary, selecting 8-month FU percentage (51% reduction) from Fairburn (2004) as criterion, expanding to binge symptoms as well; at week 3	50% ($n = 21$) of patients showed ER	Abstinence from bingeing and purging 4 weeks prior EOT 52.3% ($n = 22$) of patients achieved remission 28.6% ($n = 6$) of patients with ER and 38% ($n = 8$) of patients with NER achieved remission

Continues

Table 2. (Continued)

Author, year	Patient group	Statistical modelling for defining ER	ER measure and time point	Patients within ER category (percentage and number)	Definition of Remission (percentage and number of remitted patients)
Grilo, 2006	Adult outpatient	ROC curves and AUC analysis	>65% reduction in binge eating episodes by week 4 predicts remission at EOT	44% ($n = 48$) of patients showed ER	Abstinence from bingeing in 28 days prior to EOT 40.7% ($n = 44$) of patients achieved remission 60.4% ($n = 29$) of patients with ER and 25% ($n = 15$) of patients with NER achieved remission
Grilo, 2007	Adult outpatient	ROC curves and AUC analysis	>70% reduction in binge eating episodes by week 4 predicts remission at EOT	42% ($n = 21$) of patients showed ER	Zero binges (OBEs) during the previous month determined by EDE interview 76.2% ($n = 16$) of patients with ER and 31% ($n = 9$) of patients with NER achieved remission
Grilo, 2012	Adult outpatient	ROC curves and AUC analysis	>70% reduction in binge eating episodes by week 4 predicts remission at EOT	67% ($n = 30$) of patients in CBT and 47% ($n = 21$) of patients in BWL showed ER 56.7% ($n = 51$) in total showed ER	Zero binges (OBEs) during the previous 28 days determined by EDE interview 58.8% ($n = 30$) of patients with ER and 17.9% ($n = 7$) of patients with NER achieved remission
Grilo, 2014	Adult outpatient	Definition of ER based on Grillo et al. (2006), which obtained definition by ROC and AUC.	>65% reduction in binge eating episodes by week 4 predicts remission at EOT	47% ($n = 49$) patients showed ER	Zero binges (OBEs) during the previous 28 days determined by EDE interview 51% ($n = 25$) of patients with ER and 9% ($n = 5$) of patients with NER achieved remission.
Hilbert, 2015	Adult outpatient	Definition of ER based on Grilo et al. (2012). This study obtained definition by ROC and AUC.	>70% reduction in binge eating episodes by week 4 predicts remission at EOT	70.7% ($n = 145$) of study patients showed ER 73.4% ($n = 47$) patients in BWL; 74.2% ($n = 49$) patients in CBT and 65.3% ($n = 49$) patients in IPT showed ER	Zero binges (OBEs) during the previous 28 days determined by EDE interview (% and n N.R.)
Masheb, 2007	Adult outpatient	ROC curves and AUC analysis; maximum likelihood linear mixed model analysis; Chi square analysis	>65% reduction in binge eating episodes at week 4 predicts remission at EOT	54.7% ($n = 41$) of patients showed ER	Abstinence from bingeing in the last 28 days prior to EOT. 46.3% ($n = 19$) of patients with ER and 14.7% ($n = 5$) with NER achieved remission
Safer, 2011	Adult outpatient	Chi square analysis	≥ 65% reduction in frequency of binge eating episodes at week 4 predicts remission at EOT following Grilo et al. (2006) and Masheb and Grilo (2007).	40.6% (n=41) of patients showed ER	Abstinence from binge eating, defined as no OBE days (per the EDE) over the 28 days prior to EOT. 70.7% ($n = 29$) patients with ER and 33.3% ($n = 20$) of patients with NER achieved remission
Schlup, 2010	Adult outpatient	Based on definition provided by Grillo and Masheb. (2007), Masheb and Grillo. (2007) and Grillo, Masheb and Wilson. (2006).	>65% reduction in binge eating episodes at week 4 predicts remission at EOT	55% ($n = 42$) of patients showed ER	Abstinence from bingeing in the last 28 days prior to EOT. 51% ($n = 39$) of patients achieved remission

Continues

Table 2. (Continued)

Author, year	Patient group	Statistical modelling for defining ER	ER measure and time point	Patients within ER category (percentage and number)	Definition of Remission (percentage and number of remitted patients)
		These definitions were obtained through ROC curve and AUC analysis.			50% ($n = 21$) of patients with ER and 41.2% ($n = 14$) of patients with NER achieved remission
Zunker, 2010	Adult outpatient	ROC curves and AUC analysis; intention-to-treat analysis	15% reduction in binge eating episodes by week 1 predicts remission at EOT	73.7% ($n = 141$) of patients showed ER	Abstinence from binge eating for 30 days prior to EOT (% and n N.R.)

Legend: N.A. = not applicable; N.R. = not reported; EOT = end of treatment; ER = early response; NER = non-early response; BMI = body mass index; IBW = ideal body weight; EBW = expected body weight; EDE-Q = Eating Disorders Examination Questionnaire.

assign groups. The definitions for response and remission provided by each study, as well as the statistical modeling employed to obtain them and the AUC yielded by such methods, are presented in **Table** 2. The different time points that defined an 'early' response in each study are also presented in **Table** 2.

Early response for Anorexia Nervosa

Although only three studies could be included in the meta analysis, eight studies (Doyle et al., 2010; Hartmann, Wirth, & Zeeck, 2007; Le Grange et al., 2014; Lock et al., 2006; MacDonald et al., 2015; Madden et al., 2015; Raykos, Watson, Fursland, Byrne, & Nathan, 2013; Wales et al., 2016) included patients with AN. The characteristics of all AN studies are summarized in **Tables** 1 **and** 2.

Early weight gains in outpatient adolescents with AN were predictive of remission in studies using FBT (Doyle et al., 2010; Le Grange et al., 2014; Lock et al., 2006), adolescent focused therapy (Le Grange et al., 2014) and cognitive behavioural therapy adapted to eating disorders (CBT-E) (Raykos et al., 2013). The same result was found with inpatient AN, where early weight gains at different time points during the first six weeks of treatment could predict remission (Hartmann et al., 2007; Wales et al., 2016).

Early response studies in Bulimia Nervosa

Altogether nine studies investigated the predictive value of early response to BN treatment, two of which were included in transdiagnostic samples described above (McFarlane et al., 2008; Raykos et al., 2013). Eight studies assessed adult outpatients (Agras et al., 2000; Fairburn, Agras, Walsh, Wilson, & Stice, 2004; Marrone, Mitchell, Crosby, Wonderlich, & Jollie-Trottier, 2009; Thompson-Brenner et al., 2015; Vaz et al., 2014), one study reported results for adolescent outpatients (Le Grange, Doyle, Crosby, & Chen, 2008), one investigated adolescent and adult outpatients (Raykos et al., 2013) and two analysed adult day hospital treatment (MacDonald et al., 2015; McFarlane et al., 2008). All interventions consisted of psychotherapy without medication.

Interestingly, the predictive utility of early response has been demonstrated across different forms of cognitive behaviour therapy (CBT) treatment delivery, either face-to-face (Agras et al., 2000; Agüera et al., 2013; Vaz et al., 2014), through telemedicine (Marrone et al., 2009) or in self-help formats (either guided or not) (Vaz et al., 2014). Other studies also found that early response to interpersonal therapy (Fairburn et al., 2004) in adult BN, and to either individual supportive psychotherapy or FBT (Le Grange et al., 2008) in adolescent BN, could predict remission. It has been argued that longer protocols are needed, as brief psychotherapeutic interventions did not find early responders to achieve remission more frequently (Fernàndez-Aranda et al., 2009).

Reductions in frequency or percentage of binge/purge episodes were also associated with end of treatment remission in adult BN patients receiving day hospital treatment (MacDonald et al., 2015).

Not only is an early reduction in bulimic symptoms indicative of later remission, but reductions in depressive symptoms early in treatment are also predictive of treatment outcome in BN (Thompson-Brenner et al., 2015).

Early response studies in Binge Eating Disorder

Nine studies investigated whether an early reduction in binge eating predicted remission at discharge from outpatient treatment

in adults with BED (Grilo et al., 2012; Grilo et al., 2006; Grilo & Masheb, 2007; Grilo et al., 2015; Hilbert, Hildebrandt, Agras, Wilfley, & Wilson, 2015; Masheb & Grilo, 2007; Safer & Joyce, 2011; Schlup et al., 2010; Zunker et al., 2010). Each of these studies examined the early response to psychological treatments, while three also included an adjunctive pharmacological treatment (Grilo et al., 2006; Grilo & Masheb, 2007; Grilo et al., 2015). Three studies (Grilo et al., 2015; Hilbert et al., 2015; Schlup et al., 2010) used a hypothesis testing approach, while the others used a hypothesis generating approach. For several definitions of early response, Zunker et al. (2010) reported that, only binge reductions at week one predicted remission in participants receiving CBT.

For both CBT and behavioural weight loss interventions, Grilo et al. (2012) and Masheb and Grilo (2007) found that early reductions in binge episode frequency predicted remission at end of treatment. Hilbert et al. (2015) found similar results for CBT in the guided self-help format but not for interpersonal therapy or behavioural weight loss treatment.

Analysing studies using medication associated with psychotherapy, Grilo et al. (2006) found that binge reductions by week 4 predicted remission in a fluoxetine plus CBT trial. Studies using CBT combined with anti-obesity agents found similar results (Grilo & Masheb, 2007; Grilo et al., 2015).

Quantitative synthesis (meta-analysis)

The results from the meta-analysis are presented in **Table** 3. The synthesised graphics for AN, BN and BED accuracy measures are presented in the **online Supporting Information**. The SROC curve for BED is presented as an example in **Figure** 2, and the ones for AN and BN are in the online Supporting Information.

The initial meta-analysis conducted on AN studies included data from Le Grange et al. (2014), Madden et al. (2015) and Wales et al. (2016). The data from AN studies ($n = 3$) (Le Grange et al., 2014; Madden et al., 2015; Wales et al., 2016), using results from week four, provided a pooled sensitivity of 0.57 (95% CI: .49–.66) and a specificity of 0.78 (95% CI: .72–.84). The pooled positive likelihood ratio was 2.43 (95%CI: 1.82–3.25), while the negative likelihood ratio was 0.58 (95% CI: .42–.81). The summary DOR was 4.85 (95% CI: 2.94–8.01). AUC analysis revealed a pooled

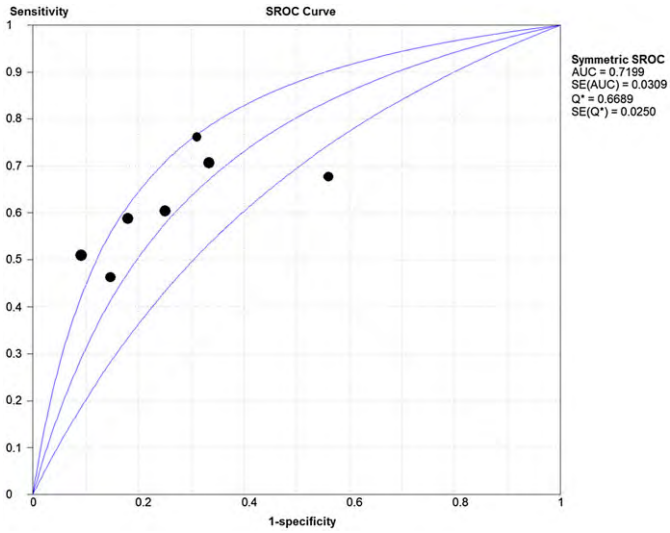


Figure 2. Synthetic receiver operating characteristics curve for BED

Table 3 Summary of diagnostic test accuracy meta-analyses

				Q-statistics		
Group analysed (sample size)	Accuracy measure	Pooled value (95% CI)	Interpretation [#]	X^2	*p*-Value	I^2
AN ($n = 3$)	Sensitivity	.57 (.49–.66)	High specificity/low sensitivity	21.61	<.001	81.5%
	Specificity	.78 (.72–.84)	High specificity/low sensitivity	8.76	.06	54.4%
	Positive likelihood ratio	2.43 (1.82–3.25)	+(15–30)%	1.72	.78	0%
	Negative likelihood ratio	.58 (.42–.81)	− (0–15)%	11.47	.02	65.1%
	Diagnostic odds ratio	4.85 (2.94–8.01)	N.A.	3.29	.51	0%
	AUC (S.E.)	.77 (.03)*	Moderate accuracy	N.A.	N.A.	N.A.
BN ($n = 4$)	Sensitivity	0.64 (0.56–0.71)	Balanced specificity/sensitivity	20.91	<.001	85.7%
	Specificity	0.63 (0.54–0.71)	Balanced specificity/sensitivity	3.88	.27	22.6%
	Positive likelihood ratio	1.67 (1.19–2.33)	+ (0–15)%	4.11	.25	27%
	Negative likelihood ratio	0.62 (0.37–1.02)	− (0–15)%	13.03	.005	77%
	Diagnostic odds ratio	2.75 (1.24–6.09)	N.A.	6.42	.09	53.3%
	AUC (S.E.)	0.67 (0.04)	Low accuracy	N.A.	N.A.	N.A.
BED ($n = 7$)	Sensitivity	0.59 (0.54–0.65)	High specificity/low sensitivity	10.06	.12	40.3%
	Specificity	0.75 (0.69–0.79)	High specificity/low sensitivity	25.85	<.001	76.8%
	Positive likelihood ratio	2.41 (1.69–3.43)	+(15–30)%	15.54	.01	61.4%
	Negative likelihood ratio	0.53 (0.46–0.68)	− (0–15)%	3.81	.70	0%
	Diagnostic odds ratio	5.01 (3.38–7.42)	N.A.	6.38	.38	5.9%
	AUC (S.E.)	0.71 (0.03)	Moderate accuracy	N.A.	N.A.	N.A.

Legend: AUC = area under the curve; S.E. = standard error; N.A. = not applicable.

*Pooled data excluding 1 outlier (Raykos).

[#]For positive likelihood ratio and negative likelihood ratio, refer to approximate % of increase or decrease in presence of outcome; For AUC, refer to diagnostic accuracy of a test identifying outcome.

area of 0.77 (S.E. = .03). This value suggests that the early response is a good predictor of AN remission.

For BN ($n = 4$) (MacDonald et al., 2015; Raykos et al., 2013; Thompson-Brenner et al., 2015; Vaz et al., 2014), only adult studies had data available for the meta-analysis. The summary of the combined sensitivity was of 0.64 (95% CI: 0.56–0.71), while the specificity was 0.63 (95% CI: 0.54–0.71). The positive likelihood ratio for BN studies was 1.67 (95% CI: 1.19–2.33), and the negative likelihood ratio was 0.62 (95% CI: 0.37–1.02). The pooled DOR was 2.75 (95% CI: 1.24–6.09). The combined AUC was 0.67 (S.E. = 0.04), which suggests that it has a moderate capacity for predicting remission.

In the BED studies ($n = 7$) (Grilo et al., 2012; Grilo et al., 2006; Grilo & Masheb, 2007; Grilo et al., 2015; Masheb & Grilo, 2007; Safer & Joyce, 2011; Schlup et al., 2010), the pooled sensitivity was 0.59 (95% CI: 0.54–0.65), with a specificity of 0.75 (95% CI: 0.69–0.79). The positive likelihood ratio for BED studies was 2.41 (95% CI: 1.69–3.43), and the negative likelihood ratio was 0.53 (95% CI: 0.46–0.68). The pooled DOR was 5.01 (95% CI: 3.38–7.42). The combined AUC was 0.71 (S.E. = 0.03), which suggests that it has a fair capacity to classifying later outcome.

Discussion

The aim of this systematic review is to collate the literature relating to the early response to treatment in eating disorders and conduct a meta-analysis using diagnostic test accuracy methodology to examine the robustness of the early response concept as a predictor of outcome.

We were able to synthesize information from 24 studies. The meta-analytic procedures suggest that the characterization of early response as a predictor of remission is more robust for AN and BED, than for BN.

The high specificity and low sensitivity of the pooled accuracy measures from AN studies suggest that a failure to respond to outpatient psychological treatment in the early phase is associated with persistent symptoms at 1 year. The pooled AUC shows that there is a 77% chance that a patient with an early response will have a remission of symptoms at the end of treatment using the current criteria. The therapeutic input or 'dose' ranged across studies, from three to ten sessions. Moreover, the time by which a specified reduction in symptoms was considered to be an 'early response' varied across studies, ranging from the first week to the first three months of treatment. These differences in the criteria used for 'early' may explain some of the variability found in individual weight curves.

Furthermore, uncertainty surrounds how to define remission, and changing the parameters has been found to have a profound effect on outcome (Couturier & Lock, 2006). Most studies in adolescent AN used a strict criteria (≥95% ideal body weight and scores within 1 standard deviation of Eating Disorders Examination community norms).

In BN studies, early response did not strongly predict outcome. An early response in BN only increased the chance of predicting remission by approximately 15%. Both sensitivity and specificity were low. The definitions of early response ranged from a 51 to 95% reduction in binge/purge behaviours, whereas all studies used abstinence from these behaviours as part of the definition of remission. However, the duration of abstinence required in order to be classified as remitted varied across studies; while most studies used a four week period, others used one or two week abstinence as the criteria (Williams, Watts, & Wade, 2012). This variation may account for the low accuracy. The small number of studies precluded the use of a meta-regression.

The results of the meta-analysis for the BED studies demonstrated a high specificity and low sensitivity in predicting remission. There was an approximate 30% increase in the chance of remission in a BED patient with an early response based on the positive likelihood ratio. Using pooled DOR, BED patients with an early response were five times more likely to achieve remission.

Strengths and limitations

There were too few studies available for a meta-regression to examine factors that might explain the variance. Access to individual data would enable the different early response and remission criteria to be modeled. Furthermore, although the early response definitions provided by the eating disorder studies were similar in terms of the time cut-off, they varied with regard to the symptom change required for early response classification. This might explain the heterogeneity and inconsistency of accuracy measures or even their discriminative function for the same disorder.

Clinical implication

These findings suggest that for adolescent AN early weight gain during the first four weeks of psychotherapeutic outpatient treatment is predictive of later improvements in eating disorder psychopathology and attainment of a healthy expected body weight. This holds true regardless of the psychotherapeutic protocol used.

Predicting a good response early in the course of treatment is particularly relevant for AN in which the 'standard dose' of therapy can be high, for example, ranging from 15 × 1.5 h sessions during 12 months (FBT, plus monitoring) in adolescents, through to 40 sessions over 40 weeks in adults (CBT-E) and 20 weeks or more for inpatient care. If it is indeed possible to adapt treatment in the early phase in order to produce change, this would be of great therapeutic benefit. Previous research which investigated the effects of adding intensive parental coaching to standard FBT attested the beneficial impact of such an adaptive treatment strategy (Lock et al., 2015). Other modules that might increase the early response are adding a motivational intervention (Brewin et al., 2016) and modules to increase relatedness through including families (Treasure & Nazar, 2016) and people who have recovered (Cardi et al., 2015). Additionally, adding modules to improving cognitive abilities (e.g. Cognitive Remediation Therapy; Tchanturia, Lounes, & Holttum, 2014) or training modules to increase social connection (Cardi et al., 2015) or eating behavior (Turton, Bruidegom, Cardi, Hirsch, & Treasure, 2016) might be of benefit.

Also, the early development of a strong therapeutic aliance can impact upon outcome in adolescentes receiving treatment for AN (Pereira, Lock, & Oggins, 2006), especially during the first four weeks of inpatient treatment (Sly, Morgan, Mountford, & Lacey, 2013). Elsewhere, evidence suggests that interventions that focus on reducing shame and improving self-compassion early in

treatment also aid in promoting a better outcome (Brewin et al., 2016; Kelly, Carter, & Borairi, 2014).

For BED, results suggest that a reduction of at least 65% in binge eating frequency at the fourth week of treatment (both psychotherapy alone or with adjunctive pharmacotherapy) predicts binge-eating abstinence at the end of treatment.

Conclusion

These studies show that current definitions of early behaviour change have fair accuracy in predicting later symptomatic remission in treatments used for AN and BED. There is less predictive accuracy using the criteria presently used for BN treatment. It may be possible to adapt treatment in the early phase and improve later outcome for AN and BED, but further work is needed to establish whether such an approach is reliable for BN.

Acknowledgement

Janet Treasure is partly funded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Bruno Palazzo Nazar is supported by an international doctoral scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil, and by the Federal University of Rio de Janeiro, Institute of Psychiatry (IPUB-UFRJ).

REFERENCES

Agras, W. S., Crow, S. J., Halmi, K. A., Mitchell, J. E., Wilson, G. T., & Kraemer, H. C. (2000). Outcome predictors for the cognitive behavior treatment of bulimia nervosa: Data from a multisite study. *The American Journal of Psychiatry*, *157*(8), 1302–1308. 10.1176/appi.ajp.157.8.1302.

Agüera, Z., Riesco, N., Jiménez-Murcia, S., Islam, M. A., Granero, R., Vicente, E., et al. (2013). Cognitive behaviour therapy response and dropout rate across purging and nonpurging bulimia nervosa and binge eating disorder: DSM-5 implications. *BMC Psychiatry*, *13*(1), 285. 10.1186/1471-244X-13-285.

Attia, J. (2003). Moving beyond sensitivity and specificity: Using likelihood ratios to help interpret diagnostic tests. *Australian Prescriber*, *26*(5), 111–113.

Cardi, V., Ambwani, S., Crosby, R., Macdonald, P., Todd, G., Park, J., et al. (2015). Self-Help And Recovery guide for Eating Disorders (SHARED): Study protocol for a randomized controlled trial. *Trials*, *16*, 165. 10.1186/s13063-015-0701-6.

Cochrane handbook for DTA reviews. (2010). Retrieved from http://methods.cochrane.org/sdt/handbook-dta-reviews

Couturier, J., & Lock, J. (2006). What is remission in adolescent anorexia nervosa? A review of various conceptualizations and quantitative analysis. *International Journal of Eating Disorders*, *39*(3), 175–183. 10.1002/eat.20224.

Doyle, P. M., Le Grange, D., Loeb, K., Doyle, A. C., & Crosby, R. D. (2010). Early response to family-based treatment for adolescent anorexia nervosa. *The International Journal of Eating Disorders*, *43*(7), 659–662. 10.1002/eat.20764.

Fairburn, C. G., Agras, W. S., Walsh, B. T., Wilson, G. T., & Stice, E. (2004). Prediction of outcome in bulimia nervosa by early change in treatment. *The American Journal of Psychiatry*, *161*(12), 2322–2324. 10.1176/appi.ajp.161.12.2322.

Fernàndez-Aranda, F., Álvarez-Moya, E. M., Martínez-Viana, C., Sànchez, I., Granero, R., Penelo, E., et al. (2009). Predictors of early change in bulimia nervosa after a brief psychoeducational therapy. *Appetite*, *52*(3), 805–808. 10.1016/j.appet.2009.03.013.

Fernández-Aranda, F., Krug, I., Jiménez-Murcia, S., Granero, R., Núñez, A., Penelo, E., et al. (2009). Male eating disorders and therapy: A controlled pilot study with one year follow-up. *Journal of Behavior Therapy and Experimental Psychiatry*, *40*(3), 479–486. 10.1016/j.jbtep.2009.06.004

Grilo, C. M., & Masheb, R. M. (2007). Rapid response predicts binge eating and weight loss in binge eating disorder: Findings from a controlled trial of orlistat with guided self-help cognitive behavioral therapy. *Behaviour Research and Therapy*, *45*(11), 2537–2550. 10.1016/j.brat.2007.05.010.

Grilo, C. M., Masheb, R. M., & Wilson, G. T. (2006). Rapid response to treatment for binge eating disorder. *Journal of Consulting and Clinical Psychology*, *74*(3), 602–613. 10.1037/0022-006X.74.3.602.

Grilo, C. M., White, M. A., Masheb, R. M., & Gueorguieva, R. (2015). Predicting meaningful outcomes to medication and self-help treatments for binge-eating disorder in primary care: The significance of early rapid response. *Journal of Consulting and Clinical Psychology*, *83*(2), 387–394. 10.1037/a0038635.

Grilo, C. M., White, M. A., Wilson, G. T., Gueorguieva, R., & Masheb, R. M. (2012). Rapid response predicts 12-month post-treatment outcomes in binge-eating disorder: Theoretical and clinical implications. *Psychological Medicine*, *42*(4), 807–817. 10.1017/S0033291711001875.

Hartmann, A., Wirth, C., & Zeeck, A. (2007). Prediction of failure of inpatient treatment of anorexia nervosa from early weight gain. *Psychotherapy Research*, *17*(2), 218–229. 10.1080/10503300600702315.

Hilbert, A., Hildebrandt, T., Agras, W. S., Wilfley, D. E., & Wilson, G. T. (2015). Rapid response in psychological treatments for binge eating disorder. *Journal of Consulting and Clinical Psychology*, *83*(3), 649–654. 10.1037/ccp0000018.

Kelly, A. C., Carter, J. C., & Borairi, S. (2014). Are improvements in shame and self-compassion early in eating disorders treatment associated with better patient outcomes? *The International Journal of Eating Disorders*, *47*(1), 54–64. 10.1002/eat.22196.

Lalkhen, A. G., & McCluskey, A. (2008). Clinical tests: Sensitivity and specificity: Fig 1. *Continuing Education in Anaesthesia, Critical Care & Pain*, *8*(6), 221–223. 10.1093/bjaceaccp/mkn041.

Le Grange, D. (2016). Anorexia nervosa in adults: The urgent need for novel outpatient treatments that work. *Psychotherapy*, *Chicago, Ill53*(2), 251–254. 10.1037/pst0000057.

Le Grange, D., Accurso, E. C., Lock, J., Agras, S., & Bryson, S. W. (2014). Early weight gain predicts outcome in two treatments for adolescent anorexia nervosa. *The International Journal of Eating Disorders*, *47*(2), 124–129. 10.1002/eat.22221.

Le Grange, D., Doyle, P., Crosby, R. D., & Chen, E. (2008). Early response to treatment in adolescent bulimia nervosa. *The International Journal of Eating Disorders*, *41*(8), 755–757. 10.1002/eat.20566.

Linardon, J., Brennan, L., & de la Piedad Garcia, X. (2016). Rapid response to eating disorder treatment: A systematic review and meta-analysis. *The International Journal of Eating Disorders*, *49*(10), 905–919. 10.1002/eat.22595.

Lock, J., Couturier, J., Bryson, S., & Agras, S. (2006). Predictors of dropout and remission in family therapy for adolescent anorexia nervosa in a randomized clinical trial. *The International Journal of Eating Disorders*, *39*(8), 639–647. 10.1002/eat.20328.

Lock, J., Le Grange, D., Agras, W. S., Fitzpatrick, K. K., Jo, B., Accurso, E., et al. (2015). Can adaptive treatment improve outcomes in family-based therapy for adolescents with anorexia nervosa? Feasibility and treatment effects of a multi-site treatment study. *Behaviour Research and Therapy*, *73*, 90–95. 10.1016/j.brat.2015.07.015.

MacDonald, D. E., Trottier, K., McFarlane, T., & Olmsted, M. P. (2015). Empirically defining rapid response to intensive treatment to maximize prognostic utility for bulimia nervosa and purging disorder. *Behaviour Research and Therapy*, *68*, 48–53. 10.1016/j.brat.2015.03.007.

Madden, S., Miskovic-Wheatley, J., Wallis, A., Kohn, M., Hay, P., & Touyz, S. (2015). Early weight gain in family-based treatment predicts greater weight gain and remission at the end of treatment and remission at 12-month follow-up in adolescent anorexia nervosa. *The International Journal of Eating Disorders*, *48*(7), 919–922. 10.1002/eat.22414.

Manea, L., Gilbody, S., & McMillan, D. (2015). A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *General Hospital Psychiatry*, *37*(1), 67–75. 10.1016/j.genhosppsych.2014.09.009.

Marrone, S., Mitchell, J. E., Crosby, R., Wonderlich, S., & Jollie-Trottier, T. (2009). Predictors of response to cognitive behavioral treatment for bulimia nervosa delivered via telemedicine versus face-to-face. *The International Journal of Eating Disorders*, *42*(3), 222–227. 10.1002/eat.20603.

Masheb, R. M., & Grilo, C. M. (2007). Rapid response predicts treatment outcomes in binge eating disorder: Implications for stepped care. *Journal of Consulting and Clinical Psychology*, *75*(4), 639–644. 10.1037/0022-006X.75.4.639.

Mitchell, A. J., Shukla, D., Ajumal, H. A., Stubbs, B., & Tahir, T. A. (2014). The Mini-Mental State Examination as a diagnostic and screening test for delirium: Systematic review and meta-analysis. *General Hospital Psychiatry*, *36*(6), 627–633. 10.1016/j.genhosppsych.2014.09.003.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine*, *6*(7) e1000097. 10.1371/journal.pmed.1000097.

Pereira, T., Lock, J., & Oggins, J. (2006). Role of therapeutic alliance in family therapy for adolescent anorexia nervosa. *The International Journal of Eating Disorders*, *39*(8), 677–684. 10.1002/eat.20303.

Raykos, B. C., McEvoy, P. M., Erceg-Hurn, D., Byrne, S. M., Fursland, A., & Nathan, P. (2014). Therapeutic alliance in Enhanced Cognitive Behavioural Therapy for bulimia nervosa: Probably necessary but definitely insufficient. *Behaviour Research and Therapy*, *57*, 65–71. 10.1016/j.brat.2014.04.004.

Raykos, B. C., Watson, H. J., Fursland, A., Byrne, S. M., & Nathan, P. (2013). Prognostic value of rapid response to enhanced cognitive behavioral therapy in a routine clinic sample of eating disorder outpatients. *International Journal of Eating Disorders*, *46*(8), 764–770. 10.1002/eat.22169.

Safer, D. L., & Joyce, E. E. (2011). Does rapid response to two group psychotherapies for binge eating disorder predict abstinence? *Behaviour Research and Therapy*, *49*(5), 339–345. 10.1016/j.brat.2011.03.001.

Schlup, B., Meyer, A. H., & Munsch, S. (2010). A non-randomized direct comparison of cognitive-behavioral short- and long-term treatment for binge eating disorder. *Obesity Facts*, *3*(4), 261–266. 10.1159/000319538.

Sly, R., Morgan, J. F., Mountford, V. A., & Lacey, J. H. (2013). Predicting premature termination of hospitalised treatment for anorexia nervosa: The roles of therapeutic alliance, motivation, and behaviour change. *Eating Behaviors*, *14*(2), 119–123. 10.1016/j.eatbeh.2013.01.007.

Takwoingi, Y., Riley, R. D., & Deeks, J. J. (2015). Meta-analysis of diagnostic accuracy studies in mental health. *Evidence-Based Mental Health*, *18*(4), 103–109. 10.1136/eb-2015-102228.

Tchanturia, K., Lounes, N., & Holttum, S. (2014). Cognitive remediation in anorexia nervosa and related conditions: A systematic review. *European Eating Disorders Review: The Journal of the Eating Disorders Association*, *22*(6), 454–462. 10.1002/erv.2326.

Thompson-Brenner, H., Shingleton, R. M., Sauer-Zavala, S., Richards, L. K., & Pratt, E. M. (2015). Multiple measures of rapid response as predictors of remission in cognitive behavior therapy for bulimia nervosa. *Behaviour Research and Therapy*, *64*, 9–14. 10.1016/j.brat.2014.11.004.

Treasure, J., & Russell, G. (2011). The case for early intervention in anorexia nervosa: Theoretical exploration of maintaining factors. *The British Journal of Psychiatry: The Journal of Mental Science*, *199*(1), 5–7. 10.1192/bjp.bp.110.087585.

Vall, E., & Wade, T. D. (2015). Predictors of treatment outcome in individuals with eating disorders: A systematic review and meta-analysis. *The International Journal of Eating Disorders*, *48*(7), 946–971. 10.1002/eat.22411.

Vaz, A. R., Conceição, E., & Machado, P. P. P. (2014). Early response as a predictor of success in guided self-help treatment for bulimic disorders. *European Eating Disorders Review: The Journal of the Eating Disorders Association*, *22*(1), 59–65. 10.1002/erv.2262.

Wales, J., Brewin, N., Cashmore, R., Haycraft, E., Baggott, J., Cooper, A., et al. (2016). Predictors of positive treatment outcome in people with anorexia nervosa treated in a specialized inpatient unit: The role of early response to treatment. *European Eating Disorders Review: The Journal of the Eating Disorders Association*. 10.1002/erv.2443.

Williams, S. E., Watts, T. K. O., & Wade, T. D. (2012). A review of the definitions of outcome used in the treatment of bulimia nervosa. *Clinical Psychology Review*, *32*(4), 292–300. 10.1016/j.cpr.2012.01.006.

Wilson, G. T., Vitousek, K. M., & Loeb, K. L. (2000). Stepped care treatment for eating disorders. *Journal of Consulting and Clinical Psychology*, *68*(4), 564–572.

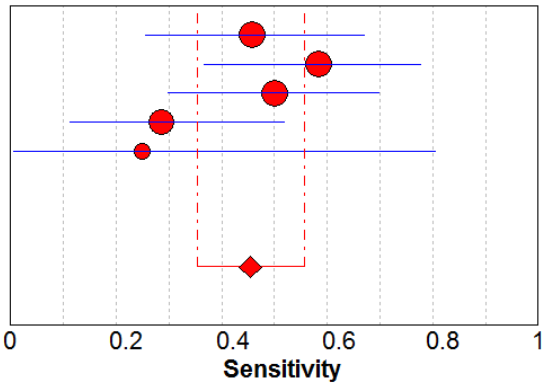
Zamora, J., Abraira, V., Muriel, A., Khan, K., & Coomarasamy, A. (2006). Meta-DiSc: A software for meta-analysis of test accuracy data. *BMC Medical Research Methodology*, *6*(1), 31. 10.1186/1471-2288-6-31.

Zunker, C., Peterson, C. B., Cao, L., Mitchell, J. E., Wonderlich, S. A., Crow, S., et al. (2010). A receiver operator characteristics analysis of treatment outcome in binge eating disorder to identify patterns of rapid response. *Behaviour Research and Therapy*, *48*(12), 1227–1231. 10.1016/j.brat.2010.08.007.

Supporting information

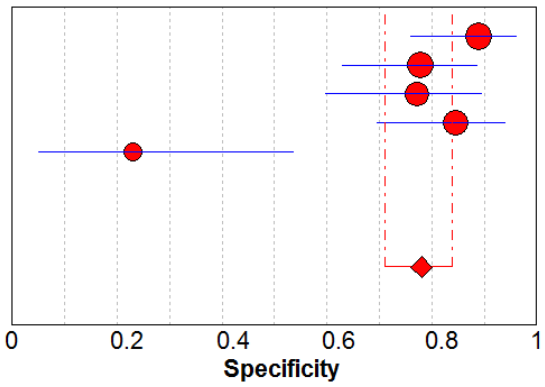
Additional Supporting Information may be found in the online version of this article at the publisher's web site.

Support materials 1 – Meta Analysis of Accuracy Measures for Anorexia Nervosa



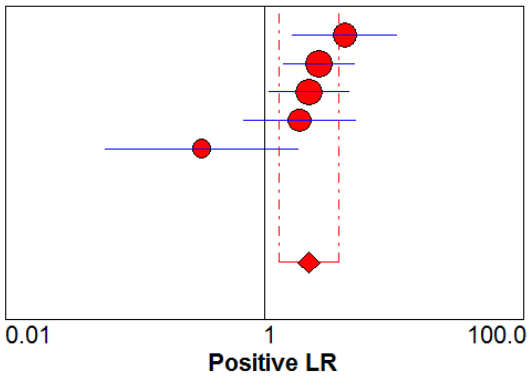
	Sensitivity (95% CI)	
Madden. 2015	0.46	(0.26 - 0.67)
Madden. 2015 (b)	0.58	(0.37 - 0.78)
Le Grange. 2014	0.50	(0.30 - 0.70)
Le Grange. 2014 (b)	0.29	(0.11 - 0.52)
Raykos 2013	0.25	(0.01 - 0.81)

Pooled Sensitivity = 0.45 (0.35 to 0.56)
Chi-square = 5.05; df = 4 (p = 0.2823)
Inconsistency (I-square) = 20.8 %



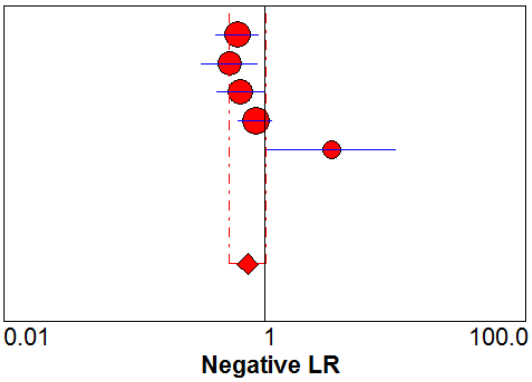
	Specificity (95% CI)	
Madden. 2015	0.89	(0.76 - 0.96)
Madden. 2015 (b)	0.78	(0.63 - 0.89)
Le Grange. 2014	0.77	(0.60 - 0.90)
Le Grange. 2014 (b)	0.85	(0.69 - 0.94)
Raykos 2013	0.23	(0.05 - 0.54)

Pooled Specificity = 0.78 (0.71 to 0.84)
Chi-square = 22.45; df = 4 (p = 0.0002)
Inconsistency (I-square) = 82.2 %



	Positive LR (95% CI)	
Madden. 2015	4.13	(1.62 - 10.50)
Madden. 2015 (b)	2.63	(1.38 - 4.99)
Le Grange. 2014	2.19	(1.06 - 4.49)
Le Grange. 2014 (b)	1.86	(0.68 - 5.05)
Raykos 2013	0.33	(0.06 - 1.82)

Random Effects Model
Pooled Positive LR = 2.18 (1.28 to 3.70)
Cochran-Q = 6.91; df = 4 (p = 0.1409)
Inconsistency (I-square) = 42.1 %
Tau-squared = 0.1490



	Negative LR (95% CI)	
Madden. 2015	0.61	(0.42 - 0.89)
Madden. 2015 (b)	0.54	(0.33 - 0.88)
Le Grange. 2014	0.65	(0.42 - 0.99)
Le Grange. 2014 (b)	0.84	(0.62 - 1.14)
Raykos 2013	3.25	(1.04 - 10.19)

Random Effects Model
Pooled Negative LR = 0.74 (0.53 to 1.02)
Cochran-Q = 10.24; df = 4 (p = 0.0366)
Inconsistency (I-square) = 60.9 %
Tau-squared = 0.0791

Figure S2 - Meta Analysis of ROC curves for Anorexia Nervosa

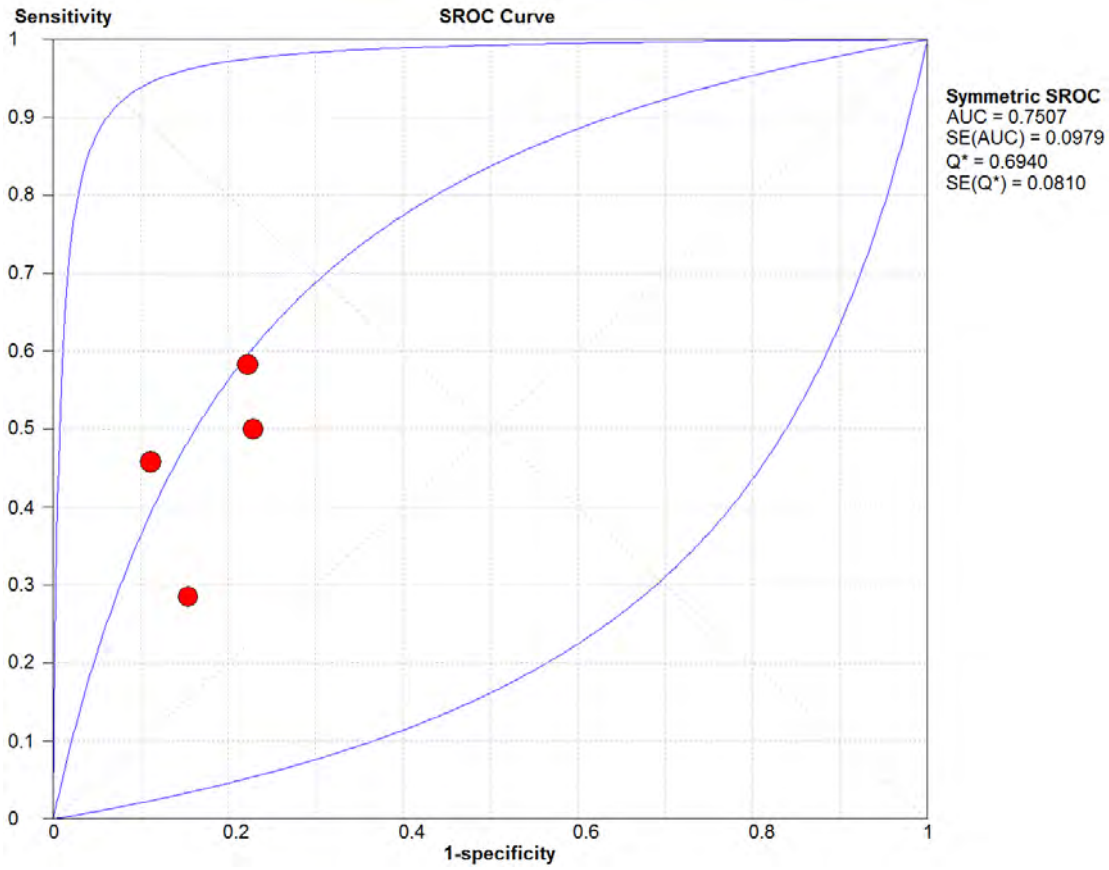
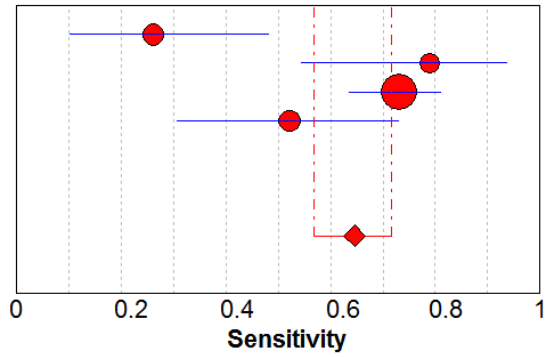
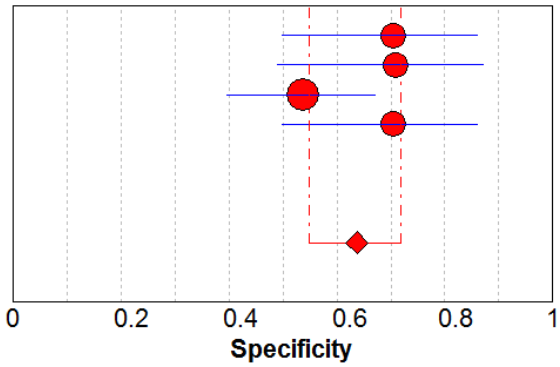


Figure S3 - Meta Analysis of Accuracy Measures for Bulimia Nervosa



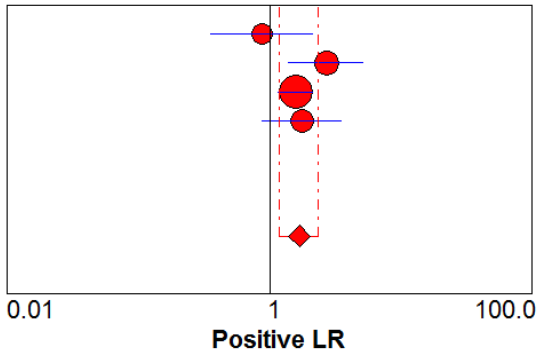
	Sensitivity (95% CI)
Vaz	0.26 (0.10 - 0.48)
Thompson-Brenner	0.79 (0.54 - 0.94)
MacDonald	0.73 (0.63 - 0.81)
Raykos	0.52 (0.31 - 0.73)

Pooled Sensitivity = 0.64 (0.57 to 0.72)
Chi-square = 20.91; df = 3 (p = 0.0001)
Inconsistency (I-square) = 85.7 %



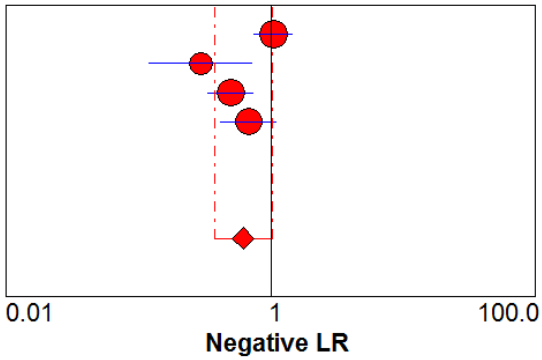
	Specificity (95% CI)
Vaz	0.70 (0.50 - 0.8
Thompson-Brenner	0.71 (0.49 - 0.8
MacDonald	0.54 (0.40 - 0.6
Raykos	0.70 (0.50 - 0.8

Pooled Specificity = 0.64 (0.55 to 0.72)
Chi-square = 3.88; df = 3 (p = 0.2749)
Inconsistency (I-square) = 22.6 %



	Positive LR (95% CI)
Vaz	0.88 (0.36 - 2.17)
Thompson-Brenner	2.71 (1.39 - 5.26)
MacDonald	1.58 (1.16 - 2.15)
Raykos	1.76 (0.87 - 3.55)

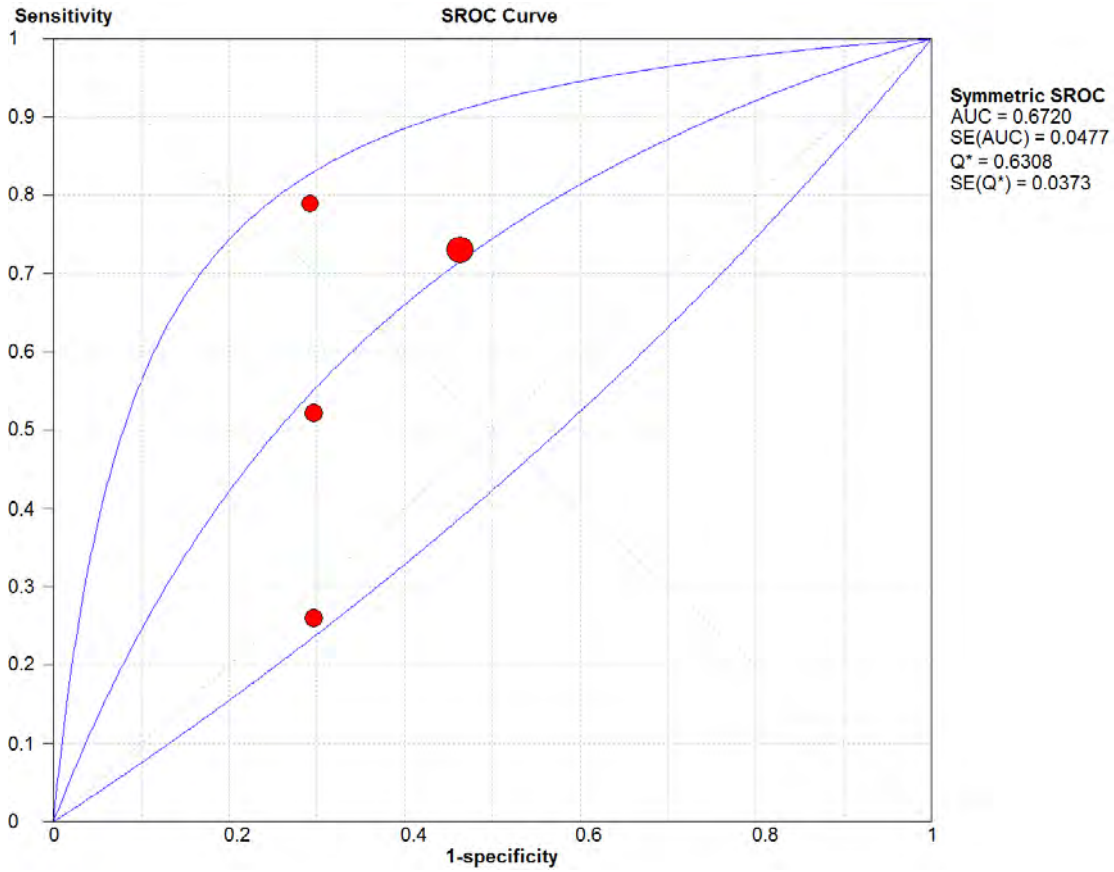
Random Effects Model
Pooled Positive LR = 1.67 (1.19 to 2.34)
Cochran-Q = 4.11; df = 3 (p = 0.2498)
Inconsistency (I-square) = 27.0 %
Tau-squared = 0.0342



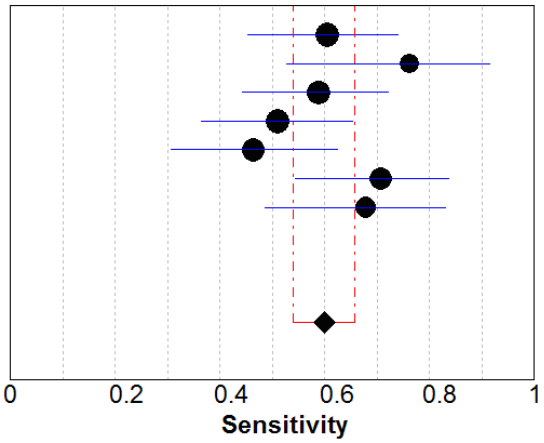
	Negative LR (95% CI
Vaz	1.05 (0.74 - 1.48)
Thompson-Brenner	0.30 (0.12 - 0.74)
MacDonald	0.50 (0.34 - 0.75)
Raykos	0.68 (0.42 - 1.11)

Random Effects Model
Pooled Negative LR = 0.62 (0.37 to 1.03)
Cochran-Q = 13.03; df = 3 (p = 0.0046)
Inconsistency (I-square) = 77.0 %
Tau-squared = 0.1927

Figure S4 - Meta Analysis of ROC curves for Bulimia Nervosa

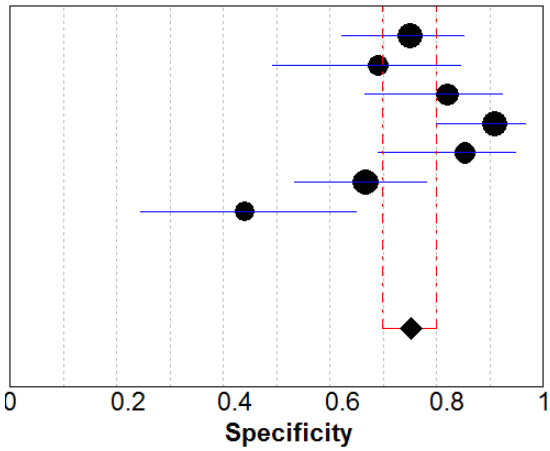


Support materials 2 – Meta Analysis of Accuracy Measures in Binge Eating Disorder



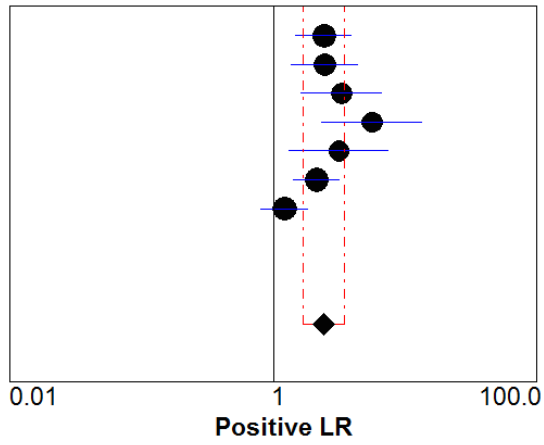
	Sensitivity (95% CI)	
Grilo. 2006	0.60	(0.45 - 0.74)
Grilo. 2007	0.76	(0.53 - 0.92)
Grilo. 2012	0.59	(0.44 - 0.72)
Grilo. 2014	0.51	(0.36 - 0.66)
Masheb. 2007	0.46	(0.31 - 0.63)
Safer. 2011	0.71	(0.54 - 0.84)
Schlup. 2010	0.68	(0.49 - 0.83)

Pooled Sensitivity = 0.60 (0.54 to 0.66)
Chi-square = 10.06; df = 6 (p = 0.1223)
Inconsistency (I-square) = 40.3 %



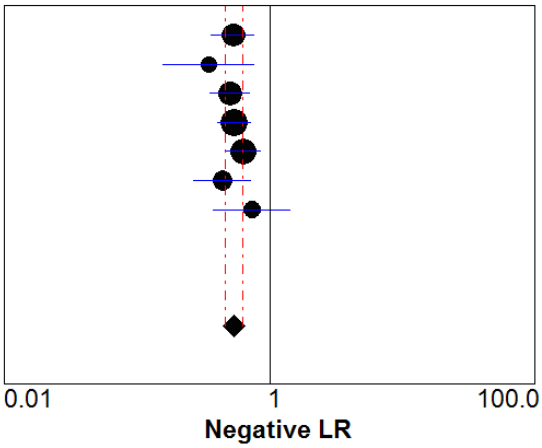
	Specificity (95% CI)	
Grilo. 2006	0.75	(0.62 - 0.85)
Grilo. 2007	0.69	(0.49 - 0.85)
Grilo. 2012	0.82	(0.66 - 0.92)
Grilo. 2014	0.91	(0.80 - 0.97)
Masheb. 2007	0.85	(0.69 - 0.95)
Safer. 2011	0.67	(0.53 - 0.78)
Schlup. 2010	0.44	(0.24 - 0.65)

Pooled Specificity = 0.75 (0.70 to 0.80)
Chi-square = 25.85; df = 6 (p = 0.0002)
Inconsistency (I-square) = 76.8 %



	Positive LR (95% CI)	
Grilo. 2006	2.42	(1.47 - 3.96)
Grilo. 2007	2.46	(1.36 - 4.44)
Grilo. 2012	3.28	(1.61 - 6.66)
Grilo. 2014	5.61	(2.33 - 13.53)
Masheb. 2007	3.15	(1.31 - 7.55)
Safer. 2011	2.12	(1.41 - 3.19)
Schlup. 2010	1.21	(0.79 - 1.85)

Random Effects Model
Pooled Positive LR = 2.41 (1.69 to 3.44)
Cochran-Q = 15.54; df = 6 (p = 0.0164)
Inconsistency (I-square) = 61.4 %
Tau-squared = 0.1322



	Negative LR (95% CI
Grilo. 2006	0.53 (0.36 - 0.77)
Grilo. 2007	0.35 (0.15 - 0.77)
Grilo. 2012	0.50 (0.35 - 0.72)
Grilo. 2014	0.54 (0.40 - 0.73)
Masheb. 2007	0.63 (0.46 - 0.86)
Safer. 2011	0.44 (0.26 - 0.73)
Schlup. 2010	0.73 (0.37 - 1.44)

Random Effects Model
Pooled Negative LR = 0.54 (0.46 to 0.63)
Cochran-Q = 3.81; df = 6 (p = 0.7026)
Inconsistency (I-square) = 0.0 %
Tau-squared = 0.0000

9.5 Artigo:

Interventions for the carers of patients with

Eating Disorders

Curr Psychiatry Rep (2016) 18:16
DOI 10.1007/s11920-015-0652-3

EATING DISORDERS (C GRILO, SECTION EDITOR)

Interventions for the Carers of Patients With Eating Disorders

Janet Treasure[1] · **Bruno Palazzo Nazar**[1]

Abstract The aim of this study is to evaluate the recent literature on carers/parenting interventions for people with eating disorders. Interesting and important new findings are highlighted as well as the implications that this may have for treatment. We have reviewed and critically analysed the recent literature. Close others often play an important role in recognising the early signs of eating disorders and accessing and implementing treatment. Their role in helping with recovery is to give support and hold a united front themselves and with the professional team to avoid those common interpersonal reactions that adversely impact on outcome such as accommodating to the illness and reacting with high expressed emotion (overprotection and hostility). Managing this role is difficult, and coping resources are often strained. Carers ask for and are now getting expert training in skills to manage this role. There is an overlap between carer/parenting interventions and family therapies. The interface with close others is critical both for early recognition and access and implementation of treatment. Interventions which equip families and close others with the skills to manage eating disorder behaviours are showing potential at improving outcomes.

Keywords Eating disorders · Experienced caregivers helping others (echo) · Caregivers · Family intervention · Behaviour change

This article is part of the Topical Collection on *Eating Disorders*

✉ Janet Treasure
janet.treasure@kcl.ac.uk

[1] Psychological Medicine, IoPPN, King's College London (KCL), London SE5 8AF, UK

Introduction

An individual with anorexia nervosa (AN) writing about her personal journey said that if she had to describe the illness in one word it would be isolation [1]. The loneliness of an eating disorder [2] can be ameliorated by family members and other carers. However, social problems of the individual her or himself combined with the secondary social problems that arise from abnormal eating behaviours can make support for recovery difficult.

Social factors are both risk and maintaining factors for eating disorders [3]. Individual vulnerabilities in terms of problems in social cognition are found in the acute phase of AN [4] and include deficits in nonverbal emotional expression [5] and sensitivity to threat and to social comparison [6]. In part, these may be a consequence of starvation but a subgroup of patients with AN have social problems that antedate the eating disorder (ED) and remain after recovery [7, 8]. Also, the offspring of people with ED may present anomalies in aspects of social cognition [9]. Thus, problems in social cognition may be an endophenotype that increases the risk of developing an ED.

Patients with bulimia nervosa (BN) experience interpersonal difficulties before the onset of their ED [10] and bulimic behaviours can impair socio-emotional processing [11]. There is limited evidence about social deficits in obesity and binge eating disorder (BED). Individuals with BED experience difficulties of emotional regulation as high as those in AN or BN patients, with high levels of emotional suppression and low levels of emotional reappraisal [12].

The ED itself has a profound interpersonal impact particularly on the family as the age of onset is usually before the individual has left home [13]. Moreover, as the median duration of illness is 6–7 years [14], the passage through developmental milestones is impeded [15]. Many patients remain

Published online: 19 January 2016

dependent on their families or the state during their lifetime [16]. Close interpersonal relationships change over the trajectory of the illness and the range of interpersonal skills needed to support recovery vary. The developmental age, work and social adjustment and whether an individual is financially and socially independent have an impact on management. Thus, the impact and role of close others is not simple as it depends on these factors [17].

Caregivers are those who provide care to someone who need supervision or assistance during the course of an illness and hereafter the concept refers to family (parents, spouses) or friends. The reaction of carers to an ED depends on aspects of the illness, the context and the carer themselves and in turn these impact on the course of the illness. In the initial stages, the individual does not recognise that she/he is ill and carers can play an important role by being aware of the early signs and facilitating access to treatment. Expressed emotion is a factor that adversely impacts on the prognosis of many chronic illnesses, and eating disorders are no exception [18]. High expressed emotion is defined as a critical, hostile or overprotective, controlling style of behaviour. Also, family members may collude with ED behaviours, by organising the family around eating disorder rules, ignoring or covering up the negative consequences of the behaviours [19]. These behaviours can cause divisions amongst family members. Some carers shoulder an overly high burden, and others become disempowered from contributing to the management of the illness.

Thus, the social aspect of the illness is important for the wellbeing both of the individual and of the wider network. These two aspects are inter-related; however, interventions often have a separate focus on improving the wellbeing of carers or the patient (as in family-based therapy (FBT)) with the family members providing nutritional support and other aspects of care. The burden on caregivers can be overlooked in the latter role [20].

The Carer Giving Experience and Carer Coping

Carers express a need for information about the illness [21, 22]. Unfortunately, some literature contains unhelpful, unproved and simplified hypotheses about the families' role in the illness, which can cause offence and/or guilt [23]. A more helpful aphorism is that 'Families are the solution and not the problem'.

There are many factors that impact on the perceived and actual burden of the caregiving role and how families manage this. The three main domains that impact on caring are the illness itself, the societal reaction to the illness and carer factors, including costs and interactions with services which are illustrated in Fig. 1. Helping the carer to cope with the illness is an essential first step. In the collaborative care model, we use the metaphor of airline safety procedures, in which parents are advised to fix their own oxygen supply first before attending to the child [24].

Aspects of the care giving experience have been summarised in a systematic review [25] which has been recently updated [26]. High perceived burden, and low caregiving efficacy are common and are associated with clinical levels of depression and anxiety [25, 26].

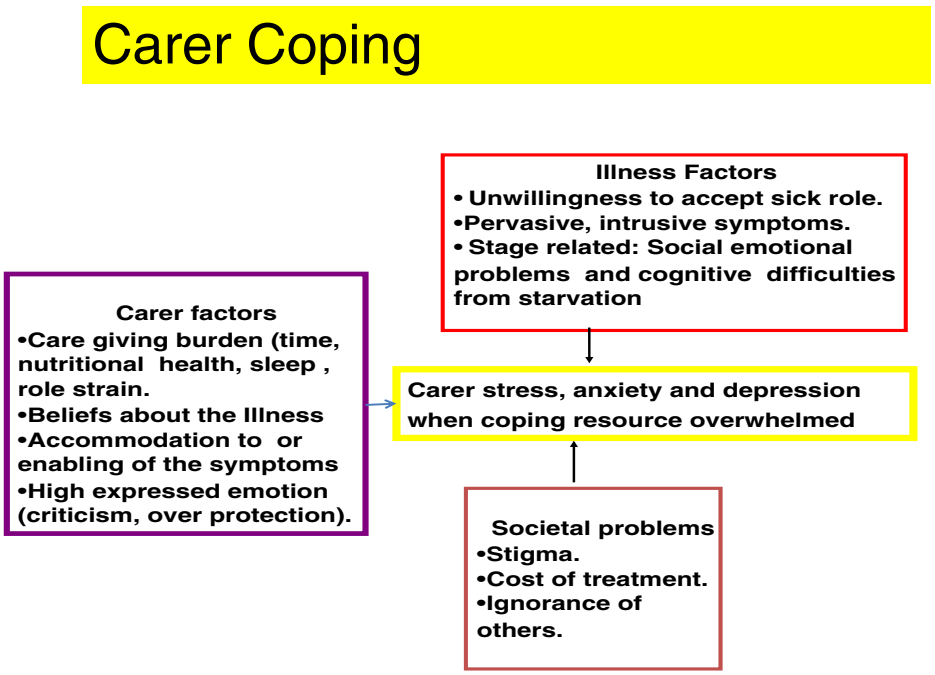


Fig. 1 The three main domains that impact on caring

A variety of specific measures have been developed to tap into the relevant problematic areas, and these are shown in Table 1. These include the Eating Disorders Symptom Impact Scale (EDSIS), which measures burden [27]. The Accommodation and Enabling Scale for Eating Disorders (AESED) which measures the tendency of the family to collude with the patient [28, 29]. The Caregiver Skills (CASK) scale measures modifiable aspects of caregiver behaviour that, according to the New Maudsley model, are thought to improve outcomes [30]. The parents versus anorexia nervosa (PvAN) scale measures parental self-efficacy and is based upon the model of FBT [31]. A new measure of carer coping is available to assess coping strategies, called the Family Coping Questionnaire for Eating Disorders (FCQ-ED) [32]. Several of these instruments assess interpersonal means of managing the symptoms, such as avoidance, collusion, confrontation, compassion and connection.

Eating disorder symptoms are pervasive and intrusive into the family life, and interpersonal relationships become entangled with the disorder in a complex manner. The patients' primary and secondary difficulties in social cognition can make these relationships even more difficult. For example, the reduced level of facial expressivity in ED patients [5, 33] makes it hard for others to appreciate their level of terror. ED patients can be impervious to the impact on close others [34] with the overt life-threatening nature of the symptoms contrasting with the individuals own unwillingness to accept the sick role.

Carers themselves have their own practical and emotional reaction to the illness, which for the most part is helpful but can impede recovery if there is division within the family, collusion with some aspects of the illness and high expressed emotion. Siblings can develop their own problems or leave home prematurely as their needs may be neglected [35]. Carers' distress and means of coping with the caring role may add to the distress of the individual with an ED, and a vicious circle develops [36]. Poor coping lead to distress, and this, in turn, increases the tendency to either overprotect the individual and accommodate to the illness or enter into unproductive fights. Many of the elements of carer stress and coping are universal, and various models have been described [37]. Models of stress have been described for caregivers of other illnesses such as Alzheimer's disease where carer coping style is determined by environmental stress and resources available [38].

Most research has focused on the caregiving for AN, there is little evidence about BN families and hardly any about BED. Caregivers of BN and BED report high levels of depression, anxiety and stress [39].

Change Processes and Techniques

This involves sharing information with carers about how to (1) increase carer coping, (2) effective support and change skills and (3) reduce unhelpful interpersonal behaviours.

1. Models of carer coping.

Social support increases carer coping [40–42], but high levels of contact time reduces resilience [17, 40]. Thus, mothers and partners often have higher levels of burden and distress [41]. Coping may be more difficult if carers have their own eating disorder [43]. Maladaptive coping, expressed emotion and carer needs predicted later carer burden [44].

No matter what the stage of illness, carers ask for information to help with their caregiving role [21, 22, 45]. It is developmentally appropriate for carers of young people to provide meal support whereas this may be less appropriate in the case of adults with a severe enduring illness. Nonetheless, carers are drawn in to provide emotional and financial support in the context of the many problems that can arise with this chronic illness. Moreover, carers play an important role in bridging the isolation and can be actively involved in treatments to ameliorate the secondary consequences [46].

A systematic review of interventions primarily targeting the needs of caregivers and increasing their coping abilities found benefits in terms of reduced burden and distress [47]. However, the quality of many of the studies was limited; the descriptions of the intervention were poorly detailed, and the change processes involved were unclear. Most of the studies focused on carer outcomes only.

2. Skills to manage the illness.

A key part of FBT is empowering the parents to provide nutritional support, and the success of this aspect of therapy is marked by an improvement in weight in the early phase [48, 49]. This can be difficult particularly if the illness has been present for some time when families may resort to critical and controlling strategies [50]. A new adaptation to family-based treatment has a focus on increasing carer skills [51•] to deal with behaviours that have become more entrenched and appears to have benefits.

The New Maudsley collaborative care approach was developed particularly to help families with prolonged illness [24]. This model teaches carers skills such as positive communication using motivational interviewing (MI), meal support and the management of other difficult behaviours. Lay and professional carers can be adequately trained to deliver these MI interventions [52]. This approach has been given in a group format [53] and also in a scalable form with a carer self-management format. DVDs (http://www.succeedfoundation.org) and books for carers describe various behaviour change strategies and how social support can be used to enhance refeeding and other eating disorder symptoms [54, 55]. Moreover, there is evidence that adding an intervention for carers can improve patient outcome, reduce service use and carer burden [56•]. Both carers and patients comment on the

Table 1 A summary of the measures that have been used to examine the needs of the carer themselves and the processes used in caregiving

Scale	Domains	Author, year
Carer burden (EDSIS)	• Nutrition (the problem related to low weight and restricted eating) • Guilt (the assumption of responsibility over the illness) • Dysregulated behaviour (e.g. bingeing, alcohol consumption) • Social isolation (for both the family and the individual)	Sepulveda et al. 2008 [23]
Accommodation and Enabling Scale for Eating Disorders (AESED)	• Avoidance and modifying routines • Providing reassurance • Accepting rituals around meals • Turning a blind eye to unwanted behaviours and allowing family functioning to be controlled	Sepulveda et al. 2009 [24]
Caregiver skills (CASK)	• Bigger picture (the ability to take the long view and not get caught up in the details of the illness) • Self-care (strategies to improve carers own mood and resilience) • Biting-your-tongue (not getting caught up in nagging and bickering about the illness) • Insight and acceptance (the ability to recognise symptoms as part of the illness and to not personalise the behaviours) • Emotional intelligence (the ability to regulate emotional reactions despite being provoked and to have empathy for the other) • Frustration tolerance (to be able to withhold getting drawn into conflict about aspects of the illness)	Hibbs et al. 2015 [25, 26]
Parents versus anorexia nervosa (PvAN)	• Perceptions of the relative influence of parents compared with the anorexia over the child • Acknowledgement of the possession of knowledge and strategies for bringing about recovery • Parental ability to privilege their own expertise and instincts above those of professionals • Parental view that the task of recovery is theirs rather than that of their child • Parental ability to stand up to anorexia despite distress caused for their child • Parental ability to act now in standing up to anorexia rather than become entangled in searching for how they might have caused it	Rhodes et al. 2005 [27]
Carer coping	Five subscales regarding coping mechanisms: • Avoidance • Coercion • Collusion • Information • Positive communication with the patient	Fiorillo et al. 2014 [28]

Legend: this table illustrates the domains of caregiving that have been examined in caring for people with eating disorders

positive changes such as increased understanding and more communion following this form of intervention [57–59].

Interventions that target other socio-emotional aspects of eating disorders [60, 61] and cognitive rigidity have also been developed [62]. Some of those suggest adaptations of novel psychological techniques with standard family interventions for ED but these warrant further investigation. An adaptation of acceptance and commitment therapy [60] integrating FBT skills (re-nourishment exposure to feared foods and situations facilitated by parents) for families of adolescent AN patients has found changes in psychological acceptance of the disorder for all family members and a half of participants attaining full remission. An integration of skills from dialectic behavioural therapy (daily review of symptom change; analysis of behaviour chains; development of crisis plans; emotional regulation skills for the whole family) with FBT (improvement of communications during mealtimes) [63] for families of adolescent bulimia nervosa has also been tried [64]. Other interventions such as cognitive remediation therapy (CRT) focus on AN thinking styles which might impair adherence and outcome of psychological therapies. A CRT self-help model delivered in collaboration of carers showed good acceptability and is also an intervention in which carers role might be important [62].

3. Reducing unhelpful behaviours—interpersonal maintaining patterns.

The cognitive interpersonal model of Schmidt and Treasure (2006) describes how interpersonal processes are impacted by the visibility of AN [65], which can elicit overprotection or conflict [66•]. Carer accommodating behaviour is higher in the early phase of illness and is associated with both patient and carer distress (Rhind, submitted). Carers' distress and carers' expressed emotion (overprotection, criticism and hostility) are similar at all stages of illness [67]. The New Maudsley model of collaborative care reduces both accommodation and expressed emotion [67] and improves patient outcomes [56•].

Conclusion

Interventions for caregivers need to take into account the stage of illness and whether interpersonal maintaining behaviours such as accommodation, expressed emotion or family division are present. A variety of psychoeducational interventions can improve carer coping. FBT successfully teaches skills to manage behaviours present in the early phase of the illness. The New Maudsley approach addresses some of the maintaining

interpersonal behaviours. New interventions specifically targeting partners [68] have been produced, and a consideration of the needs of siblings may also be of value. Most of this work has focused on anorexia nervosa, and more work is needed to understand the needs of close others in relationship to bulimia nervosa and binge eating disorder. This remains a work-in-progress, but the interim conclusions are that the psychosocial and interpersonal aspects of eating disorders play an important role in their management.

Compliance with Ethical Standards

Conflict of Interest Janet Treasure declares that she has no conflict of interest.

Bruno Palazzo Nazar is supported by an international doctoral scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil, and by the Federal University of Rio de Janeiro—Insitute of Psychiatry (IPUB-UFRJ).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. McKnight R, Boughton N. A patient's journey. Anorexia Nervosa Bmj. 2009;339:b3800. doi:10.1136/bmj.b3800.
2. Levine MP. Loneliness and eating disorders. J Psychol. 2012;146(1–2):243–57. doi:10.1080/00223980.2011.606435.
3. Krug I, Fuller-Tyszkiewicz M, Anderluh M, Bellodi L, Bagnoli S, Collier D, et al. A new social-family model for eating disorders: a European multicentre project using a case–control design. Appetite. 2015. doi:10.1016/j.appet.2015.08.014.
4. Caglar-Nazali HP, Corfield F, Cardi V, Ambwani S, Leppanen J, Olabintan O, et al. A systematic review and meta-analysis of 'systems for social processes' in eating disorders. Neurosci Biobehav Rev. 2013. doi:10.1016/j.neubiorev.2013.12.002.
5. Cardi V, Corfield F, Leppanen J, Rhind C, Deriziotis S, Hadjimichalis A, et al. Emotional processing, recognition, empathy and evoked facial expression in eating disorders: an experimental study to map deficits in social cognition. PLoS One. 2015;10(8), e0133827. doi:10.1371/journal.pone.0133827.
6. Cardi V, Di Matteo R, Gilbert P, Treasure J. Rank perception and self-evaluation in eating disorders. Int J Eat Disord. 2014;47(5):543–52. doi:10.1002/eat.22261.
7. Nielsen S, Anckarsater H, Gillberg C, Gillberg C, Rastam M, Wentz E. Effects of autism spectrum disorders on outcome in teenage-onset anorexia nervosa evaluated by the Morgan-Russell outcome assessment schedule: a controlled community-based study. Mol Autism. 2015;6:14. doi:10.1186/s13229-015-0013-4.
8. Rhind C, Bonfioli E, Hibbs R, Goddard E, Macdonald P, Gowers S, et al. An examination of autism spectrum traits in adolescents with anorexia nervosa and their parents. Mol Autism. 2014;5(1):56. doi:10.1186/2040-2392-5-56.
9. Kothari R, Barona M, Treasure J, Micali N. Social cognition in children at familial high-risk of developing an eating disorder. Front Behav Neurosci. 2015;9:208. doi:10.3389/fnbeh.2015.00208.
10. Troop NA, Bifulco A. Childhood social arena and cognitive sets in eating disorders. Br J Clin Psychol / Br Psychol Soc. 2002;41(Pt 2):205–11.
11. Schmidt U, Tiller JM, Morgan HG. The social consequences of eating disorders. In: Szmuckler G, Dare C, Treasure J, editors. Handbook of eating disorders: theory, treatment and research. Chichester, UK: Wiley; 1995.
12. Kittel R, Brauhardt A, Hilbert A. Cognitive and emotional functioning in binge-eating disorder: a systematic review. Int J Eat Disord. 2015;48(6):535–54. doi:10.1002/eat.22419.
13. Micali N, Hagberg KW, Petersen I, Treasure JL. The incidence of eating disorders in the UK in 2000–2009: findings from the General Practice Research Database. BMJ open. 2013;3(5). doi:10.1136/bmjopen-2013-002646.
14. Stoving RK, Andries A, Brixen K, Bilenberg N, Horder K. Gender differences in outcome of eating disorders: a retrospective cohort study. Psychiatry Res. 2011;186(2–3):362–6. doi:10.1016/j.psychres.2010.08.005.
15. Kessler RC, Shahly V, Hudson JI, Supina D, Berglund PA, Chiu WT et al. A comparative analysis of role attainment and impairment in binge-eating disorder and bulimia nervosa: results from the WHO World Mental Health Surveys. Epidemiol Psychiatr Sci. 2013:1–15. doi:10.1017/S2045796013000516.
16. Hjern A, Lindberg L, Lindblad F. Outcome and prognostic factors for adolescent female in-patients with anorexia nervosa: 9- to 14-year follow-up. Br J Psychiatry. 2006;189:428–32. doi:10.1192/bjp.bp.105.018820.
17. Winn S, Perkins S, Walwyn R, Schmidt U, Eisler I, Treasure J, et al. Predictors of mental health problems and negative caregiving experiences in carers of adolescents with bulimia nervosa. Int J Eat Disord. 2007;40(2):171–8. doi:10.1002/eat.20347.
18. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry. 1998;55(6):547–52. doi:10.1001/archpsyc.55.6.547.
19. Treasure J, Schmidt U, Macdonald P. The clinician's guide to collaborative caring in eating disorders: the new Maudsley method. 1st ed. East Sussex: Routledge; 2010.
20. Mair FS, May CR. Thinking about the burden of treatment. BMJ (Clin Res Ed). 2014;349:g6680. doi:10.1136/bmj.g6680.
21. Haigh RT, Treasure J. Investigating the needs of carers in the area of eating disorders: development of the Carer's Needs Assessment Measure (CaNAM). Eur Eat Disord Rev. 2003;11:125–41.
22. Graap H, Bleich S, Herbst F, Trostmann Y, Wancata J, De Zwaan M. The needs of carers of patients with anorexia and bulimia nervosa. Eur Eat Disord Rev. 2008;16(1):21–9.
23. Gull W. Anorexia nervosa (apepsia hysterica, anorexia hysterica). Trans Clin Soc London. 1874;7:22–8.
24. Treasure J, Smith G, Crane A. Skills-based learning for caring for a loved one with an eating disorder: the new maudsley method. The New Maudsley Method: Skills-based Learning for Caring for a Loved One with an Eating Disorder; 2007.
25. Zabala MJ, Macdonald P, Treasure J. Appraisal of caregiving burden, expressed emotion and psychological distress in families of

people with eating disorders: a systematic review. Eur Eat Disord Rev. 2009;17(5):338–49. doi:10.1002/erv.925.
26. Anastasiadou D, Medina-Pradas C, Sepulveda AR, Treasure J. A systematic review of family caregiving in eating disorders. Eat Behav. 2014;15(3):464–77. doi:10.1016/j.eatbeh.2014.06.001.
27. Sepulveda AR, Whitney J, Hankins M, Treasure J. Development and validation of an Eating Disorders Symptom Impact Scale (EDSIS) for carers of people with eating disorders. Health Qual Life Outcomes. 2008;6:28. doi:10.1186/1477-7525-6-28.
28. Sepulveda AR, Kyriacou O, Treasure J. Development and validation of the accommodation and enabling scale for eating disorders (AESED) for caregivers in eating disorders. BMC Health Serv Res. 2009;9:171. doi:10.1186/1472-6963-9-171.
29. Hibbs RR, Rhind C, Sallis H, Goddard E, Raenker S, Aytonc BB, et al. Confirmatory factor analysis for two questionnaires of caregiving in eating disorders. Health Psychol Behav Med. 2014;2(1):322–34.
30. Hibbs R, Rhind C, Salerno L, Lo Coco G, Goddard E, Schmidt U, et al. Development and validation of a scale to measure caregiver skills in eating disorders. Int J Eat Disord. 2015;48(3):290–7. doi:10.1002/eat.22362.
31. Rhodes P, Baillie A, Brown J, Madden S. Parental efficacy in the family-based treatment of anorexia: preliminary development of the Parents Versus Anorexia Scale (PVA). Eur Eat Disord Rev. 2005;13(6):399–405. doi:10.1002/erv.661.
32. Fiorillo A, Sampogna G, Del Vecchio V, Luciano M, Monteleone AM, Di Maso V, et al. Development and validation of the family coping questionnaire for eating disorders. Int J Eat Disord. 2014. doi:10.1002/eat.22367.
33. Caglar-Nazali HP, Corfield F, Cardi V, Ambwani S, Leppanen J, Olabintan O, et al. A systematic review and meta-analysis of 'systems for social processes' in eating disorders. Neurosci Biobehav Rev. 2014;42:55–92. doi:10.1016/j.neubiorev.2013.12.002.
34. Coomber K, King RM. Perceptions of carer burden: differences between individuals with an eating disorder and their carer. Eat Disord. 2013;21(1):26–36. doi:10.1080/10640266.2013.741966.
35. Dimitropoulos G, Klopfer K, Lazar L, Schacter R. Caring for a sibling with anorexia nervosa: a qualitative study. Eur Eat Disord Rev. 2009;17(5):350–65. doi:10.1002/erv.937.
36. Treasure J, Sepulveda AR, Macdonald P, Lopez C, Zabala MJ, Kyriacou O, et al. Interpersonal maintaining factors in eating disorder: skill sharing interventions for carers. Int J Child Adolesc Health. 2008;1(4):331–8.
37. Lazarus R, Folkman S. Stress, appraisal, and coping. New York: Springer; 1984.
38. Kramer BJ. Expanding the conceptualization of caregiver coping—the importance of relationship-focused coping strategies. Fam Relat. 1993;42(4):383–91. doi:10.2307/585338.
39. Tsiaka M, Treasure J, Schmidt U. An examination of parents' distress, and care giving attitudes and behaviours in patients with eating disorders in Greece Submitted.
40. Sepúlveda AR, Graell M, Berbel E, Anastasiadou D, Botella J, Carrobles JA, et al. Factors associated with emotional well-being in primary and secondary caregivers of patients with eating disorders. Eur Eat Disord Rev. 2012;20(1):e78–84. doi:10.1002/erv.1118.
41. Raenker S, Hibbs R, Goddard E, Naumann U, Arcelus J, Ayton A et al. Caregiving and coping in carers of people with anorexia nervosa admitted for intensive hospital care. Int J Eat Disord. 2012;46:346–54
42. Coomber K, King RM. Coping strategies and social support as predictors and mediators of eating disorder carer burden and psychological distress. Soc Psychiatry Psychiatr Epidemiol. 2012;47(5):789–96. doi:10.1007/s00127-011-0384-6.
43. Goddard E, Macdonald P, Sepulveda AR, Naumann U, Landau S, Schmidt U, et al. Cognitive interpersonal maintenance model of eating disorders: intervention for carers. Br J Psychiatry J Mental Sci. 2011;199(3):225–31. doi:10.1192/bjp.bp.110.088401.
44. Coomber K, King RM. A longitudinal examination of burden and psychological distress in carers of people with an eating disorder. Soc Psychiatry Psychiatr Epidemiol. 2013;48(1):163–71. doi:10.1007/s00127-012-0524-7.
45. De Zwaan M, Zipfel S, Herzog W, Herpertz-Dahlmann B, Konrad K, Hebebrand J, et al. EDNET—Eating disorders diagnostic and treatment network. Psychother Psychosom Med Psychol. 2009;59(3/4):110–6.
46. Murray SB, Anderson LK, Rockwell R, Griffiths S, Le Grange D, Kaye WH. Adapting family-based treatment for adolescent anorexia nervosa across higher levels of patient care. Eat Disord. 2015;23(4):302–14. doi:10.1080/10640266.2015.1042317.
47. Hibbs R, Rhind C, Leppanen J, Treasure J. Interventions for caregivers of someone with an eating disorder: a meta-analysis. Int J Eating Disord. 2014. doi:10.1002/eat.22298.
48. Lock J, Couturier J, Bryson S, Agras S. Predictors of dropout and remission in family therapy for adolescent anorexia nervosa in a randomized clinical trial. Int J Eating Disord. 2006;39(8):639–47. doi:10.1002/eat.20328.
49. Doyle PM, Le Grange D, Loeb K, Doyle AC, Crosby RD. Early response to family-based treatment for adolescent anorexia nervosa. Int J Eating Disord. 2010;43(7):659–62. doi:10.1002/eat.20764.
50. Darcy AM, Bryson SW, Agras WS, Fitzpatrick KK, Le Grange D, Lock J. Do in-vivo behaviors predict early response in family-based treatment for anorexia nervosa? Behav Res Ther. 2013;51(11):762–6. doi:10.1016/j.brat.2013.09.003.
51.• Lock J, Le Grange D, Agras WS, Fitzpatrick KK, Jo B, Accurso E, et al. Can adaptive treatment improve outcomes in family-based therapy for adolescents with anorexia nervosa? feasibility and treatment effects of a multi-site treatment study. Behav Res Ther. 2015;73:90–5. doi:10.1016/j.brat.2015.07.015. **This study suggests that adding extra sessions to train carers in more detail about how to implement meal support can improve early treatment response**.
52. Macdonald P, Hibbs R, Rhind C, Harrison A, Goddard E, Raenker S, et al. Disseminating skills to carers of people with eating disorders: an examination of treatment fidelity in lay and professional carer coaches. Health Psychol Behavioral Med. 2014;2(1):555–64. doi:10.1080/21642850.2014.908716.
53. Sepulveda AR, Lopez C, Todd G, Whitaker W, Treasure J. An examination of the impact of "the Maudsley eating disorder collaborative care skills workshops" on the well being of carers: a pilot study. Soc Psychiatry Psychiatr Epidemiol. 2008;43(7):584–91. doi:10.1007/s00127-008-0336-y.
54. Treasure J, Cardi V, Kan C. Eating in eating disorders. Eur Eating Disord Rev J Eating Disord Assoc. 2012;20(1):e42–9. doi:10.1002/erv.1090.
55. Treasure JS, G.; Crane, A. Skills based learning for caring for a loved one with an eating disorder. Hove: Routledge; 2007.
56.• Hibbs RM, Magill N, Goddard E, Rhind E, Raenker S, Macdonald P, et al. Clinical effectiveness of a skills training intervention for caregivers in improving patient and caregiver health following inpatient treatment for severe anorexia nervosa: pragmatic randomised controlled trial. BJPsych Open. 2015;1(1):56–66. **A scalable intervention for carers consisting of a book and DVDs and 10 coaching sessions added to treatment as usual produced gains in patient and carer outcomes with less service use and time spent care giving**.
57. Macdonald P, Murray J, Goddard E, Treasure J. Carer's experience and perceived effects of a skills based training programme for families of people with eating disorders: a qualitative study. Eur Eating Disord Rev J Eating Disord Assoc. 2011;19(6):475–86. doi:10.1002/erv.1065.

58. Macdonald P. A qualitative evaluation of adolescent patients' and their caregivers' perspective following a skills intervention for caregivers of people with eating disorders. Acta Psychopathologica. 2015.
59. Goddard E, Macdonald P, Treasure J. An examination of the impact of the Maudsley collaborative care skills training workshops on patients with anorexia nervosa: a qualitative study. Eur Eating Disord Rev 2011;19(2):150–61. doi:10.1002/erv.1042.
60. Timko CA, Zucker NL, Herbert JD, Rodriguez D, Merwin RM. An open trial of Acceptance-based Separated Family Treatment (ASFT) for adolescents with anorexia nervosa. Behav Res Ther. 2015;69:63–74. doi:10.1016/j.brat.2015.03.011.
61. Zucker NL, Marcus M, Bulik C. A group parent-training program: a novel approach for eating disorder management. Eating Weight Disord EWD. 2006;11(2):78–82.
62. Lang K, Treasure J, Tchanturia K. Acceptability and feasibility of self-help cognitive remediation therapy for anorexia nervosa delivered in collaboration with carers: a qualitative preliminary evaluation study. Psychiatry Res. 2015;225(3):387–94. doi:10.1016/j.psychres.2014.12.008.
63. Anderson LK, Murray SB, Ramirez AL, Rockwell R, Le Grange D, Kaye WH. The integration of family-based treatment and dialectical behavior therapy for adolescent bulimia nervosa: philosophical and practical considerations. Eat Disord. 2015;23(4):325–35. doi:10.1080/10640266.2015.1042319.
64. Murray SB, Anderson LK, Cusack A, Nakamura T, Rockwell R, Griffiths S, et al. Integrating family-based treatment and dialectical behavior therapy for adolescent bulimia nervosa: preliminary outcomes of an open pilot trial. Eat Disord. 2015;23(4):336–44. doi:10.1080/10640266.2015.1044345.
65. Schmidt U, Treasure J. Anorexia nervosa: valued and visible. A cognitive-interpersonal maintenance model and its implications for research and practice. Br J Clin Psychol Br Psychol Soc. 2006;45(Pt 3):343–66.
66.• Treasure JS, Schmidt U. The cognitive-interpersonal maintenance model of anorexia nervosa revisited: a summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. J Eating Disord. 2013;1:13. **This review summarises the theoretical background relating to the individual social risk and maintaining factors and the patterns of interpersonal reactions that maintain the illness**.
67. Goddard E, Salerno L, Hibbs R, Raenker S, Naumann U, Arcelus J, et al. Empirical examination of the interpersonal maintenance model of anorexia nervosa. Int J Eat Disord. 2013;46(8):867–74. doi:10.1002/eat.22172.
68. Bulik CM, Baucom DH, Kirby JS, Pisetsky E. Uniting couples (in the treatment of) Anorexia Nervosa (UCAN). Int J Eat Disord. 2011;44(1):19–28. doi:10.1002/eat.20790.

9.6 Artigo:

High-Frequency rTMS to Treat Refractory Binge Eating Disorder and Comorbid Depression: A Case Report

CNS & Neurological Disorders - Drug Targets, 2014, *13*, 000-000

High-Frequency rTMS to Treat Refractory Binge Eating Disorder and Comorbid Depression: A Case Report

Tathiana Pires Baczynski[1], Carolina Hanna de Aquino Chaim[1], Bruno Palazzo Nazar[2], Mauro Giovanni Carta[3], Oscar Arias-Carrión[4], Adriana Cardoso Silva[1], Sergio Machado[*,1,5,6] and Antonio Egidio Nardi[1]

[1]*Panic & Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro; INCT Translational Medicine (CNPq), Brazil*

[2]*Eating Disorders and Obesity Group, Institute of Psychiatry, Federal University of Rio de Janeiro, Brazil*

[3]*Department of Public Health and Clinical and Molecular Medicine, University of Cagliari, Italy*

[4]*Movement Disorders and Transcranial Magnetic Stimulation Unit, Hospital General Dr. Manuel Gea González, Secretaría de Salud. México DF, México*

[5]*Institute of Phylosophy, Federal University of Uberlândia (IFILO/UFU), Brazil*

[6]*Physical Activity Neuroscience, Physical Activity Sciences Postgraduate Program - Salgado de Oliveira University, Niterói, Brazil*

Abstract: Binge eating disorder (BED) has limited therapeutic options. Repetitive transcranial magnetic stimulation (rTMS) is a modulation technique of cortical excitability that has shown good results in treating certain psychiatric disorders by correcting dysfunctional cortical regions. We hypothesize that rTMS could be an alternative therapy for BED through potential modulation action on frontostriatal abnormalities and dopaminergic pathways noted by neuroimaging. We report the case of a young woman presenting refractory BED and comorbid depression treated with 20 sessions of rTMS for 30 minutes over the left dorsolateral prefrontal cortex at 10 Hz for about a month (2400 stimuli per day). She answered two self-report questionnaires, the Binge Eating Scale (BES) and the Beck Depression Inventory (BDI). Before rTMS treatment, the BES score was 38, and the BDI score was 42. Three days after rTMS treatment, the BES score was 27 and the BDI score was 27, and the patient referred to no binge eating episodes for that week. Therefore, rTMS could offer a new option of treatment for BED and comorbid depression.

Keywords: Binge eating disorder, depression, dopamine, frontostriatal pathways, obesity, repetitive transcranial magnetic stimulation.

INTRODUCTION

Binge eating disorder (BED) was included in Diagnostic and Statistical Manual of the American Psychiatric Association – fifth edition (DSM-V) [1] as a valid diagnostic, in the eating disorders (ED) section. It was previously considered a residual ED, placed in the eating disorders not otherwise specified category. BED is characterized by recurrent binge eating episodes, in which patients experience loss of control over the type and amount of food ingested, and objectively ingest a larger than expected amount of food in a small time period (e.g., 2 hours) [2]. For a BED diagnosis, patients must present binge eating episodes and markers of cognitive and behavioral dyscontrol over eating habits, as listed by DSM-V [1]. Patients with BED present binge eating episodes at least twice a week for a minimum period of three months, and do not engage in recurrent and inadequate compensatory behaviors (e.g., self-induced vomiting and laxative and diuretic abuse) after binge eating episodes, as bulimia nervosa (BN) patients [2-4]. The prevalence of BED in the general population is approximately 4%, and in obese people attending weight control programs, it is approximately 30% [4]. The main psychiatric comorbidities associated with BED are affective disorders and alcohol or substance abuse disorders [3]. A systematic review of BED comorbidity, conducted by Araújo *et al.* [5], found that the majority of studies observed a significant association between depression and BED, which is also exemplified by our report.

The treatment options for BED include psychotherapy and pharmacotherapy, but even with these interventions combined, effectiveness is only moderate and relapse rates are high [6-10]. A meta-analysis by Vocks *et al.* [9] found that cognitive behavioral interventions had significant effects on the reduction of binge eating episodes, and should be recommended as a first-line treatment. Pharmacotherapy studies have been conducted using mainly antidepressants, anticonvulsants and antiobesity drugs [3]. Two meta-analyses [9, 11] and one systematic review [8] agreed that

*Address correspondence to this author at the Institute of Psychiatry, Federal Univesity of Rio de Janeiro (IPUB/UFRJ), Brazil;
Tel: ??????????????????????; Fax: ????????????????????????????;
E-mail: secm80@gmail.com

1871-5273/14 $58.00+.00

pharmacotherapies exhibited medium effects in the reduction of binge eating. Many guidelines suggest antidepressants, especially selective serotonin reuptake inhibitors, as a first-line choice for BED pharmacological therapy [3]. However, multicenter trials showed better binge eating remission rates with sibutramine and topiramate than with selective serotonin reuptake inhibitors, when compared to placebo [12-14].

Because present treatment options for BED are scarce and present many limitations, newer and safer options should be investigated. In this context, repetitive transcranial magnetic stimulation (rTMS) has been proved to be a technique capable of modulating cortical excitability, producing therapeutic effects when acting over a dysfunctional area, as has been established for depression [15, 16] and auditory hallucinations [17].

Searching for dysfunctional regions that could become a focus for the treatment of rTMS, we conducted a review of articles about the neurobiology of BED. Obesity and BED have both been correlated with poor impulse inhibition, which could lead to overeating episodes. Neuroimaging studies in obese BED patients have shown frontal cortex dysfunction in the areas responsible for cognitive processes and inhibitory control, as well as alterations in striatum activity, which could impair the physiological processes associated with reward, satiety and pleasure [18]. BED has been linked to an imbalanced and exaggerated response to suggestions of food, involving reward systems, motor planning and cognitive control [19]. This pattern, which is also related on a lesser scale to cases of obesity without BED, perpetuates a cycle that causes excessive intake of high-calorie food, which promotes ingestive reward deficits that in turn trigger even more episodes of excessive food intake [19].

Studies in obese patients have shown evidence of increased blood flow in the regions of the striatum and also in the orbitofrontal cortex in response to pictures of food, and this type of response could be associated with susceptibility to binge eating and consequent weight gain [18-22]. However, there is also a decrease in striatal BOLD signal responses related to the ingestion of food [23], which means that excessive intake of food is related to hypoactivity of the striatum but also to frontostriatal hyperactivity in the presence of visual and olfactory food cues [24]. A very similar pattern in functional neuroimaging has been observed in individuals with addiction [18, 25].

Dopamine is a neurotransmitter that has shown itself to be involved in feeding behaviors and also in the physiopathology of both obesity and BED [26]. The presentation of food cues without intake leads to the release of striatal dopamine [4, 27] and it has already been suggested that an excessive food intake in humans could be a way of compensating for dopaminergic deficiency [4, 28]. Morbidly obese individuals showed a reduction in D2 receptors [29, 30], and obese BED patients showed dopaminergic hyperactivity when there was presentation of food, in comparison with controls [4]. Volkow *et al.* [31] suggested that there is a process of modulation of the striatum over the prefrontal cortex by dopaminergic pathways, after comparing neuroimaging exams of obese individuals and controls. The availability of striatal D2 receptors was lower than in controls, and these data were positively correlated with the metabolism of the prefrontal cortex, the medial orbitofrontal cortex, the anterior cingulate gyrus and the somatosensory cortex [31]. Similar results have been shown in studies conducted in rats. The low density of D2 receptors among these rodents was a predictive factor for weight gain, while rats with a high density of striatal D2 receptors showed significantly lower body weight [18].

In this article, we report the case of a young woman suffering from refractory BED and comorbid major depressive disorder. Based on the findings mentioned above, we decided to use high-frequency stimulation over the left dorsolateral prefrontal cortex (DLPFC) to treat both the depression and BED. Extensive literature has already revealed the efficacy of rTMS in the treatment of depression [15, 16]. We also believe that rTMS could have therapeutic results for BED. Strafella *et al.* demonstrated that excitatory stimulation over left DLPFC causes ipsilateral striatal dopamine release, which could correct the striatal dopaminergic deficiency suggested above. This frontal dopaminergic deficiency could account for the continuous pursuit of immediate reward with binge eating, to satisfy this internal deficit [32]. Volkow *et al.* correlated the low availability of striatal D2 receptors with hypometabolism of prefrontal region, in particular of DLPFC [31]. Accordingly to these findings, we also attempted to intervene in altered frontostriatal circuitry in order to normalize inhibitory control and rectify inappropriate behavioral response tendencies.

METHODS

The experimental protocol was approved by the Review Board of the Institute of Psychiatry, Federal University of Rio de Janeiro. The patient signed a written consent form.

The patient was a 19-year-old, left-handed, female university student who sought treatment for binge eating and depression. During the psychiatric evaluation, she presented the DSM-V criteria for current diagnoses of BED and for a major depressive episode. The patient had a body mass index (BMI) of 48 kg/m^2 and had already treated BED with sibutramine 15 mg/day for more than 10 months with poor response. She had been taking fluoxetine 60 mg/day and topiramate 200 mg/day for approximately 18 months, also without satisfactory results. She had also received psychodynamic psychotherapy for 5 years with a poor response on binge eating and depressive symptoms. By the time of the present evaluation, the patient had been attending cognitive behavioral therapy for 4 months and family therapy for 2 months, without response regarding the binge eating and depressive symptoms. Additionally, the patient stated that her present medication did not have any clinical effects, and she used it irregularly some weeks. She wished to undergo gastric bypass surgery, but was refused because of binge eating severity, and poor adherence to pre-surgical care. Because her psychiatric status did not respond to psychopharmacological or psychotherapy, we invited her to receive rTMS.

The patient was discontinued from her medication 1 month before baseline evaluation, leaving only fluoxetine 20 mg/day, and stated she didn't note any symptomatic

difference. After initiating rTMS, no other strategies were added. Repetitive transcranial magnetic stimulation was applied to the left DLPFC, using F3 of the international 10-20 EEG system, for 20 stimulation sessions of 30 minutes each, spread over 4 weeks and 2 days. A Neuro-MS Magnetic Stimulator (Neurosoft - Equipamentos Médicos, Brasil), with an air-cooling figure-eight coil, was used. The stimulation was administered at 10 Hz for 4 s, with 26 s between trains, with intensity of 120% of the motor threshold for 30 minutes (2400 stimuli per day). The patient received weekly psychiatric evaluations. Clinical assessments were all performed by the same psychiatrist (a senior supervisor) comprising side effects evaluations, weekly binge eating frequency and eating disorder symptoms, evaluation of global psychopathology (also regarding the mood disorder) and the Clinical Global Impression – Severity Scale (CGI-S). Additionally, she was administered two self-report questionnaires: the Binge Eating Scale (BES) to evaluate binge eating severity; and the Beck Depression Inventory (BDI) to evaluate depressive symptomatology at rTMS baseline (1 week before the beginning of rTMS), during rTMS treatment (rTMS day 5, rTMS day 10 and rTMS day 20) and at endpoint (3 days after the last stimulation).

RESULTS

Data on number of binge eating episodes per week as well as the CGI-S scores collected in weekly assessments can be seen in the figure below (Fig. **1**) as well as the scores of BES and BDI questionnaires (Fig. **2**). Her BMI did not change during treatment. Clinically, her mother reported a significant enhancement in her mood. There was also an improvement in self-directedness, expressed as attending rTMS sessions without being accompanied and starting a drawing course after the second week of stimulation.

DISCUSSION

To our knowledge, this is the first article specifically about a case of BED and comorbid depression treated with rTMS for 1 month.

Previous studies have been published using rTMS as a therapeutic tool for eating disorders in which binge eating episodes also occur, particularly BN. Mangweth *et al.* [33] formulated the affective spectrum disorder model after a large family study, based on the hypothesis that certain psychiatric disorders, such as BN and depression, share a common link in their etiology. Supported by this model [33] and by the theory of imbalance in serotonin activity [34] and prefrontal hypometabolism revealed by functional imaging techniques [35] in patients with bulimia, Hausmann *et al.* [34] performed high-frequency rTMS over the left DLPFC in a bulimic patient for 2 weeks (10 sessions). They reported that the patient recovered completely from binging and purging symptoms.

In 2008, Walpoth *et al.* [33], also based on the affective spectrum disorder model and on single photon emission computed tomography scans pointing to prefrontal hypometabolism [35, 36] associated with bulimia, investigated excitatory stimulation over the left DLPFC [37]. Fourteen women with BN participated in a randomized, controlled, double-blind assay for 4 weeks, which found no significant difference in the reduction of binge episodes between sham and active TMS.

Another interesting study was published in 2010 by Van den Eynde *et al.* [38]. Thirty-eight right-handed people with bulimia-type eating disorders (BN and eating disorder not otherwise specified, including BED) were randomly allocated to receive one session of real or sham high-frequency rTMS over the DLPFC, to evaluate reductions in craving. Craving is a binging behavior precipitant [39, 40], and it is also a characteristic of bulimic eating disorders and addiction [38]. A dysfunction of the DLPFC has been suggested to underpin craving [41]. The outcome was that rTMS reduced cue-induced food craving in bulimic eating disorders.

Downar *et al.* [42] reported a case of a woman with severe and refractory BN and comorbid depression, who underwent rTMS over the dorsomedial prefrontal cortex, with full remission from depression and binge-eating/purging episodes for more than 2 months. The authors highlighted that neuroimaging studies have shown the dorsomedial prefrontal cortex to play an important role in impulsive control and that it is underactive in BN.

This study demonstrates partial, but very significant, remission of symptoms of depression and binge eating, never

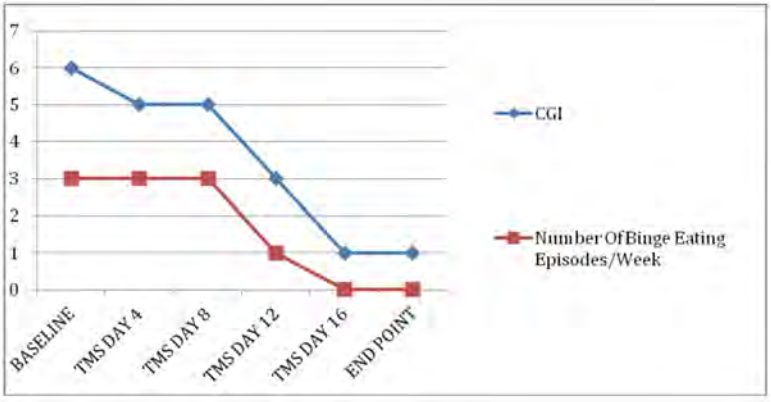


Fig. (1). Clinical Global Impression (CGI-S) scores and weekly binge eating frequency at baseline (1 week before rTMS), during 4 weeks of rTMS (TMS Day 4, TMS Day 8, TMS Day12 and TMS Day 16) and at endpoint follow up (3 days after TMS).

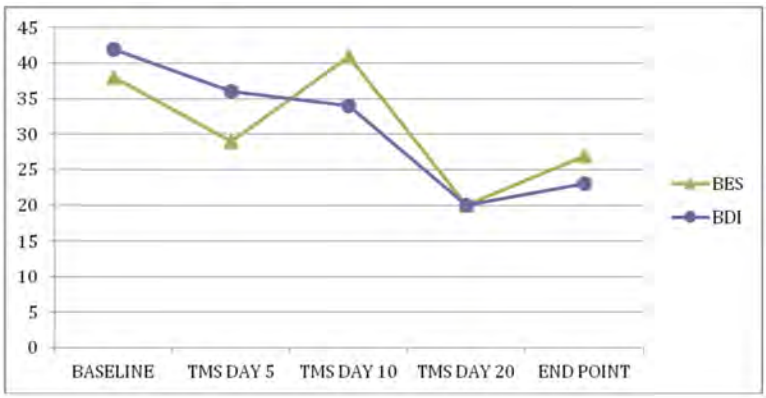


Fig. (2). Binge Eating Scale (BES) and Beck Depression Inventory (BDI) scores at baseline (1 week before TMS), during rTMS treatment (TMS day 5, TMS day 10 and TMS day 20) and at endpoint follow up (3 days after TMS).

observed before in the same patient with other treatments, including psychotherapy and psychopharmacotherapy. Another important piece of information is that the patient referred to no binge eating episodes during the last 2 weeks of evaluation, which could signal an improvement even greater than that at the end of treatment. We did not observe a difference in BMI between before and after rTMS. However, Vocks *et al.* [9] also concluded in their meta-analysis that pharmacological treatments and behavioral interventions do not appear to promote considerable weight reductions in patients with BED.

An interesting point to be discussed in this article concerns the handedness of the patient. A first important issue is while handedness is associated with obvious differences in brain hemispheric dominance related to various neurological functions, there is no clarity on whether handedness is also related to hemispheric dominance in the prefrontal cortex [43]. Another finding is left-handedness uses to be exclusion criterion in most rTMS research or the studies do not report participants' handedness [43]. Thus, there is a lack of knowledge in the literature about the existence or not of difference between behavioral, emotional and cognitive effects after rTMS over DLPFC among right and left-handed individuals [43]. Van den Eynde *et al.* (2010) conducted a complementary research to his aforementioned study and reported a new experiment with one session of real high-frequency rTMS over the left DLPFC in seven left-handed women with bulimic disorders, which showed a trend for mood to deteriorate and for craving to reduce after rTMS [43]. No significant differences were found between these left-handed women and the right-handed women who received real rTMS over left DLPFC in the previous study, used as control, except for mood. In contrast, mood improved in right-handed people. In the current case report, we did not observe the same findings, maybe because of the duration of the intervention. Our left-handed patient also showed evident improvement in depressive symptoms as mentioned above, as well as reduced of binge eating symptoms after excitatory rTMS over left DLPFC for about a month.

CONCLUSION

Further controlled, randomized studies, as well as larger studies, are required to evaluate rTMS treatment in BED. However, this case report could shed light on the pathophysiology of BED, emphasizing the important role of frontostriatal pathways and the neurotransmitter dopamine. The DLPFC seems to be a promising region of stimulation, considering its dysfunction in imaging exams in patients with obesity [31] and the potential correction of striatal dopaminergic hypoactivity with the release of striatal dopamine after rTMS over left DLPFC [32], as well as some evidence from this report and from studies in bulimic patients with binge eating episodes [34,38]. Nevertheless, we also suggest that new research could be conducted considering other regions of stimulation, such as the orbital prefrontal cortex. This structure has been implicated by neuroimaging in episodes of overeating [18-22, 31].

CONFLICT OF INTERESTS

The authors declare no competing financial interests.

ACKNOWLEDGEMENTS

Declared none.

LIST OF ABBREVIATIONS

BED = Binge eating disorder
BES = Binge Eating Scale
BDI = Beck Depression Inventory
BMI = Body mass index
BN = Bulimia nervosa
DLPFC = Dorsolateral prefrontal cortex
ED = Eating disorder
rTMS = Repetitive transcranial magnetic stimulation

REFERENCES

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-V, edited by American Psychiatric Association (Washington, DC): 2013.
[2] Claudino AM, Borges MBF. Diagnostic criteria for eating disorders: evolving concepts. Rev Bras Psiquiatr 2002; 24: 7-12.
[3] Treasure J, Claudino AM, Zucker N. Eating disorders. Lancet 2010; 375: 583-93.

[4] Wang GJ, Geliebter A, Volkow ND, *et al*. Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity 2011; 19: 1601-8.

[5] Araújo DM, Santos GF, Nardi AE. Binge eating disorder and depression: a systematic review. World J Biol Psychiatry 2010; 11: 199-207.

[6] Shapiro JR, Berkman ND, Brownley KA, *et al*. Bulimia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 321-36.

[7] Mitchell JE, Agras S, Wonderlich S. Treatment of bulimia nervosa: where are we and where are we going? Int J Eat Disord 2007; 40: 95-101.

[8] Brownley KA, Berkman ND, Sedway JA, Lohr KN, Bulik CM. Binge eating disorder treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 337-48.

[9] Vocks S, Tuschen-Caffier B, Pietrowsky R, Rustenbach SJ, Kersting A, Herpertz S. Meta-analysis of the effectiveness of psychological and pharmacological treatments for binge eating disorder. Int J Eat Disord 2010; 43: 205-17.

[10] Downar J, Sankar A, Giacobbe P, Woodside B, Colton P. Unanticipated Rapid Remission of Refractory Bulimia Nervosa, during High-Dose Repetitive Transcranial Magnetic Stimulation of the Dorsomedial Prefrontal Cortex: A Case Report. Front Psychiatry 2012; 3: 30.

[11] Reas DL, Grilo CM. Review and meta-analysis of pharmacotherapy for binge-eating disorder. Obesity 2008; 16: 2024-38.

[12] Appolinario JC, Bacaltchuk J, Sichieri R. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Arch Gen Psychiatry 2003; 60: 1109-16.

[13] Claudino AM, de Oliveira IR, Appolinario JC, *et al*. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. J Clin Psychiatry 2007; 68: 1324-32.

[14] Wilfley DE, Crow SJ, Hudson JI, *et al*. Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. Am J Psychiatry 2008; 165: 51-8.

[15] Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent *vs* the earlier rTMS studies. Acta Psychiatr Scand 2007; 116: 165-73.

[16] Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. Can J Psychiatry 2008; 53: 555-66.

[17] Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010; 71: 873-84.

[18] Michaelides M, Thanos PK, Volkow ND, Wang GJ. Dopamine-related frontostriatal abnormalities in obesity and binge-eating disorder: emerging evidence for developmental psychopathology. Int Rev Psychiatry 2012; 24: 211-8.

[19] Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obesity Rev 2012; 13: 43-56.

[20] Rothemund Y, Preuschhof C, Bohner G, *et al*. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage 2007; 37: 410-21.

[21] Stoeckel LE, Weller RE, Cook EW 3rd, *et al*. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 2008; 41: 636-47.

[22] Stice E, Yokum S, Blum K, Bohon, C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci 2010; 30: 13105-9.

[23] Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol 2008; 117: 924-35.

[24] Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci 2011; 31: 4360-6.

[25] Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. Nat Rev Neurosci 2011; 12: 652-69.

[26] Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: Implications for obesity. Trends Cogn Sci 2011; 15: 37-46.

[27] Volkow ND, Wang GJ, Fowler JS, *et al*. 'Nonhedonic' food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. Synapse 2002; 44: 175-80.

[28] Blum K, Sheridan PJ, Wood RC, *et al*. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996; 89: 396-400.

[29] Wang GJ, Volkow ND, Logan J, *et al*. Brain dopamine and obesity. Lancet 2001; 357: 354-7.

[30] de Weijer BA, van de Giessen E, van Amelsvoort TA, *et al*. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. EJNMMI Res 2011; 1: 37.

[31] Volkow ND, Wang GJ, Telang F, *et al.* Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. Neuroimage 2008; 42: 1537-43.

[32] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001; 21: RC157.

[33] Mangweth B, Hudson JI, Pope HG, *et al*. Family study of the aggregation of eating disorders and mood disorders. Psychol Med 2003; 33: 1319-23.

[34] Hausmann A, Mangweth B, Walpoth M, *et al*. Repetitive transcranial magnetic stimulation (rTMS) in the double-blind treatment of a depressed patient suffering from bulimia nervosa: a case report. Int J Neuropsychopharmacol 2004; 7: 371-3.

[35] Nozoe S, Naruo T, Yonekura R, *et al*. Comparison of regional cerebral blood flow in patients with eating disorders. Brain Res Bull 1995; 36: 251-5.

[36] Andreason PJ, Altemus M, Zametkin AJ, *et al.* Regional cerebral glucose metabolism in bulimia nervosa. Am J Psychiatry 1993; 149: 1506-13.

[37] Walpoth, M Hoertnagl C, Mangweth-Matzek B, *et al.* Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. Psychother Psychosom 2008; 77: 57-60.

[38] Van den Eynde F, Claudino AM, Mogg A, *et al*. Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. Biol Psychiatry 2010; 67: 793-5.

[39] van der Ster Wallin G, Norring C, Holmgren S. Binge eating versus nonpurged eating in bulimics: Is there a carbohydrate craving after all? Acta Psychiatr Scand 1994; 89: 376-81.

[40] Waters A, Hill A, Waller G. Internal and external antecedents of binge eating episodes in a group of women with bulimia nervosa. Int J Eat Disord 2001; 29: 17-22.

[41] Uher R, Murphy T, Brammer MJ, *et al.* Medial prefrontal cortex activity associated with symptom provocation in eating disorders. Am J Psychiatry 2004; 161: 1238-46.

[42] Downar J, Sankar A, Giacobbe P, Woodside B, Colton P. Unanticipated Rapid Remission of Refractory Bulimia Nervosa, during High-Dose Repetitive Transcranial Magnetic Stimulation of the Dorsomedial Prefrontal Cortex: A Case Report. Front Psychiatry 2012; 3: 30.

[43] Van den Eynde F, Broadbent H, Guillaume S, *et al*. Handedness, repetitive transcranial magnetic stimulation and bulim ic disorders. Eur Psychiatry 2012; 27(4): 290-3.

Received: July 26, 2013 **Revised: November 9, 2013** **Accepted: December 10, 2013**