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Contribuições para o entendimento da heterogeneidade na sintomatologia e nas taxas de tratamento do Transtorno de Déficit de Atenção/Hiperatividade

Porto Alegre, 2021

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Tese como requisito parcial à obtenção do título de doutor em Psiquiatria pelo Programa de Pós Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul.

Orientador:
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RESUMO

O Transtorno de Déficit de Atenção/Hiperatividade (TDAH) é um transtorno neurodesenvolvimental prevalente que se caracteriza por sintomas de desatenção e/ou de hiperatividade/impulsividade inapropriados para a faixa etária do indivíduo, causando-lhe prejuízo. Apesar de ser um dos transtornos psiquiátricos mais pesquisados da literatura mundial, seguem existindo debates quanto à sua existência, sobre a existência de sub ou sobrediagnóstico do transtorno, assim como um sub ou sobretratamento farmacológico dos pacientes. Estes questionamentos são alavancados pela notória heterogeneidade do TDAH, cujas apresentações variam amplamente em razão de fatores etiológicos (genéticos e ambientais), perfis e gravidade de comorbidades, evolução de sintomas ao longo do tempo, e resposta às terapias farmacológicas ou não farmacológicas. Neste trabalho, buscamos contribuir para o entendimento da heterogeneidade do TDAH, abordando a psicometria de seus sintomas sob a ótica das análises de rede e abordando a questão do sub ou sobretratamento do TDAH em nível mundial por meio de uma metanálise. Munidos das últimas atualizações e desenvolvimentos no campo de Análise de Redes, avaliamos as inter-relações de sintomas de TDAH e comparamos as estruturas de sintomas em diferentes contextos etários e amostrais. Além disso, abordamos a questão de sub e sobretratamento medicamentoso do transtorno em crianças e adolescentes através de uma revisão sistemática e metanálise de todos os estudos na literatura que avaliam o tratamento farmacológico do TDAH. Para tal, incluímos estudos baseados em prescrições, questionamentos ou registros em prontuários, de pacientes avaliados direta ou indiretamente para o diagnóstico ou ausência de diagnóstico de TDAH. As análises de rede demonstraram um bom agrupamento dos sintomas sob o formato bidimensional típico do TDAH. Os testes de estabilidade indicaram que somente o índice de força foi estável o suficiente para avaliação e, mesmo assim, apresentou alta variabilidade dentre sintomas de acordo com o contexto amostral. Encontraram-se diferenças estruturais e globais entre as amostras de crianças e adultos. Nossos achados condizem com estudos psicométricos clássicos, corroborando a alta heterogeneidade sintomática do TDAH. Os achados reforçam a importância de aplicar análises de estabilidade de rede antes de interpretações dos achados em estudos subsequentes. Apontamos diferenças nesta nova abordagem que podem contribuir para o entendimento do transtorno e para o desenvolvimento futuro de novas estratégias diagnósticas. A revisão sistemática e metanálise de toda a literatura disponível a respeito de tratamento farmacológico do TDAH focou-se primeiramente em amostras de crianças e adolescentes que usaram métodos validados de diagnóstico. Nestes, 19,1% (IC 95%: 11,5 - 29,9) dos diagnosticados com TDAH recebem tratamento farmacológico, enquanto 0,9% (IC 95%: 0,5 - 1,7) dos que possuem diagnóstico negativo também recebem tratamento farmacológico para o TDAH. Encontramos alta heterogeneidade, conforme esperado, influenciada principalmente pela avaliação da qualidade, país e desenho dos estudos incluídos. Nossos achados demonstram claramente a existência concomitante dos fenômenos de sub e sobretratamento do Transtorno de Déficit de Atenção/Hiperatividade e que tais estão presentes difusamente por países culturalmente distintos.

Palavras-chave: TDAH, heterogeneidade, psicometria, tratamento, estimulantes, intervenções farmacológicas, metanálise, revisão sistemática

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by age-inappropriate symptoms of inattention and/or hyperactivity/impulsivity, causing impairment. Albeit being one of the world's most studied psychiatric disorders, controversies remain regarding the existence of the disorder, it's under or over diagnosis, as well as under or over treatment of affected ones. Such controversies are fueled by ADHD's notorious heterogeneity, as presentation of the disorder is highly variable by function of etiological factors (genetic or environmental), profiles and severity of comorbidities, evolution of symptoms through lifespan, and response to pharmacological and nonpharmacological therapies. In this work, we aim to contribute to the understanding of ADHD's heterogeneity, addressing its symptoms psychometrics under the perspective of network analysis, and addressing the issue of under or overtreatment of ADHD worldwide through a meta-analysis. Armed with the last updates and developments in the Network Analysis field, we evaluate the inter-relations between ADHD symptoms and compare symptom structure in different age and sampling contexts. Furthermore, we evaluate the issue of ADHD's pharmacological under or over treatment among children and adolescents through a systematic review and meta-analysis of all available studies in the literature evaluating pharmacological treatment of ADHD. We included studies based on prescriptions, questioning or medical registry, of patients directly or indirectly screened for ADHD diagnosis or its absence. The network analysis demonstrated a good cluster of symptoms under the typical bidimensional structure of ADHD. Stability tests indicated that strength was the single measurement stable for evaluation, and even such measurement presented high variability according to sampling contexts. Comparative analysis demonstrated structural variability between youth and adult samples. Our findings agree with classical psychometric studies, confirming the high symptomatological heterogeneity of ADHD. The findings reinforce the importance of applying stability analysis of networks before inferences over findings in subsequent studies. We indicate differences in this new approach that might contribute to the understanding of the disorder and future development of new diagnostic strategies. The systematic review and meta-analysis of all available literature on the pharmacological treatment of ADHD focused primarily on children and adolescents identified through validated diagnostic methods. Among those, 19,1% (CI 95%: 11,5 - 29,9) of diagnosed individuals received pharmacological treatment, while 0,9% (CI 95%: 0,5 - 1,7) of those with a negative diagnosis were also receiving pharmacological treatment for ADHD. We found high heterogeneity among studies as predicted, influenced mainly by the quality of assessment, country of origin and study design. Our findings demonstrate a clear coexistence of the phenomena of undertreatment and overtreatment of ADHD, and such are present across distinct countries.

Keywords: ADHD, heterogeneity, psychometric, treatment, stimulant, pharmacological intervention, meta-analysis, systematic review

SUMÁRIO

1. INTRODUÇÃO

O transtorno de déficit de atenção/hiperatividade (TDAH) se caracteriza por sintomas de desatenção e/ou de hiperatividade/impulsividade inapropriados para a faixa etária do indivíduo, causando-lhe prejuízo. (1) É o transtorno neurodesenvolvimental de maior prevalência, apresentando taxas que atingem 5-7% entre crianças e adolescentes (2) e 2,5% em populações de adultos. (3) A presença de TDAH gera impacto negativo em diversas esferas da vida do indivíduo, a exemplo da qualidade de vida em geral, (4) sucesso educacional, (5) risco de envolvimento em acidentes de trânsito, (6) ferimentos acidentais em geral e atendimentos em unidades de pronto socorro, (7-8) envolvimento com atividades criminosas (9) e uso de substâncias ilícitas. (10) Alguns estudos indicam a associação de TDAH com mortalidade, embora saiba-se que em grande parte este desfecho esteja relacionado às comorbidades dos pacientes. (11) Estas características tornam o TDAH um problema de saúde pública de relevante impacto socioeconômico. (12)

Entretanto, apesar da vasta literatura sobre sua validade diagnóstica, o TDAH continua sendo visto como um transtorno controverso, tanto por uma parcela do meio científico quanto pela mídia leiga. Na mídia leiga, as maiores controvérsias giram em torno da existência ou não do transtorno. (13,14) No meio científico, os questionamentos são referentes ao sub ou sobrediagnóstico do transtorno (15) e ao sub ou sobretratamento dos pacientes. (16-18) Estes questionamentos são alavancados pela notória heterogeneidade do TDAH, cujas apresentações variam amplamente de acordo com fatores etiológicos (genéticos e ambientais), perfis e gravidade de comorbidades, evolução de sintomas ao longo do tempo, e resposta às terapias farmacológicas ou não farmacológicas. (19)

2. REVISÃO DA LITERATURA

Diversos fatores contribuem para a heterogeneidade de apresentações do TDAH. A diversidade de fatores etiológicos genéticos e ambientais em sobreposição são possivelmente a maior explicação para tamanha heterogeneidade no TDAH. (19) A heterogeneidade observada impacta na facilidade de reconhecimento e diagnóstico do TDAH, no acesso aos tratamentos farmacológicos ou não-farmacológicos, e na resposta terapêutica e prognóstico do transtorno. (20) Indiretamente, a

heterogeneidade também fomenta questionamentos acerca da validade das ferramentas disponíveis para se diagnosticar o TDAH, e questionamentos acerca da legitimidade de se usar medicações em pacientes jovens.

2.1. ASPECTOS GERAIS SOBRE HETEROGENEIDADE

Embora o objeto desta tese seja a contribuição para o entendimento da heterogeneidade na sintomatologia e nas taxas de tratamento de TDAH, para contextualizar o leitor abordam-se inicialmente as outras principais heterogeneidades pesquisadas no TDAH.

2.1.1 Etiologia

A alta heterogeneidade do TDAH passa pela etiologia do transtorno. O TDAH tem uma etiologia multifatorial, envolvendo determinantes genéticos e ambientais. (19) Diversos estudos suportam a ideia de que genes e interações gênicas possuem um papel expressivo na causalidade do TDAH. Estudos familiares e de gêmeos indicam que o TDAH possui uma herdabilidade alta, atingindo valores de 70% a 80%. (21) Através de estudo de associação de varredura genomica (*genome-wide association studies*; GWAS), identificou-se um grupo de genes associados ao TDAH, porém que individualmente possuem efeito pequeno sobre o risco de apresentar o transtorno, fortalecendo assim a teoria poligênica de causalidade do TDAH. (22) Os mesmos genes que explicaram parte do risco anterior, porém, também demonstraram associação com o risco de sintomas neurodesenvolvimentais, externalizantes e depressivos, apesar de serem fortemente ligados a sintomas de desatenção e hiperatividade, explicando até 50% da variância para TDAH enquanto só 1% da variância para psicopatologias em geral. (23) Genes específicos foram avaliados, porém ainda sem replicação e validação de seus achados. Interessantemente, as correlações genéticas do TDAH se estendem não só às psicopatologias, mas também a diversas doenças não psiquiátricas, até mesmo ao câncer de pulmão. (24) O impasse da etiologia genética se apresenta quando observamos que, apesar do esforço em encontrar genes de susceptibilidade, os estudos de associação genômica ampla conseguem localizar somente 22% da

herdabilidade do TDAH, o que nos deixa com uma lacuna de 50% de herdabilidade ainda sem explicação. (22)

Exposições ambientais também estão associadas à presença de TDAH e são implicados em sua etiologia. Franz e colegas (25) demonstraram em metanálise de 12 estudos que crianças nascidas pré-termo e pequenos para a idade gestacional (PIG) apresentam um aumento de 3 vezes nas taxas de TDAH conforme seu desenvolvimento. Semelhantemente, outra metanálise descreve correlação entre crianças nascidas com pequeno peso para a idade gestacional e TDAH. (26) Não surpreendentemente, fatores relacionados a partos pré-termo e PIG, como hipertensão (27), pré-eclâmpsia (28) e obesidade maternas (29) também possuem papel no risco de TDAH. Em uma revisão sistemática recente, estudos prospectivos meta-analisados demonstraram que o tabagismo durante a gestação acarreta em um risco relativo de 1.58 para desenvolvimento de TDAH. (30) A cessação do tabagismo durante o primeiro trimestre persiste apresentando associação com a presença do transtorno na prole, e somente a cessação previamente à gestação aparenta ser protetora. (31) Em um estudo dinamarquês, crianças cuja mãe perdeu um ente próximo durante a gestação apresentaram o dobro de chance de desenvolver TDAH. (32) Durante a primeira infância, observamos que condições socioculturais implicam em maior risco de desenvolver o transtorno. Abuso sexual e negligência física na infância, (33) baixo poder econômico, (34) e o acúmulo de adversidades na infância (35) foram identificados como preditores de TDAH. Exposições a agentes tóxicos demonstraram associações significativas com o transtorno, a exemplo da relação a acetaminofeno pré-natal, (36) corantes alimentícios, (37) ácido valpróico pré-natal (38) e níveis de chumbo sérico. (39)

A heterogeneidade etiológica do TDAH, a lacuna de “herdabilidade não encontrada” e a grande quantidade de fatores etiológicos identificados induziram a criação de uma hipótese de interações gene-ambiente. (40) Neste sentido, estudos buscam combinar alelos de alto risco com exposições específicas, buscando um sinergismo consistente e replicável. Interações entre fatores psicossociais e genes específicos (DAT1 e 5HTT) fornecem razões de chances para presença de TDAH nos valores 2.76 e 2.66, respectivamente. (41) A relação de genes e exposições parece promissora e grandes estudos estão em andamento, com a expectativa de trazerem bons resultados em um futuro breve. (40)

2.1.2 Características demográficas

Em relação a variáveis demográficas, o sexo biológico impacta a apresentação e a informação de sintomas. Pacientes femininas tendem a ser diagnosticadas como perfis predominantemente desatentos, com menos sintomas de hiperatividade e menores chances de receberem diagnóstico e tratamento para o TDAH de forma apropriada. (42) Alguns estudos também indicam diferenças em perfis de sintomas, gravidade e comorbidades dentre pacientes diagnosticados com TDAH de diferentes etnias/descendências. Porém, confundidores importantes, como: nível socioeconômico; educação materna; emprego paterno e questões culturais sobre tolerância a sintomas e limiares de tratamento, parecem ser os fatores mais importantes nestas populações. (43) Tais fatores levam a menores taxas de diagnóstico e tratamento nas populações etnicamente minoritárias. (44)

2.1.3 Fontes de informação

A informação de sintomas depende de fontes distintas e são observadas discrepâncias entre os informantes, especialmente pelo fato de que grande parcela da população estudada no contexto de TDAH seja de crianças/adolescentes. Pais geralmente tendem a reportar sintomas em maior número e maior gravidade do que professores. Observa-se que os coeficientes de correlação destes grupos tendem a ser de moderados a insignificantes. (45, 46) Há também diferenças em informação de sintomatologias quando são comparados pais de gêneros diferentes, sendo que as mães dos pacientes tendem a valorizar mais os sintomas de desatenção do que os pais. (47).

2.1.4 Comorbidades

Comorbidades possuem um papel clinicamente muito importante na heterogeneidade do TDAH. Em uma minoria dos casos, podemos observar a presença do TDAH isoladamente. Em mais da metade dos casos, porém, lidamos com pacientes com múltiplas comorbidades, (48) como transtornos de comunicação e deficiência intelectual, (49) transtornos do sono, (50) transtornos de aprendizado, (49) transtorno de humor, transtornos de comportamento disruptivo, transtornos de

ansiedade, (49) transtornos do espectro autista (51) e abuso de substâncias. (52) A literatura indica que, do ponto de vista terapêutico, a classificação do TDAH em subtipo ansioso e subtipo agressivo pode sugerir opções de tratamento diferenciadas. (53)

2.1.5 Trajetória

As variações em sintomatologia e comorbidades são também importantes através do desenvolvimento do indivíduo e a evolução do transtorno. Em termos gerais, crianças apresentam uma redução dos sintomas de hiperatividade conforme a maturidade, enquanto os sintomas de desatenção e impulsividade são mais persistentes durante a adolescência, até mesmo chegando à fase adulta. (54, 55) As comorbidades também se alteram, partindo de associações comuns com transtorno de oposição e desafio e transtorno de conduta na fase da infância, para maiores prevalências de transtornos de humor, ansiedade, e transtornos de abuso de substâncias. (56)

Apesar de todas as tendências identificadas em estudos, é frequente a ocorrência dos opostos. Resultados do *Multimodal Treatment Study of ADHD* (MTA) publicados recentemente demonstram que cerca de 10% das crianças e adolescentes diagnosticados apresentam remissão sustentada de sintomas, e outros 10% apresentam a persistência dos sintomas de TDAH no mesmo período. Nos demais indivíduos, observa-se flutuação entre recorrência e remissão de sintomas, em geral com sintomas residuais durante períodos de remissão do transtorno. (57) Recentemente, estudos de coortes puderam acompanhar o desenvolvimento de indivíduos ao longo dos anos. Com avaliações seriadas de diagnósticos psiquiátricos, observou-se padrões de trajetória de TDAH totalmente diferentes dos tipicamente conhecidos, com o estabelecimento de diagnósticos novos já na fase adulta em indivíduos sem histórico. Diagnósticos com início na fase adulta, por sua vez, seriam a maioria dos diagnósticos de TDAH dentre adultos. (58)

2.2 HETEROGENEIDADE DE SINTOMAS

O diagnóstico de TDAH em crianças e adolescentes atualmente baseia-se sobretudo em identificar a presença e persistência de sintomas do transtorno, de no

mínimo 6 em um mesmo domínio, que devem ser inapropriados para a idade do indivíduo e gerar prejuízo ao mesmo. (1) A diferenciação de domínios por si já é uma estratégia para lidar com a heterogeneidade do transtorno, levando o paciente a ser categorizado em três apresentações típicas conforme a prevalência de sintomas: predominantemente desatento, predominantemente hiperativo/impulsivo ou combinado. Contudo, a gama de sintomatologias do TDAH é extensa e podemos observar indivíduos de idades e perfis socioeconômicos semelhantes apresentando sintomas totalmente diferentes, ambos com diagnóstico formal. (59)

Muitos estudos buscam aprimorar estas definições e identificar, dentre sintomas informados pelas diferentes fontes, características mais homogêneas de forma a contribuir no desenvolvimento de abordagens diagnósticas refinadas e modelos de predição de desfechos desfavoráveis. As principais ferramentas usadas para buscar este refinamento são modelos psicométricos clássicos, de Análise Fatorial Confirmatória (60) e Análise de Classes Latentes, (61) com o objetivo de revisar os agrupamentos de sintomas do DSM. Estas análises conseguem formar grupos de forma consistente e replicável ao longo de diversos estudos, porém possuem limitações em lidar com a alta heterogeneidade do transtorno em geral e a aplicabilidade de seus achados não é clara. Ferramentas mais modernas também vêm sendo aplicadas. Modelos de Teoria de Resposta ao Item, (62) que conseguem individualizar sintomas conforme sua presença e intensidade individual, aparentemente lidam melhor com a heterogeneidade do transtorno e sua relação com comorbidades. Mais recentemente, Análises de Rede, (63) que por sua vez buscam investigar complementarmente a estrutura de sintomas e a inter-relação de sintomas dentro daquela população, também estão sendo aplicadas a amostras de sintomas de TDAH.

2.2.1 – Principais achados dos Estudos de Regressões Logísticas, Lineares e Análises Fatoriais

O extenso arranjo de sintomas possíveis e a heterogeneidade fenotípica do TDAH fez com que pesquisadores buscassem identificar preditores de prejuízo ou mesmo de diagnóstico dentre os sintomas de TDAH, lançando mão de estratégias como regressões logísticas. Kessler e colegas (64) buscaram os sintomas mais preditivos de diagnóstico de TDAH em uma amostra de adultos, dentre um

questionário mais abrangente do que somente os sintomas de TDAH do DSM-IV na época. Neste estudo, fez-se uso de regressão logística passo a passo, seguida por uma análise de regressão de todos os subconjuntos possíveis (APS), um método que busca selecionar o melhor subgrupo dentre um grande número de preditores, quando estes preditores são altamente inter-relacionados. (65) Os autores identificaram que o sintoma do DSM-IV, “dificuldade de manter a atenção”, junto com 3 sintomas relacionados à função executiva, foram os maiores preditores de diagnóstico dentre todos os sintomas avaliados. (61) Em estudo semelhante, aplicando a técnica do APS à uma amostra populacional representativa de jovens adultos, porém focado em sintomas centrais do diagnóstico do TDAH, 5 sintomas de desatenção e 2 sintomas de hiperatividade destacaram-se com preditores de prejuízo: “dificuldade de manter a atenção”, “dificuldade de organizar tarefas”, “distrair-se facilmente”, “perder objetos”, “não prestar atenção aos detalhes”, “estar a mil” e “levantar-se”. (66) Usando a mesma estratégia, porém em uma amostra diferente de adultos, Vitola e colegas identificaram 5 sintomas de desatenção e 1 de hiperatividade relacionados ao prejuízo do transtorno: “não escuta”, “não segue instruções”, “perde objetos”, “facilmente distraído”, “esquece tarefas” e “dificuldade de esperar sua vez”. (67) Por fim, em uma amostra turca, os três sintomas mais relacionados com prejuízo foram “inquieto”, “não começa atividades”, “não presta atenção aos detalhes”, “sempre a mil” e um sintoma novo proposto ao DMS-5 para a dimensão de impulsividade: “impaciente”. (68) Independente da semelhança das amostras avaliadas e de técnicas idênticas, notamos a discrepância entre os sintomas mais impactantes de cada amostra. É importante ressaltar que isso ocorre mesmo quando comparamos duas amostras provenientes de adultos da mesma cidade, no caso as amostras das coortes de Pelotas de 1984 e 1993.

Análises fatoriais vêm sendo utilizadas no TDAH a fim de identificar dimensões subjacentes dentre os sintomas, avaliando a correlação dos sintomas com um modelo, que pode ser feito de forma exploratória ou confirmatória. Enquanto no modelo exploratório espera-se identificar um fator a partir das correlações de sintomas, nos modelos confirmatórios os sintomas são distribuídos dentre fatores conhecidos ou teóricos e avaliados estatisticamente quanto ao adequamento daquele modelo. (69) Análises exploratórias de sintomas de TDAH encontram consistentemente que um modelo bidimensional distinguindo sintomas de desatenção e de hiperatividade/impulsividade seria o mais adequado. (70) Tal fato foi reproduzido

em diversos países socioeconomicamente distintos, a exemplo dos Estados Unidos da América (71), Brasil, (72), Porto Rico, (73), Finlândia, (74) África do Sul (75), entre outros, com raras exceções. (76)

Análises fatoriais confirmatórias, por sua vez, foram ambíguas em definir qual o melhor modelo, visto que estudos indicam que os dados de sintomas de TDAH adequam-se bem a modelos com 2 ou 3 fatores. Nestes, as dimensões de sintomas foram definidas por desatenção e hiperatividade/impulsividade nos modelos de 2 fatores, ou desatenção, hiperatividade e impulsividade nos modelos de 3 fatores. Por vezes, embora o modelo de 3 fatores pudesse ser mais adequado matematicamente, o modelo de 2 fatores se apresentava mais parcimonioso e plausível, o que foi corroborado por amostras de crianças e adolescentes da Espanha (77), Austrália (78), Alemanha (79) e Estados Unidos da América. (80) O mesmo foi verdade para amostra norte-americana de indivíduos pré-escolares, embora nesta, quando usados dados informados por professores, as análises demonstraram que nenhum modelo foi satisfatoriamente aceitável em definir a estrutura de sintomas do transtorno. (81)

Um subgrupo de análises fatoriais incorpora um fator geral englobando fatores específicos. Estas análises de segunda ordem, ou bifatoriais, assumem que fatores latentes (as diferentes dimensões do TDAH, desatenção e hiperatividade/impulsividade) são englobados por um fator geral (o próprio TDAH). Portanto, pretendem, com isso, adequar melhor o modelo à inerente heterogeneidade do transtorno, reduzindo o impacto de condições gerais, como as diversas etiologias do transtorno e o perfil psicossocial variado dos pacientes, sobre as medidas das dimensões do TDAH. Estudos de amostras diversas, realizados na Austrália, (82) Brasil, (83, 84) Canadá, (85, 86) Noruega, (87) e um estudo multinacional com amostras de 7 países da Europa e mais Israel (88) chegaram à conclusão de que modelos bifatoriais apresentam melhor adequação estatística e, portanto, seriam mais adequados que os modelos anteriores, absorvendo melhor a heterogeneidade em forma deste fator geral. Contudo, ao serem analisados os índices de cada fator computado, constatou-se que o fator geral possui maior confiabilidade estatística e explicava a maior parte da variância comum, de modo que fatores de primeira ordem, as dimensões do TDAH, fornecem pouca informação residual, o que as torna fatores menos confiáveis e demanda cautela na interpretação de seus achados. Tal análise questiona os estudos anteriores, tanto fatoriais quanto bifatoriais, indicando a necessidade de redirecionar o foco ao fator geral do TDAH e destacando a

necessidade de melhores instrumentos para aferir sintomas dentro de cada domínio. (84)

2.2.2 – Principais achados das Análise de Classes Latentes

Análises de classes latentes, ao contrário de análises fatoriais, consideram os sintomas como variáveis observáveis que representam uma variável subjacente e usam modelos estatísticos para identificar um número finito de classes nas quais estas variáveis observáveis se agrupam. (89) Os estudos de análises de classes latentes tendem a apresentar maior variabilidade entre si, o que é secundário a diferentes metodologias, perfis de indivíduos na amostra e informantes de sintomas. Em geral, os estudos de classes latentes, apesar de não comparáveis com os estudos de análise fatorial devido à sua natureza distinta, endossam modelos bidimensionais de TDAH. Contudo, a maioria dos estudos que usam amostras comparáveis, com sintomas informados por pais, encontram variações dentre 3 a 8 classes latentes como sendo o modelo mais adequado. (90-93) Embora exista essa alta variabilidade de classes formadas, frequentemente ao menos as seguintes 3 classes latentes estão presentes nos estudos: a) classe com pouco endosso de sintomas; b) classe com sintomas graves desatentos; c) classe com sintomas graves desatentos e hiperativos/impulsivos. (70)

2.2.3 - Principais achados de Modelos de Teoria de Resposta ao Item

Para além das teorias de teste clássicas, foi proposto o uso de abordagens mais modernas para avaliar as propriedades psicométricas dos sintomas de TDAH, visto os impasses atingidos pelas teorias anteriores. A Teoria de Resposta ao Item se diferencia das teorias clássicas, pois possui a capacidade de conferir um escore diferenciado para cada item que compõe um traço. Ela fornece valores de confiabilidade de cada item em diferentes níveis de um traço, controlando para a dificuldade ou frequência em que aquele item está presente na escala. Suas propriedades psicométricas são assumidas como independentes e invariáveis através de amostras distintas. (94) Em uma amostra cujos sintomas foram informados por pais, os sintomas da dimensão desatenção (“descuidado”, “não presta atenção”, “não segue instruções”, “dificuldade de organizar tarefas”, “não inicia tarefas” e “distraído

facilmente”) e de hiperatividade/impulsividade (“corre/sobe” e “não espera sua vez”) foram os melhores em discriminar e identificar corretamente o TDAH. (95) Em estudo americano semelhante, todos os sintomas foram aceitáveis na identificação correta do TDAH, porém destacou-se a alta discriminação pelos sintomas “não presta atenção” e “não segue instruções”. (96) Em um estudo espanhol, todos os sintomas foram discriminadores satisfatórios, mas o destaque foi para os sintomas de desatenção "distraído facilmente” e “não segue instruções”, e para os sintomas de hiperatividade “levanta-se da cadeira” e “corre/sobe”. (97) Por fim, em um estudo chileno, “distraído facilmente” e “dificuldade em manter atenção nas tarefas” na dimensão de desatenção, e “sempre a mil” na dimensão de hiperatividade foram os mais informativos. (98) Diferentes estudos em países distintos cultural e economicamente informaram que, geralmente, sintomas de desatenção são mais discriminadores do TDAH, porém não foi possível identificar algum sintoma predominante em absoluto.

2.2.4 – Principais achados de Análises de Rede

Análise de rede consiste em uma relativa nova abordagem que está sendo aplicada ao estudo de psicopatologias, tendo como característica principal a capacidade de melhor entender a relação causal individual entre os itens avaliados. (99) Nesta ferramenta, um constructo psicológico é considerado um sistema composto por itens individuais e suas inter-relações. Com isso, a análise de redes permite que o pesquisador investigue o quanto cada item, que pode ser um sintoma, é relevante ao constructo, desvendando as associações entre estes sintomas e quais são os sintomas centrais ou mesmo de ligação entre terceiros sintomas. Permite assim, avaliar os efeitos de cada sintoma sobre os outros, buscando inferir uma causalidade escondida. (100). Estudos de estresse pós-traumático (101), esquizofrenia (102) e depressão (103) dentre outros utilizam esta abordagem para complementar a literatura de psicometria clássica.

Tais análises são criadas a partir de correlações entre itens que, no contexto deste trabalho, são constituídos de sintomas e que apresentam relações matemáticas entre si, que aqui chamamos de conexões. As redes podem ser construídas utilizando diferentes métodos de correlação. Correlações totais fazem a análise bruta das redes de sintomas e seus índices, enquanto correlações parciais avaliam a independência

de sintomas diferentes dentro da rede, controlando as conexões de um sintoma para todos os sintomas da rede e inferindo conexões relevantes somente quando um limiar aceitável de independência deste sintoma for atingido. (104) Este controle pode inclusive utilizar estratégias matemáticas clássicas de regressão para distinguir de maneira mais precisa quais conexões e interações de sintomas são realmente significativas. Desta forma, as redes tornam-se mais parcimoniosas e podem demonstrar com mais facilidade conexões realmente relevantes e estruturas subliminares adjacentes. (105)

Visto que uma análise de rede é uma solução matemática para avaliar padrões de conexões de sintomas dentro de um constructo, tais padrões são traduzidos em índices de centralidade inerentes a cada sintoma, que são as peças-chave da interpretação das redes formadas. Os índices constituem-se em três: força *(strength)*, proximidade *(closeness)* e intermediação *(betweenness)*. Força é uma medida de centralidade calculada pela soma das conexões diretas deste sintoma dentro de uma rede e representa a influência direta que este sintoma implica sobre os demais sintomas conectados de forma direta. Proximidade é uma medida composta pelo inverso das distâncias de um sintoma a todos os demais sintomas e representa relações com os demais sintomas e a amplitude da influência deste sintoma dentro da rede. Intermediação é uma medida da soma de conexões indiretas que dependem do sintoma e o atravessam e representa a influência do sintoma sobre as conexões dos outros sintomas entre si. Por fim, tais informações podem ser reproduzidas em forma gráfica de maneira a tornar padrões de relações mais claros e influências diretas mais observáveis. (104)

Martel e colegas (64) publicaram o primeiro estudo de Análise de Redes para avaliar sintomas de TDAH em grupos de idade distinta. Neste, utilizando redes de correlações, observou-se que os grupos apresentavam maior diferenciação de sintomas conforme a maturação neurodesenvolvimental, sendo que crianças tendiam a apresentar um grande agrupamento de sintomas, enquanto adultos já apresentavam grupos mais diferenciados de sintomas, sugerindo maior diferenciação de sintomatologias conforme a idade do indivíduo.

Silk e colegas (106) publicaram recentemente uma análise de rede de sintomas de 209 crianças, na qual identificaram que 92% dos padrões de sintomas encontrados são únicos e que poucos sintomas seriam os maiores responsáveis pelo domínio em que o indivíduo estava inserido. Os sintomas mais influentes foram

“interromper os outros” dentre os sintomas de impulsividade, “não parar” dentre os sintomas de hiperatividade, “perder objetos” e “não seguir instruções” dentre os sintomas de desatenção. Contudo, é importante notar que os primeiros trabalhos sobre análise de redes aplicadas a psicometria datam de 2013 e que esta é uma área em constante desenvolvimento. (107) Novas estratégias para construir análises de rede já não usam mais redes de correlação conforme as usadas por Martel *et al.*, visto que tal método gera correlações espúrias. (104) Da mesma forma, os índices de centralidade analisados necessitam de conferência estatística que não foi aplicada em nenhum dos estudos acima, a fim de avaliar estatisticamente os resultados das análises e suas acurácias, sendo que sua falta limita a confiabilidade e interpretação dos achados. (107)

A utilização de análises de rede pode ser expandida além dos sintomas, a exemplo da aplicação realizada por Goh e colegas, (108) que realizaram análises de rede com sintomas informados por pais e professores e, também, com medidas de função executiva. Seus achados indicam conexões fortes entre funções cognitivas de controle e TDAH, especialmente relacionadas aos sintomas de desatenção informados pelos pais. Porém, ao replicar seus achados em amostra distinta, encontrou-se relação entre funções cognitivas de controle e sintomas de hiperatividade/impulsividade informadas pelos pais. Além de identificar um potencial marcador do TDAH usando esta nova abordagem, o estudo indica a possibilidade de se pensar em abordagens terapêuticas futuras direcionadas à essa função cognitiva.

2.3 HETEROGENEIDADE NAS TAXAS DE TRATAMENTO NO MUNDO

Essa heterogeneidade abre portas para questionamentos acerca da validade do TDAH, resultando em diversas elucubrações, como por exemplo de que o transtorno seria um constructo social. Nesta teoria, o conjunto cultural ocidental determinaria o transtorno, supostamente por efeitos da redução de suporte familiar, aumento da pressão escolar, da perda de autoridade moral paterna e do padrão hiperativo das atividades familiares, aliados à uma economia que estimula a individualidade, competitividade e independência. (109) Neste contexto propício para o desenvolvimento do perfil hiperativo que conhecemos, estaríamos sendo induzidos pelos motivos escusos da indústria farmacêutica visando lucro, expondo crianças a drogas viciantes e perpetuando o comportamento que então é visto como patológico.

(110) Embasados na heterogeneidade do transtorno para criticar a existência ou não do TDAH, os críticos complementam que há transferência de responsabilidades onde um problema social é transformado em doença por comodidade inerente ao tratamento farmacológico. (111, 112)

O denso embasamento científico e a transcontinentalidade observada pelos estudos genéticos, epidemiológicos e clínicos, reproduzida em diversos ambientes culturalmente distintos, reforça que muitas das diferenças, quando não atribuíveis à própria heterogeneidade do TDAH, são de fato efeito de diferenças metodológicas e que a ideia de o TDAH ser um construto social não tem sustentabilidade. (113) Todavia, tais questionamentos perpetuam-se, especialmente no meio leigo, e implicam em uma barreira terapêutica importante a ser vencida.

2.3.1 Tratamento farmacológico

As opções terapêuticas para o tratamento do TDAH disponíveis hoje são baseadas em intervenções medicamentosas, comportamentais ou combinadas. Enquanto estimulantes são altamente efetivos e a primeira linha da maioria dos casos, medicamentos não estimulantes podem ser uma melhor opção em casos específicos, e terapias não farmacológicas também são uma ótima opção, especialmente quando utilizadas em crianças muito novas ou em terapia adjunta a fármacos. (114) Não existe, até o momento, uma terapia curativa. Contudo, ensaios clínicos randomizados evidenciam a eficácia superior do tratamento farmacológico com estimulantes ou atomoxetina e justificam sua importância, (115) recomendados como tratamento de primeira linha na maioria das diretrizes internacionais. (116-119) Os diferentes perfis sociais dos pacientes diagnosticados, suas características cognitivas e as diferentes comorbidades associadas ao TDAH nestes indivíduos tornam a resposta farmacológica variável conforme a classe da medicação escolhida, suas doses e seu perfil de efeitos colaterais. (114, 115, 120-122) Todavia, com o crescente corpo literário construído em torno do transtorno, observaram-se também crescentes índices de uso de medicamentos para seu tratamento, instigando questionamentos sobre os excessos de prescrição de estimulantes. (123)

É de grande interesse público e científico saber se estamos prescrevendo medicações excessivamente para pacientes com TDAH. Até o momento, uma única metanálise avaliou a prevalência de tratamento de TDAH a nível mundial buscando

dados de registros de pacientes, a fim de identificar taxas de tratamento medicamentoso em indivíduos afetados por TDAH. (124) Entretanto, ao se basear em populações que buscam tratamento (portanto, amostras de natureza clínica) e dados registrados em prontuário, o estudo em questão não diferencia a relevante questão de diagnóstico apropriado e tratamento corretamente direcionado em populações não referenciadas. Nos indica, porém, que as taxas de tratamento em geral não condizem com as taxas de diagnóstico esperadas em cada região avaliada. Observou-se grande heterogeneidade entre as amostras, evidenciando que além das heterogeneidades implicadas pelo transtorno, há ainda a heterogeneidade de condutas clínicas tanto de diagnóstico quanto de tratamento frente a estes indivíduos. De fato, metanálises de prevalência de TDAH mundial já indicavam a alta heterogeneidade nos estudos epidemiológicos do transtorno, (2) possivelmente indicativos de menor acesso a serviços de saúde próprios de cada região estudada, diferenças culturais e diretrizes locais. Estes achados indicam a necessidade de maior investimento educacional e maior atenção às diretrizes, a fim de homogeneizar as condutas clínicas.

2.3.2 Taxas de sub e sobre tratamento farmacológico

As discrepâncias nos estudos que avaliam a taxa de tratamento medicamentoso do TDAH podem ser vistas ao analisarmos estudos individuais realizados com amostras populacionais. Estimulados por emergentes questionamentos públicos referentes à crescente prescrição de estimulantes para tratamento de TDAH nos Estados Unidos da América, estudos contemporâneos e de perfis socioeconômicos semelhantes já apresentaram diferenças significativas em taxas encontradas tanto de sub quanto de sobretratamento de TDAH.

Em estudo publicado em 2000, Adrian Angold e colegas avaliaram uma amostra comunitária probabilística representativa de crianças e adolescentes, de 9 a 16 anos de idade, selecionados dentre 11 condados da Carolina do Norte. Neste estudo, constataram que existia uma taxa de 63% tratamento farmacológico de TDAH em pacientes diagnosticados com o transtorno e uma taxa de 6,8% de tratamento de pacientes que não possuíam critérios diagnósticos para tal, reforçando um padrão de uso local inconsistente com os *guidelines* da época. (125) Entretanto, em estudo publicado em 1999, Peter Jensen e seus colegas avaliaram uma amostra comunitária

probabilística de quatro regiões americanas (Atlanta, Georgia; New Haven, Connecticut; Westchester, Nova Iorque; e San Juan, Porto Rico). Diferentemente do primeiro, neste estudo encontraram uma taxa de 13,1% de tratamento de TDAH dentre indivíduos diagnosticados, bem como uma taxa de 0,9% de tratamento de TDAH dentre indivíduos não diagnosticados, observações que, então, discordaram dos receios leigos da época de sobretratamento. (126) Nota-se, portanto, uma importante lacuna na literatura a ser preenchida.

3. OBJETIVOS

3.1 Objetivos Primários

Contribuir para o entendimento da heterogeneidade do TDAH de duas formas. Primeiramente, abordando a psicometria de seus sintomas através de análise de redes. Em seguida, avaliando a heterogeneidade de tratamento do TDAH a nível mundial, averiguando as taxas de tratamento medicamentoso em indivíduos portadores de TDAH e indivíduos sem o transtorno.

3.2 Objetivos secundários

a) Avaliar se há diferenças entre redes de sintomas de TDAH entre amostras de crianças/adolescentes cuja informação de sintomas foi fornecida por pais ou professores;

b) Avaliar se há diferenças entre redes de sintomas de TDAH entre amostras de crianças/ adolescentes e adultos;

c) Avaliar se há diferenças entre redes de sintomas de TDAH entre amostras de crianças/ adolescentes oriundas de ambientes clínicos e populacionais;

d) Avaliar a inter-relação de sintomas dentro de cada rede, buscando replicar sintomas mais influentes conforme estudos da literatura psicométrica clássica;

e) Avaliar a taxa de tratamento de TDAH a nível mundial, dentre indivíduos apropriadamente diagnosticados com TDAH;

f) Avaliar a taxa de tratamento de TDAH a nível mundial, dentre indivíduos cujo diagnóstico de TDAH foi descartado;

g) Avaliar a heterogeneidade dos estudos identificados e seus fatores influenciadores;

h) Estimar taxas nacionais de subtratamento extrapolando dados demográficos e estimativas realizadas;

i) Estimar taxas nacionais de sobretratamento extrapolando dados demográficos e estimativas realizadas.

4. CONSIDERAÇÕES ÉTICAS

Este projeto foi financiado pelo Programa de Transtornos de Déficit de Atenção/Hiperatividade do HCPA e pelo Fundo de Incentivo à Pesquisa e Eventos do mesmo hospital.

A presente pesquisa foi feita através de dados disponíveis: a) no banco de dados do Projeto de Desenvolvimento do PRODAH submetido e aprovado pelo Grupo de Pesquisa e Pós-Graduação e pelo Comitê de Ética em Pesquisa do HCPA (número 2012-0231); b) dados de estudos disponíveis nas bases de dados internacionais.

5. ESTUDOS QUE COMPÕEM A TESE

5.1 Análise de rede de sintomas de TDAH (Artigo 1)

Munidos das últimas atualizações e desenvolvimentos no campo de Análise de Redes, buscamos realizar uma Análise de Rede de sintomas de TDAH mais completa, equipando-se de ferramentas que controlem a qualidade dos achados ainda não aplicados clinicamente. As análises foram planejadas para serem realizadas em diferentes contextos para comparar matematicamente as estruturas de sintomas de: diferentes fontes de informação (pais ou professores); diferentes naturezas de amostra (clínicas ou comunitárias) e diferentes períodos desenvolvimentais (crianças/adolescentes ou adultos).

5.2 Avaliação de prevalência de tratamento de TDAH (Artigo 2)

A fim de desvendar com a maior precisão e abrangência disponível as taxas de subtratamento e sobretratamento de TDAH no mundo, realizou-se uma revisão sistemática e metanálise de todos os estudos na literatura que avaliam o tratamento farmacológico do TDAH, por meio de prescrições, questionamentos ou registros em prontuários, de pacientes avaliados de forma direta ou indireta para o diagnóstico ou ausência de diagnóstico de TDAH.

1. ARTIGO 1

Em submissão

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Network Analysis of ADHD symptoms across different samples and informants

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Conflict of interest:
Dr. Rohde has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis, and Shire in the last 3 years. He receives authorship royalties from Oxford Press and ArtMed. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. He received travel grants from Shire and Novartis for attending the WFADHD 2015 and 2016 AACAP meetings. He also receives research support from Brazilian government institutions (CNPq, FAPERGS, HCPA, and CAPES). Dr. Grevet has served as a speaker to Shire and Novartis Pharmaceuticals in the past 3 years. He also received travel awards for taking part in 2017 WFADHD meeting from Shire. All other authors report no financial interests or potential conflicts of interest.

ABSTRACT

Little is known on the interrelation of Attention-deficit/hyperactivity disorder (ADHD) symptoms since traditional psychometric studies disregard influences symptoms have on one another. In this study, we use Network Analysis across different samples and informants to better understand symptom profiles and their interrelations. We included 3 samples of ADHD subjects in this study: a) 420 children and adolescents from a clinical sample with symptoms reported by parents and teachers; b) 274 children and adolescents from a non-referred cohort, using parents as information source; and c) 572 adults from a clinical sample, relying on self-reported symptoms. ADHD symptoms were assessed through the Swanson, Nolan, and Pelham IV scale (SNAP-IV) and the Development and Well-Being Assessment (DAWBA). While network analyses derived well-drawn clusters of ADHD symptoms, hyperactive and impulsive symptoms tend to create two separate subsystems in all samples. Since stability analysis indicated strength as the only reliable centrality measurement for all networks, we focused our interpretations on this measure. ADHD symptoms' strength presents low agreement across different samples and informants. Among the connections with significant higher strength in each network, only 1 was the same for all networks. Network Comparison tests indicated more significant differences according to the nature of the samples and age range than information source. While replicating findings from traditional psychometrics on ADHD dimensions and on high symptomatic heterogeneity across different samples, our results suggest more substantial effects based on nature of the samples and age range than information sources in the symptom networks.

Keywords: ADHD, psychometrics, heterogeneity.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by pervasive and impairing symptoms in the dimensions of inattention and hyperactivity-impulsivity (American Psychiatric Association, 2013). This is the most prevalent neurodevelopmental disorder with a worldwide prevalence in children and adolescent estimated around 5% (Polanczyk et al., 2007) and a pooled prevalence in adults of 2.5% (Simon et al., 2009). ADHD negatively impacts overall quality of life (Danckaerts et al., 2010) and educational success (Robb et al., 2011), as well as increases risk for accident involvement (Lange et al., 2016; Vaa, 2014), engagement in criminal activities (Fletcher and Wolfe, 2009), and substance use (Huntley et al., 2012).

However, there are some controversies about the validity of the disorder (Moncrieff and Timimi, 2010; Timimi et al., 2004). Major reasons for this controversy are the heterogeneous nature of its clinical presentation, comorbid profile, dimensional distribution of symptoms in the population, diverse trajectories, and lack of an objective marker (Faraone et al., 2015). Moreover, ADHD symptomatic constellation and structure also vary across different informants, developmental periods and sampling settings. *First,* studies observed a great discrepancy between symptoms as reported by different informant sources. Parents usually report higher levels of symptoms when compared to teachers, and correlation coefficients between informants range from insignificant to moderate (Lavigne et al., 2016, 2012; Takeda et al., 2016). *Second*, ADHD varies widely across the lifespan. Children usually present with more prominent hyperactive symptoms that diminish through development, while inattentive and impulsive symptoms are more persistent, even through adulthood (Hart et al., 1995; Martel et al., 2012). *Third*, ADHD clinical samples of children and adolescents have lower female proportions (Gaub and Carlson, 1997) and higher comorbid profiles (Cohen and Cohen, 1984; Gadow et al., 2001; Sprafkin et al., 2007) than community samples, scenarios associated with an increase of both hyperactivity and case severity. These studies reveal the necessity of a better understanding of ADHD symptom profiles across different contexts to improve the validity of symptoms in capturing the disorder construct and providing more precise diagnostic approaches in the future.

Albeit the vast knowledge in the area, we know little concerning the interrelation of symptoms of ADHD. More traditional psychometrics approaches, such as Confirmatory Factor (Parke et al., 2015) and Latent Profile (Martel et al., 2010) analyses, disregard the influence variables have on one other at a micro-level and assume that a measured variable is caused by a composite single condition while allowing for some heterogeneity in the expression of such a condition. Recently, a relatively novel approach for psychopathology studies has been appropriated that may allow for better understanding of the causal relationship between individual items (Schmittmann et al., 2013). In the Network Analysis approach, a psychological construct is considered a system composed of individual items and their interrelations. Network analysis allows researchers to determine how relevant each symptom is to the construct, assess associations among symptoms through identification of core and bridge symptoms, and evaluate each symptom's effect on other symptoms, in search of hidden causal effects (Borsboom and Cramer, 2013). Studies on Post Traumatic Stress (Bryant et al., 2017), Schizophrenia (Galderisi et al., 2018), and Depression (Mullarkey et al., 2018) among many others, have utilized this approach.

Martel and colleagues published a study using Network Analysis to assess ADHD symptoms in different developmental age groups for the first time in literature. Applying correlation networks, they observed that preschoolers presented one cluster of ADHD symptoms, children exhibited 2 symptom dimensions of inattention and hyperactivity-impulsivity, while adolescent and adults presented 3 or more clusters, suggesting increasing differentiation of symptoms in older populations (Martel et al., 2016). A recent study by Silk and colleagues also applied Network Analysis on a sample of children with ADHD, demonstrating that symptoms present different importance to the networks (Silk et al., 2019). However, network analyses methods have continuously been improved in areas of data measurements, visualization, and estimations of accuracy (Epskamp et al., 2018). Recently, these advances suggest more cutting-edge approaches to network constructions than the correlation networks conducted by Martel and colleagues, a method that may lead to spurious correlations (Costantini et al., 2015). The use of optimal techniques for assessing centrality indices, network stability and network comparisons, as used in the current paper for the first time in ADHD symptoms, represent an important improvement, especially relevant for the analysis of constructs with highly variable profiles such as ADHD.

In this study, we incorporate the latest psychometric developments in the area of Network Analysis to present a more updated analysis of ADHD symptom networks in order to understand the importance of individual symptoms and their interrelation across different types of samples and developmental age of ADHD. To achieve this global objective, we will focus on differences in centrality indices, connection strengths and network comparison tests between the following: a) different information sources (parents vs. teachers' symptom report of children and adolescents); b) different nature of samples (clinical vs. community samples of children and adolescents); and c) different developmental periods (adult vs. child/adolescent samples). Based on data from previous studies using traditional psychometric approaches, we expect to: a) derive networks composed by well clustered symptoms in two or three groups; b) find high heterogeneity in symptoms' centrality indexes among the 4 samples; c) observe significant differences in global strength of symptoms and network structures when samples' information source, nature and age differ.

METHODS

Samples

Our first sample was recruited from 954 children and adolescents participating in research projects at the child division of the ADHD Outpatient Program in the Hospital de Clínicas de Porto Alegre, from years 2000 to 2017. Trained research assistants applied a semi-structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version, K-SADS-PL; (Kaufman et al., 1997) to all parents. Afterward, subjects were clinically evaluated for ADHD and comorbid conditions by a child psychiatrist using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, supported by K-SADS-PL results, as described in detail elsewhere (Rohde, 2002). Symptoms were assessed by the Swanson, Nolan, and Pelham IV scale (SNAP-IV; (Swanson, 1992), a reliable, valid and culturally adapted instrument that assesses the 18 DSM-IV ADHD symptoms (Mattos et al., 2006). SNAP-IV items are rated from 0 to 3. Inclusion criteria were the fulfillment of both ADHD diagnosis according to DSM-IV criteria and the availability of the SNAP-IV scale fulfilled by both parents and teachers, resulting in 420 subjects included for analysis.

Our second sample was recruited from 2,511 children and adolescents participating in the Brazilian High-Risk Cohort Study for Psychiatric Disorders. This is a large community school-based study comprehending 57 public schools in two Brazilian cities, Porto Alegre (n=22) and São Paulo (n=35), with both random and high-risk selected groups. All subjects were clinically evaluated for ADHD and comorbid conditions by trained psychologists using the Development and Well-Being Assessment (DAWBA; (Goodman et al., 2000). The DAWBA is a reliable and widely used structured interview answered by the caregiver of the child or adolescent, containing questions related to DSM-IV criteria. Structured questions and verbatim answers were carefully evaluated by psychiatrists, confirming or not the psychiatric diagnosis, as described in detail elsewhere (Salum et al., 2015). Symptoms of ADHD were assessed through DAWBA, which contains questions related to DSM-IV criteria, and they were rated from 0 to 2. Inclusion criteria were the fulfillment of ADHD diagnosis according to DSM-IV criteria and availability of reports of individual symptoms, resulting in 274 subjects included for analysis. They represent the totality of eligible cases.

Our third sample was recruited from 576 adults from the adult division of the ADHD Outpatient Program in the Hospital de Clínicas de Porto Alegre, from years 2002 to 2017. Psychiatrists applied to all subjects the modules of ADHD and ODD from the K-SADS-PL adapted for adults (Grevet et al., 2005), the module of Conduct Disorder from the Mini-International Neuropsychiatric Interview (M.I.N.I.; (Sheehan et al., 1998), and the Structured Clinical Interview for DSM-IV (SCID-IV; (First et al., 1997) for other comorbidities. Afterward, subjects were clinically evaluated for ADHD and comorbid conditions by a psychiatrist using DSM-IV criteria, except for age-of-onset criteria for ADHD that was extended to 12 years of age, as described in detail elsewhere (Grevet et al., 2006). Symptoms of ADHD were assessed using the SNAP-IV scale, described above (Swanson, 1992). It is important to highlight that the symptom described as “Runs About” is adapted into “Feeling Restless” in this scale for better understanding and appropriateness to adulthood. Inclusion criteria were the fulfillment of both ADHD diagnosis according to DSM-IV criteria and SNAP-IV scale by the subject, resulting in 572 subjects included.

The clinical sample of children and adolescents provided symptom information by both Parent and Teacher informants. Thus, we constructed two distinct networks denominated in this study as Parent and Teacher networks, respectively.

The community sample of children or adolescents provided only parent reports, and the clinical sample of adults provided self-reported symptoms, and they are denominated in this study as Community and Adult networks, respectively.

Statistical Analysis

We used the R-package *qgraph* to create the proposed networks, composed of symptoms (or nodes) connected by relations (or edges). We chose to construct our network structures using partial correlation networks, a method in which the connections are only present when symptoms are not independent after conditioning on all other symptoms in the dataset. In this model, the absence of a connection between symptoms means conditional independence (Costantini et al., 2015). To improve sparsity while maintaining a high likelihood of true positive connections in our model, we used the Least Absolute Shrinkage and Selection Operator (LASSO; (Tibshirani, 1996), converging the model to a parsimonious network and facilitating the discovery of its underlying structure (Foygel and Drton, 2011). We chose to reproduce the networks in a graphical layout where green lines between symptoms represent positive connections, while red lines represent negative connections. Thicker lines, more vivid colors and a shorter distance between symptoms represent stronger and more significant connections.

To better understand the measures of symptoms importance in the networks, we resort to three well-documented centrality indices in this study: strength, closeness, and betweenness. *Strength* represents the sum of weights of connections around a symptom, and a higher *strength* means a more direct influence of the symptom over other connected symptoms. *Closeness* represents the inverse of the summed distances of the symptom from all others, and a higher *closeness* means overall nearest relation with other symptoms and possibly more influence over most symptoms. *Betweenness* represents the sum of connections between other symptoms that pass through the symptom in focus, and a higher *betweenness* means more influence of the symptom over other symptoms connections.

We evaluated the stability of our networks centrality indices using the R-package *bootnet*, which indicates whether centrality indices are stable after ‘n’ re-samplings and reductions of the dataset employing *m-out-of-n bootstrap*. Stability values over 0.50 indicate good stability of centrality measurements, and values over 0.25 indicate that measurements are acceptable. We also evaluated the bootstrapped

Confidence Intervals (CI) of estimated connection weights, selecting the ten with highest weight for comparison. At last, we performed difference tests between all connection weights of the network, and between all centrality indices (Epskamp et al., 2018).

We compared different networks using the R package *NetworkComparisonTest*. This method applies permutation testing to compare independent datasets directly, and evaluates invariance of: a) *Network Structure*, concerning the distribution of the networks connections weights; and b) *Global Strength*, concerning the overall connectivity between symptoms in networks (Borkulo et al., 2017). For better comparability of our data, ratings in SNAP-IV scales equal to '3' were truncated into '2' to fit the DAWBA scale three-level structure.

RESULTS

We report demographic and clinical characteristics of all included cases from the three samples in Table 1. Included and excluded cases from our clinical sample of children or adolescents only differed significantly on IQ and ethnicity. The community sample of children or adolescents did not have excluded subjects, and 4 subjects were excluded from the clinical sample of adults due to missing data, precluding comparison.

We present the graphical reproduction of independently constructed networks in Figure 1. All symptoms were coded as seen in Table 2, distinguishing those from inattentive (i), hyperactive (h) and impulsive (im) dimensions, and the same code was used in supplemental materials. Stability analyses of the networks are presented in Table 3, and indicated Strength as the only acceptable centrality measurement in all created networks. Based on these findings, we focused our analyses on Strength measurements. All centrality measurements are presented in Figure 1 of Supplemental materials, and the standardized estimates of Strength were ranked for each network as described in Table 2. Bootstrapped confidence intervals of estimated connections ranked from highest to lowest strength, difference test of all connections, and difference test of Strength between symptoms are presented in Supplemental Materials.

Network analysis

In the Parent network, the stronger connections inside the net were, in decrescent order: *Difficulty waiting turn* and *Interrupts or intrudes, Loses objects* and *Forgetful, Does not follow through instructions* and *Difficulty organizing tasks, Blurts out answers* and *Difficulty waiting turn, Gets up* and *Runs about, Talks excessively* and *Blurts out answers, Fidgets* and *Gets up, Difficulty organizing tasks* and *Reluctant to engage in mental tasks, Runs about* and *On the go, Difficulty sustaining attention* and *Does not follow through instructions* (Figure 2 at Supplemental materials). The symptoms with the highest strength (defined arbitrarily as a strength over 1 SD) are *On the go* and *Does not follow through instructions*, in descending order. The two least strong symptoms (defined arbitrarily as a strength under 1 SD) are *Does not seem to listen* and *Talks excessively*, in descending order.

In the Teacher network, the stronger connections were: *Difficulty waiting turn* and *Interrupts or intrudes, Blurts out answers* and *Difficulty waiting turn, Does not follow through instructions* and *Difficulty organizing tasks, Runs about* and *On the go, Runs about* and *Excessively loud, Fails to give attention to details* and *Difficulty sustaining attention, Talks excessively* and *Interrupts or intrudes, Does not follow through instructions* and *Reluctant to engage in mental tasks, Fidgets* and *On the go, Gets up* and *Runs about* (Figure 3 at Supplemental materials). The strongest symptoms are *On the go*, *Difficulty waiting turn* and *Difficulty organizing tasks*, and the least strong symptoms are *Loses objects* and *Does not seem to listen*.

In the Community network, the stronger connections were: *Fidgets* and *Gets up, Excessively loud* and *On the go, Talks excessively* and *Interrupts or intrudes, Gets up* and *Runs about, Reluctant to engage in mental tasks* and *Easily distracted, Runs about* and *On the go, Does not follow through instructions* and *Difficulty organizing tasks, Fails to give attention to details* and *Does not follow through instructions, Easily distracted* and *Forgetful, Runs about* and *Excessively loud* (Figure 4 at Supplemental materials). The symptoms found to have the highest strength are *Easily distracted*, *Gets up*, and *Does not follow through instructions*, and the least strong symptoms are *Blurts out answers* and *Difficulty organizing tasks* (Table 2).

In the Adult network, the stronger connections were: *Gets up* and *Runs about, Fidgets* and *Runs about, Blurts out answers* and *Interrupts or intrudes, Loses objects* and *Forgetful, Does not follow through instructions* and *Difficulty organizing tasks, Difficulty waiting turn* and *Interrupts or intrudes, Talks excessively* and *Interrupts or intrudes, Difficulty organizing tasks* and *Forgetful, Fails to give attention to details*

and *Difficulty sustaining attention, Easily distracted* and *Forgetful* (Figure 5 at Supplemental materials). The symptoms found to have the highest strength are *Runs about* and *Fails to give attention to details*, and the least strong symptoms are *Reluctant to engage in mental tasks*, *Fidgets*, and *Loses objects* (Table 2).

Comparison of networks

From a first visual inspection, we perceived that all networks generally had positive connections, with well-formed clusters encompassing ADHD dimensions of inattention and hyperactivity/impulsivity. Inattentive symptoms are well distributed and interconnected while remaining symptoms are gathered in two unexpected sets: the first with all impulsive plus the hyperactive symptom *Talks excessively*, and a second with the remaining hyperactive symptoms (Figure 1).

Among the ten connections with highest weight inside each network (Figure 6 of Supplemental material), two were found in all networks (*Difficulty waiting turn* and *Interrupts or intrudes*, and *Gets up* and *Runs about*). The symptom *On the go* presents the highest strength in both Parent and Teacher networks, while the stronger symptom of other networks and general rank of symptoms wildly varied among networks (Table 2). Interestingly, the difference tests on both connection weights and strength of symptoms presented more significant differences in the Adult network when compared to all other networks (Figures 7-14 of Supplemental materials). To test the influence of symptom's prevalence over strength centrality measurements, we conducted secondary analyses testing the correlation between symptoms ranked according to their prevalence and strength on each network. Spearman correlations were very weak and non-significant for all our networks (Parents = -0.61, p-value = 0.810; Teachers = 0.57, p-value = 0.823; Community = 0.17, p-value = 0.498; Adults = -0.14, p-value = 0.570).

All network comparison tests performed are presented in Table 3. We did not observe significant differences between Parent and Teacher networks in both Network Structure and Overall Global Strength. Clinical and community samples of children and adolescents (Parent and Community networks), both based on parental informant report, did not differ in Network Structure, but differed in Overall Global Strength. Clinical children and adult samples (Parent and Adult networks) were significantly different in both Network Structure and Overall Global Strength.

DISCUSSION

In all networks constructed in this study, we observed well-drawn clusters of the ADHD dimensions of inattention and hyperactivity/impulsivity. We observed mostly positive relations of symptoms and the few negative relations were generally across different ADHD dimensions. No symptom in our analysis was isolated from others. For the first time in the literature, we performed stability analysis tests on networks analysis of ADHD symptoms, which indicated that strength is the only reliable centrality measurement in all networks constructed. Moreover, although the strongest symptom *On the go* was the same for both parent and teacher networks, this was not true for the other networks. Generally, we found a poor agreement of ranked symptoms according to their strength in the net across different samples and informants. Finally, our network comparison tests were enlightening. We observed that networks constructed from the same clinical sample of children, with different informants, were not significantly different towards both network structures and overall global strength. Clinical and community sample of children and adolescents did not significantly differ structurally from each other, although a significant difference in overall global strength was found. Clinical samples of children/adolescents and adults, on the contrary, demonstrated significant differences in both structure and global strength.

All networks visually derived well-drawn clusters of ADHD symptoms, although all networks tend to create two subsystems of inattentive and hyperactive/impulsive symptoms, congruent to the vast literature suggesting two ADHD presentations (i.e., Inattentive and Hyperactive/Impulsive). There was a predominance of connections inside each of these clusters, with few connections between them. A literature review of factor analyses supported the cross-cultural consistency of ADHD bidimensional models (Bauermeister et al., 2010). Our findings corroborate findings from these previous traditional psychometric studies, especially the bidimensional factor models. However, the authors highlight that their findings might have been different if impulsivity symptoms in DSM criteria were more than three, possibly shifting to support a three-dimensional model. In the present study, all networks displayed a pronounced visual proximity between the so-called hyperactive symptom *Talks excessively* and the three impulsivity symptoms of ADHD. Similar patterns were also previously found in traditional psychometric studies (Ghanizadeh

and Jafari, 2010), opposing conventional concepts present in DSM-5 and ICD-11 that include this symptom as part of the list of hyperactive symptoms (American Psychiatric Association, 2013; World Health Organization, 1992).

We observed a significant difference in Overall Global Strength of connections between Parent and Community networks (both parent informed samples) while no difference was found regarding Network Structure. Moreover, we also observed different demographic characteristics between those samples, especially concerning gender and comorbid profiles. The clinical sample of children and adolescents presented a higher male-to-female ratio when compared to the community sample (approximately 5:1 and 3:1, respectively). Those differences are congruent to the ones found in literature in similar contexts (Gaub and Carlson, 1997). Prior literature reviews found that females are more likely to present the inattentive subtype alone, although both genders share similar comorbidity and impairment patterns (Staller and Faraone, 2006). Indeed, our clinical sample presented a lower proportion of Inattentive and a significant higher proportion of the Combined subtypes of ADHD, and higher prevalence of comorbidity. This finding is explained both by sample origins (Gadow et al., 2001) and by possible associations between Combined subtypes of ADHD and overall comorbid disorders (Cumyn et al., 2009; Sprafkin et al., 2007; Wilens et al., 2009). Our findings regarding Network Structure support the idea of a validity of the different instruments in capturing ADHD profile among subjects in the same development age. We hypothesize that the significant difference observed in Overall Global Strength was due to these demographic differences found between samples, since the clinical sample probably possess different ADHD profiles with probably more severe cases of ADHD.

Parents and teachers from the clinical sample of children and adolescents reported symptoms somewhat differently for the same children. This agrees with literature, in which the correlation between different informants is usually poor (Lavigne et al., 2016, 2012; Takeda et al., 2016). However, in our comparison tests both Global Strength and Structure of Parent and Teacher networks were not significantly different. This finding suggests that changes in information source might have a smaller effect on Global Strength and Structure than changes in the developmental age of subjects or the origin of the sample. Nonetheless, it is important to notice that our Adult network was based on self-reported information, and we are not able to separate the effect of age and information source on network comparisons.

In the Adult sample, as expected from literature review, we observed a well-balanced male-to-female ratio (Cumyn et al., 2009; Sobanski et al., 2008) and higher prevalence of the Combined subtype of ADHD (Soendergaard et al., 2016). Furthermore, we found more significant differences between both connection weights and strength of symptoms when compared to all other networks. More significant differences reinforce the prominence of some connections and symptoms toward others and the concept of increasing differentiation of symptoms profile. This finding is congruent with the previous Network Analysis study by Martel and colleagues which observed an increasing differentiation of symptoms across developmental age (Martel et al., 2016). Surprisingly, while previous studies in literature state that hyperactive symptoms decrease along development (Biederman, 2000; Faraone et al., 2005), inattentive and hyperactive symptoms of our Adult network present similar rankings of strength and well-distributed connections. This might be found due to an advantage of the network analysis, which allows us to observe symptoms individually, enabling insights from a non-individual dimensional perspective.

The strongest symptoms in each network were variable in our analysis. In the clinical networks (parent and teacher), the strongest symptom was *On the go*. On the other hand, the strongest symptom in our adult network was *Runs about*, and in our community network was *Easily distracted*. Traditional psychometrics also demonstrate a poor agreement of factor loadings across different samples (Burns et al., 2006; Gomez et al., 2013). When analyzing the influence symptoms have on each other and the network, our findings support the understanding that individual symptoms might possess different weights in the diagnosis of ADHD. Silk and colleagues found similar evidence in their recent study using Network Analysis on ADHD children (Silk et al., 2019). Previous studies using Item Response Theory Analysis (Li et al., 2016; Lindhiem et al., 2015; Makransky and Bilenberg, 2014) have found evidence that symptoms present variable discrimination of latent traits according to age, gender, informants and severity of ADHD. Taking together available evidence, both traditional and novel psychometric approaches suggest a large symptomatic heterogeneity in ADHD, particularly as conceptualized as a continuous dimension.

One particular advantage unique for Network Analysis is the opportunity to dismantle different aspects of the symptoms not observed so far. Network analysis allows perceiving that strong symptoms may be inflating weak symptoms when both are strongly connected. In our analysis, a strong connection is found between *Difficulty*

waiting his turn and *Interrupts or intrudes*. Both symptoms present high strength, supporting that both symptoms capture ADHD construct independently and are not replaceable by the other. The opposite happens between the symptoms of *Difficulty waiting his turn* and *Blurts out answers*, especially in the Teacher network. Both symptoms are strongly connected, but *Difficulty waiting his turn* presents a much higher strength and therefore strong influence among nearest symptoms, including *Blurts out answers*. Although our study could not provide a complete set of centrality indices due to stability issues, this novel information increases our understanding of the interrelation of ADHD symptoms and might contribute to future diagnostic calibrations. However, the heterogeneity found highlights how difficult it might be to propose reduction on the number of DSM ADHD symptoms to characterize ADHD phenotype, since relevance of symptoms and connections among them strongly varies in different samples.

Some limitations of this study must be brought to attention. First, the lower stability found in our networks for two of the centrality measurements might be dependent on sample sizes. Second, we truncated scores in SNAP scales for better comparability of different samples, which also contributed to the reduction of stability in our analysis. Third, we conducted this analysis disregarding the effects of comorbid symptoms and severity of symptoms, which might present influence over our measurements. However, it is important to notice that Network Structure was not significantly different between clinical and community samples of children and adolescents even though two different instruments were used between them. On the other hand, in this study, we were able to construct four distinct networks of ADHD symptoms from different samples and informants, and we managed to compare their resultant ADHD constellation of symptoms using a novel psychometric interpretation. Further on, for the first time in literature, we applied stability analysis on the ADHD network, which has demonstrated to be highly necessary before interpretations and assumptions of the several measurements obtained. Finally, for the first time in literature, we performed mathematical comparisons of ADHD networks across different contexts.

Our study supports the idea of high heterogeneity in ADHD symptom relevance across different contexts, especially those associated with different sample origin and development across the life cycle. Besides, this approach reinforces the relevance of different ADHD symptomatic dimensions. We were able to detect more

influential symptoms in each context, and they might be possible candidates for weighted score instruments. As demonstrated by stability analysis, more studies are needed, especially with larger sample sizes. Furthermore, our study demonstrates that although different informants do not generally agree, symptom networks seem to be similar when the age and nature of the sample is similar. More significant differences in network structure and strength are found between samples of different nature or in different developmental stages.

Table 1: Demographic characteristics of samples and statistical comparison against included clinical children/adolescent cases.

	Clinical Children	Community Children	Clinical Adults
N	420	274	572
female (%)	92 (21.9)	98 (35.8)**	262 (45.8)**
age mean (sd)	10.3 (2.9)	10.0 (1.8)	33.7 (10.8)**
caucasian (%)	331 (79.0)[a]	160 (58.8)**[b]	480 (84.8)**[c]
IQ mean (sd)***	88.4 (15.70)[d]	98.1 (17.4)[e]	101.6 (9.1)[f]
ADHD subtype			
Combined (%)	255 (60.7)	105 (38.3)**	293 (51.2)*
Inattentive (%)	115 (27.4)	95 (34.7)	246 (43.0)**
Hyperactive (%)	20 (4.8)	40 (14.6)**	33 (5.8)
Comorbidities			
Oppositional Defiant Disorder (%)	184 (43.9)[a]	69 (25.2)**	216 (37.8)[a]
Conduct Disorder (%)	47 (11.2)[a]	19 (6.9)	2 (3.0)[g]
Any Anxiety Disorder (%)	112 (26.8)[b]	24 (8.8)**	100 (17.5)*[b]
Mood (%)	15 (3.6)[a]	14 (5.1)	218 (38.1)**[a]

(*) = p-value < 0.05; (**) = p-value < 0.001; (***) = In the clinical sample of children and adolescents, IQ was measured through american correction of values, while in the adults and community samples it was used brazilian correction. Generally, the mean difference is 10 points lower for the american correction; Number of missings: (a) = 1; (b) = 2; (c) = 7; (d) = 9; (e) = 24; (f) = 180; (g) = 506.

Table 2: Codes used for ADHD symptoms, *strength* values of each symptom in each sample, and rank of symptom strengths.

code	**ADHD symptom**	**Parents**	*rank*	**Teachers**	*rank*	**Adults**	*rank*	**Community**	*rank*
i1	*Fails to give attention to details*	-0.430	*13*	0.238	*7*	1.099	*2*	-0.846	*16*
i2	*Difficulty sustaining attention*	-0.182	*11*	-0.548	*10*	-0.933	*15*	-0.776	*14*
i3	*Does not seem to listen*	-1.811	*18*	-1.403	*17*	-0.573	*13*	-0.364	*10*
i4	*Does not follow through instructions*	1.362	*2*	0.950	*5*	0.155	*10*	1.125	*3*
i5	*Difficulty organizing tasks*	0.235	*8*	1.105	*4*	0.411	*7*	-1.221	*17*
i6	*Reluctant to engage in mental tasks*	0.778	*3*	-0.575	*12*	-1.868	*18*	-0.547	*13*
i7	*Loses objects*	0.011	*10*	-1.445	*18*	-1.394	*16*	-0.534	*12*
i8	*Easily distracted*	-0.987	*15*	-0.164	*9*	0.255	*9*	2.243	*1*
i9	*Forgetful*	0.165	*9*	0.206	*8*	0.492	*6*	-0.794	*15*
h1	*Fidgets*	-1.167	*16*	-0.806	*15*	-1.414	*17*	-0.193	*9*
h2	*Gets up*	0.289	*7*	-0.587	*13*	0.123	*11*	1.435	*2*
h3	*Runs about*	0.512	*5*	1.251	*3*	2.112	*1*	0.535	*6*
h4	*Excessively loud*	-0.685	*14*	-0.572	*11*	0.913	*3*	0.389	*7*
h5	*On the go*	2.352	*1*	1.788	*1*	0.555	*5*	-0.368	*11*
h6	*Talks excessively*	-1.214	*17*	-0.684	*14*	-0.163	*12*	0.899	*4*
im1	*Blurts out answers*	-0.352	*12*	-0.954	*16*	0.261	*8*	-1.590	*18*
im2	*Difficulty waiting turn*	0.718	*4*	1.401	*2*	-0.706	*14*	0.724	*5*
im3	*Interrupts or intrudes*	0.405	*6*	0.799	*6*	0.674	*4*	-0.120	*8*

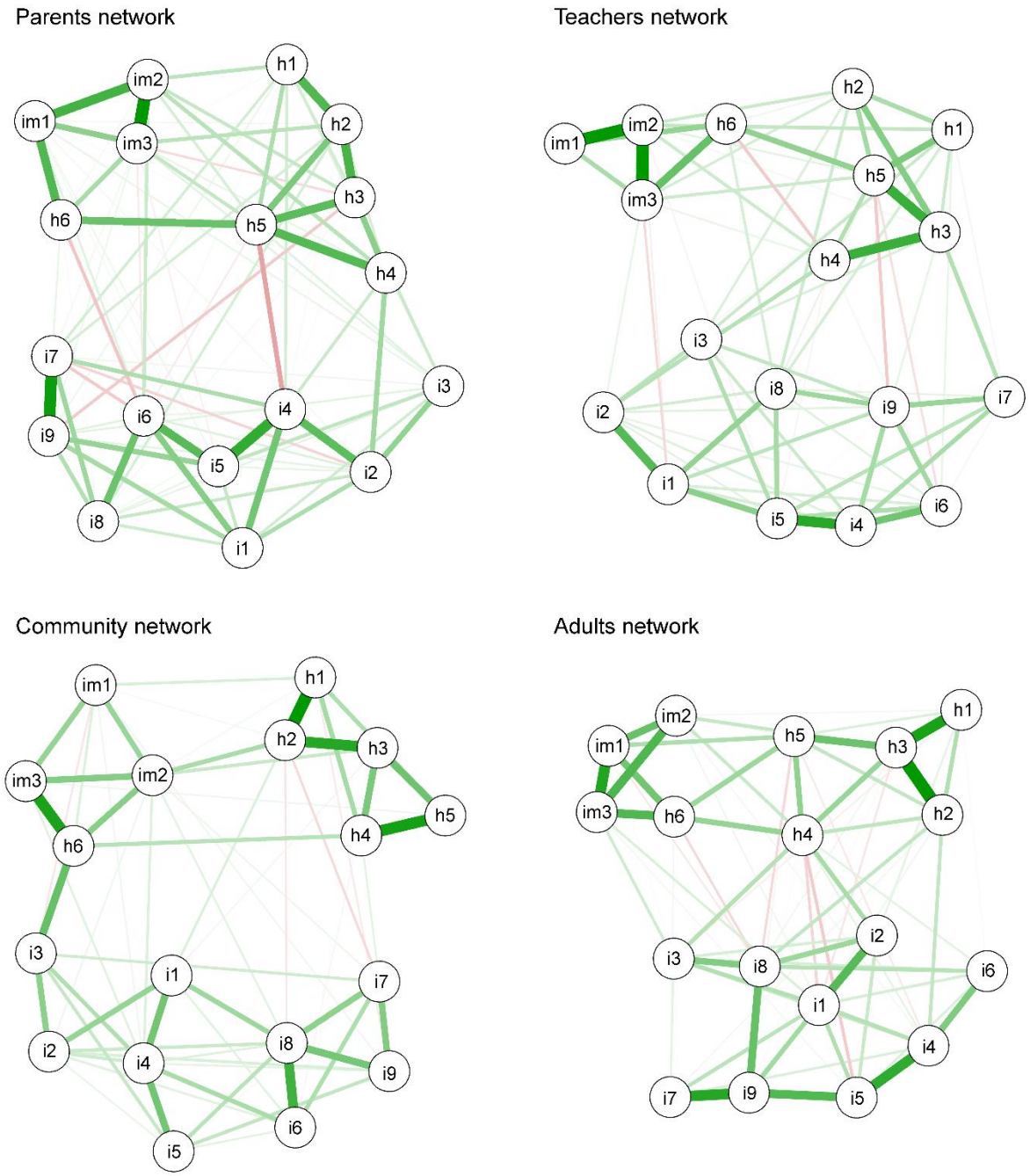
Dimensions of ADHD are represented as “i” (inattentive) and “h” (hyperactive/impulsive); *Strength* is represented in z-scores; Rank ordered from strongest to weakest symptom among each sample.

Table 3: Network Comparison Tests and Network Stability Analysis

Network	(P)	(T)	(C)	(A)	Stability Analysis		
	Overall Global Strength				between..	closeness	strength
Parents (P)		.240	.000*	.006	0.050	0.050	0.283**
Teachers (T)	.220		.000*	.006	0.050	0.050	0.283**
Community (C)	.078	.074		.302	0.051	0.051	0.361**
Adults (A)	.002*	.002*	.000*		0.051	0.206	0.518**
	Network Structure						

Network Comparison Tests are represented as p-value. (*) significant p-value = p-value < 0.05; (**) acceptable results for stability

Figure 1: Graphics of networks constructed with ADHD symptoms



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2. ARTIGO 2

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Assessing Undertreatment and Overtreatment/Misuse of ADHD medications in children and adolescents across continents: a systematic review and meta-analysis

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Conflict of interest:

LAR has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Medice, Novartis/Sandoz, and Shire/Takeda in the last 3 years. He receives authorship royalties from Oxford Press and ArtMed. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Novartis/Sandoz, and Shire/Takeda. He received travel grants from Shire/Takeda for attending the 2018 APA meetings. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), Healthcare Convention, and British Psychopharmacology Association (BPA) in

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Author contributions:

RM had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CRMM, SC, GP and LAR were responsible for the study concept, and RM, CRMM, GP, SC and LAR were responsible for the study design. RM, CRMM, FC, MS, JA, LT and GCAM were involved in the acquisition of data. RM and LAR were involved in statistical analysis and interpretation of data. RM, LAR, SC, and GP drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

ABSTRACT

A controversy exists on whether there is an over or underuse of medications for Attention-Deficit/Hyperactivity Disorder (ADHD). We conducted the first meta-analysis to estimate the rate of ADHD pharmacological treatment in both diagnosed and undiagnosed individuals. Based on a pre-registered protocol (CRD42018085233), we searched a broad set of electronic databases and grey literature. After screening 25,676 abstracts, we retained 36 studies including 104,305 subjects, from which 18 studies met our main analysis criteria. The pooled pharmacological treatment rates were 19.1% and 0.9% in school-age children/adolescents with and without ADHD, respectively. We estimated that for each individual using medication without a formal ADHD diagnosis, there are three patients with a formal diagnosis who might benefit from medication but do not receive it in the US. Our results indicate both overtreatment/misuse of medication in individuals without ADHD and pharmacological undertreatment in youths with the disorder. Our findings reinforce the need for public health policies improving education on ADHD and discussions on the benefits and limitations of ADHD medications.

Keywords: ADHD, prevalence, treatment, stimulants, pharmacological interventions

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders, characterized by developmentally-inappropriate and impairing inattention and/or hyperactivity-impulsivity.[1] The worldwide prevalence of the disorder is estimated at around 5-7% among children/adolescents and 2.5% in adults.[2,3] Individuals diagnosed with ADHD are at higher risks of several negative outcomes (e.g., substance misuse,[4] car accidents,[5] unintentional injuries,[6] emergency department visits,[7] depression,[8] criminality[9] and suicide[10]). They also present a mortality rate of 2.64-fold higher than the one in non-affected individuals,[11] although Sun et al. (2019) found that such high mortality rates are mostly but not exclusively driven by comorbidities. [12] All these consequences, and the substantial economic impact associated with them,[13] turn ADHD into a relevant public health problem. However, ADHD diagnosis continues to be controversial in lay media.[14,15] In the scientific community, one of the most intense controversies is whether the disorder is under or over-diagnosed,[16] and, more importantly, under or over-treated with medications.[17–19]

Pharmacotherapy for ADHD is supported by meta-analytic evidence, at least in the short-term,[20] and recommended as the first-line treatment in most of the international guidelines/practice parameters.[21–25] In some of them, pharmacological treatment is reserved for severe cases,[26] or as a treatment strategy for patients who have not responded to non-pharmacological interventions.[26,27] There has been an increase in the prescription rates of ADHD medications over the last decades, leading to concerns of overdiagnosis and overtreatment.[17–19] A large study on the prevalence of ADHD treatment worldwide relied on data referring to treatment-

seeking populations. [28] Thus, this investigation could not establish prescription rates of medication for affected and non-affected individuals in the community. As a result, it remains unclear which proportion of patients with ADHD, who may benefit from pharmacological treatment, indeed do receive it and which proportion of non-affected individuals are potentially misusing ADHD medication.

In this systematic review and meta-analysis, we aimed to estimate the pooled rates of ADHD medication use in both children and adolescents with and without ADHD across continents, filling this critical gap in the literature. To our knowledge, no previous meta-analysis with this objective has been conducted. We hypothesized that global pooled estimates in affected individuals would suggest overall undertreatment of ADHD.

METHODS

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[29] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE).[30] The MOOSE checklist is reported in supplemental materials, page 4. The protocol for this study is registered in the International Prospective Register of Systematic Reviews (PROSPERO), CRD42018085233, and is published elsewhere.[31]

Selection criteria

We searched for population-based, cross-sectional or longitudinal studies published since inception up to April 30th, 2020, with no language or age restrictions. Studies had to report data on participants primarily diagnosed with ADHD or

Hyperkinetic Disorder (HKD) and/or on non-affected individuals. We accepted all the following definitions of ADHD: a) medical diagnosis according to any DSM versions (II, III, IV(-TR), 5), ICD- 9 or ICD-10, confirmed by validated diagnostic instruments (Supplemental materials, Table S1) or clinical interviews; b) diagnosis using a validated ADHD symptom scales with a pre-specified threshold (Supplemental materials, Table S1); or c) diagnosis reported by participants/caregivers (e.g., an affirmative answer to the question “did any doctor diagnosed you [or your familiar] with ADHD?”). We included studies presenting information on stimulants (methylphenidate, dexmethylphenidate, amphetamines), and atomoxetine, which are recommended by the majority of the international guidelines.[21–26] We also retained studies with ADHD medication use reported by participants/caregivers (e.g., an affirmative answer to the question: “Are you [or your familiar] currently taking medication for ADHD?”).

We excluded studies: a) based on clinical samples, including those relying on insurance health system and third-party reimbursement data sets, as our research question was on the rates of ADHD treatment use in the population and not in individuals searching for treatment; b) with no clear description of the diagnostic process; and c) using solely ADHD pharmacological treatment as an indication (proxy) for ADHD diagnosis (without proper confirmation of the diagnosis), thus avoiding a tautological approach. Before exclusion, we systematically contacted all the authors of studies lacking relevant information via e-mail to request missing information, making at least three attempts to gather missing information/data.

Search strategy and data extraction

The search strategies/syntaxes were developed with the support of a librarian at the University of Southampton, UK. The following main databases were searched: Medline, Embase, CINAHL, PsychINFO, Web of Science, and Scopus. Details on search strategy/syntax and a list of additional databases and websites searched, including sources of conference abstracts, are described in supplemental material (pages 10-16). Papers selected for full-text reading and relevant systematic reviews were hand-searched for references of interest. The first author of each included study and experts in the field were contacted to retrieve gray literature. However, no unpublished studies of interest were found.

Data extraction followed standard procedures (see supplemental material, page 17). We extracted the following data: a) Study author, year of publication, country, year of data collection, name of the sample (if any), study design and response/completion rates (if reported); b) Patient age range, age mean, gender, method of ADHD diagnosis, diagnostic criteria, comorbidities, co-medication, name of diagnostic instrument and/or rating scale (if described), socioeconomic status, level of care (primary, secondary, or tertiary); c) Medication class and formulation, dose range, mean dose, length of treatment and medication assessment method (e.g., only question exploring if the individual was using or not ADHD medication, request for showing the container of the medication, or confirmation of the of ADHD medication prescription in medical records).

Study outcome measure and quality of the studies

The primary outcomes of our meta-analyses were the rates of ADHD medication use by children and adolescents with a clinical diagnosis of ADHD or HKD, and the prevalence rates of ADHD medication use in non-affected individuals.

We assessed the quality of studies using a modified version of the Newcastle–Ottawa scale (NOS)[32] (see details in supplementary materials, page 17 to 19).

Data Analysis

A meta-analysis of proportions was performed with the *"meta"* package in R software. The Metaprop function was used to compute the independent pooled prevalence and 95% confidence interval (95% CI) of medication use in pharmacologically treated and untreated individuals, both with and without a diagnosis of ADHD.[33] Normality tests of study rates were performed using Log, Logit, and Freeman-Tukey Double Arcsine transformations, and the Logit transformation was the most appropriate. The confidence intervals were computed using the Clopper-Pearson exact method with continuity correction, a proper method for small proportions.[34] We used the DerSimonian and Laird method for random-effect model due to expected heterogeneity among studies.[35] Heterogeneity was evaluated with the Cochran's chi-squared test (Cochran's Q), and the I^2.[36] Publication bias was explored through the visual inspection of the funnel plot asymmetry and the Egger's linear regression test.[37] The jackknife sensitivity analysis was used to explore the effect of individual studies in both prevalence and heterogeneity.[38] Additionally, individual random-effect meta-regression analyses were conducted exploring the impact of following covariates (individually entered in the model): year, quality of the study, continent, country, method of diagnosis, type of medication, method of medication assessment and study design.

Any deviation of the published protocol is reported in the supplementary materials, page 20.

RESULTS

As presented in Figure 1, 25,676 records were screened, and 36 studies from 10 countries were retained, including a total of 104,305 participants.[39–74] The list of studies excluded after the full-text screening with reasons of exclusions can be found in Supplemental Material, Table S4. We found 5 studies with adult samples (n = 6,620), the majority being restricted to university students. In addition, we found two studies exclusively on preschoolers (5 years old or younger, n = 20,174). Adult and preschooler analyses are reported separately in Supplemental materials (Tables S5 and S6, Figures S1 and S2).

Most of the studies with samples of children and adolescents included in our analyses were cross-sectional with ADHD diagnosis according to DSM criteria (see Table 1). The population included in these studies encompassed youth mostly from Western developed countries, predominantly from the United States of America. The few control samples that described other psychiatric diagnoses had lower rates of mental disorders than ADHD samples. The mean response/completion rate of the studies included in the main analysis was 68%.

Our main analyses were restricted to studies including children and adolescents where the diagnosis was made either according to DSM/ICD criteria or to validated scales. The pooled pharmacological treatment rate for the DSM/ICD ADHD diagnosis group (18 studies; n = 3,311) was 0.191 (95% CI: 0.115-0.299; Figure 2). Regarding the non-ADHD group (14 studies; n = 29,559), the pooled ADHD medication use rate was 0.009 (95% CI: 0.005-0.017; Figure 3).

The mean NOS score was 3.7 for studies included in our main analyses, and the most critical item affecting total scores was comparability (see Table 1). Funnel plots for both groups are shown in supplemental material (Figures S3 and S4). Egger's test was non-significant for both diagnosed and undiagnosed groups (p-values of 0.29 and 0.10, respectively), not suggesting a significant risk of publication bias.

We identified high heterogeneity in our main analyses involving both diagnosed and undiagnosed groups. Jackknife sensitivity analyses demonstrated that, in no instance, single study exclusion significantly modified the heterogeneity (Supplemental material, Figures S5 and S6). When exploring the impact of covariates (e.g., year, quality of the study, continent, country, medication assessment method, type of medication and study design) on heterogeneity and estimates of our main analyses, we observed that heterogeneity was reduced when the studies were grouped according to continents; specifically, it was lower in Europe and Oceania (Supplemental material: Figures S7-S16). Meta-regressions findings for the studies that used DSM and/or ICD criteria for ADHD diagnosis (main analyses) in children and adolescents presented the following significant covariates: quality of the study (p-value 0,0349: heterogeneity accounted for [HAF] = 23.54%), country (p-value = 0.0391; HAF = 14.97%) and study design (p-value = 0.0230, HAF = 33.69%), indicating that these variables did significantly impact heterogeneity, while meta-regression findings in relation to non-ADHD children and adolescents were non-significant (Supplemental material: Tables S7 and S8).

To assess influence of diagnostic method, we also meta-analyzed all samples of children and adolescents with and without ADHD diagnosis (29 and 17 studies, respectively) in which ADHD diagnosis was assessed either by DSM/ICD

criteria or just through a question about previous ADHD diagnosis. As studies where the diagnosis was made based on the answer to only one question about previous ADHD diagnosis include treatment-seeking populations, they presented inflated rates of treatment for children and adolescents with the diagnosis [0.516 (95% CI: 0.435-0.596) vs. 0.191 (95% CI: 0.115-0.299), Supplemental material: Figure S17], and deflated rates of treatment for children and adolescents without a diagnosis [0.001 (95% CI: 0.000-0.049) vs. 0.009 (95% CI: 0.005-0.017), Supplemental material: Figure S18].

Finally, in our analyses with all 29 included studies with samples of children and adolescents diagnosed with ADHD (n = 24,106), the pooled pharmacological treatment rate was 0.315 (95% CI: 0.255-0.382), as shown in Supplemental material, Figure S19. Data from all 17 studies of children and adolescents without an ADHD diagnosis (n = 48,681) indicated a pooled rate of medication use of 0.007 (95% CI: 0.004-0.013), as reported in Supplemental material, Figure S20.

Extrapolation of the findings based on available population data for three countries in different continents (the US, the Netherlands and Australia)

For the purpose of our subsequent analyses, we conservatively assumed that at least 70% of the children and adolescents with a proper ADHD diagnose might benefit from a trial with ADHD medication (see discussion for reasons to establish this threshold). Combining our findings for the US, the Netherlands and Australia (Supplemental materials, figures S10 and S15) with the estimated youth population between 5 and 19 years of age in these countries according to the United Nations[75], and the estimated prevalence of ADHD using DSM criteria in this age range in these countries,[76-78] we estimated the rates of

treatment for children and adolescents affected by ADHD and use of medication for ADHD by those without the disorder in these three countries from different continents.

In the US, data indicates that: a) an estimated 1.97 million youths diagnosed with ADHD are treated with medication (33.3% of total ADHD cases); b) 2.17 million individuals might still benefit from ADHD pharmacological treatment but do not receive it (36.7%: 70% eligible for medication minus the 33.3% already treated); and c) 677,425 children and adolescents without a formal ADHD diagnosis might be using medication for the disorder (total population between 5-19 years of age in the US [62,378,000] minus those affected by ADHD [9.5%] multiplied by the prevalence of medication for ADHD use in those without a formal diagnosis for the disorder [1.2%]). Thus, for each child and adolescent without ADHD using medication for the disorder, there are more than 3 children with ADHD who might benefit from pharmacological interventions and are not receiving it in the US.

In Australia, while 45,000 children/adolescents with ADHD (12.8%) are estimated to be treated with medication, 202,000 children/adolescents may be diagnosed and are still not pharmacologically treated despite eligible, and only 18,000 children/adolescents without formal diagnosis of ADHD (0.4%) may be using ADHD medication, representing an 11-fold difference between under pharmacological treatment and overtreatment/misuse rates.

In the Netherlands, while 17,000 children/adolescents with ADHD (22.2%) are estimated to be treated with medication, 37,000 may be diagnosed and are still not pharmacologically treated despite eligible, and 22,000 youths without formal diagnosis of ADHD (0.8%) may be using ADHD medication, representing less than 2-fold difference between under and overtreatment/misuse.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis investigating the prevalence of ADHD medication use in both individuals diagnosed with ADHD and in those without the disorder. Our main analyses suggest that 19.1% (95% CI: 11.5-29.9) of the school-age children and adolescents affected by ADHD are treated with medication for the disorder, and 0.9% (95% CI: 0.5-1.7) of individuals without the diagnosis use medication for ADHD. As expected, substantial heterogeneity was found in our analyses.

Even though ADHD guidelines worldwide recommend medication as part of the treatment of the disorder, they present differences regarding their recommendations on pharmacological treatment. While some guidelines, mostly from America, recommend pharmacotherapy as the first-line treatment,[21–25] some European guidelines tend to recommend non-pharmacological treatments prior to medications, or for moderate/severe cases of ADHD. [26,27] Although the evidence for efficacy of non-pharmacological treatment in ADHD and for the percentage of patients who respond to them are controversial,[79] available randomized clinical studies using sequential approaches (e.g., medication or placebo after no response to non-pharmacological interventions) suggest that 18-23% of the patients might respond to an initial trial of parent training[80] or behavioral interventions without a need for medication.[81] In the same direction, the definition of what constitutes a moderate/severe ADHD case is not clear in the literature. However, some epidemiological studies describe the percentage of ADHD cases categorized according to its severity.[62,82] In these studies, 70-76% of all ADHD cases defined by

DSM criteria are classified as moderate or severe. Thus, a conservative appraisal of this literature indicates that around 70% of the patients with ADHD might benefit from a trial with pharmacological treatment (no dispute among different guidelines). Thus, we conservatively assumed this figure (70%) as the one reflecting the proportion of the children and adolescents with properly diagnosed ADHD who might unequivocally benefit from a trial with ADHD medication.

It is important to highlight that we could not exclude from our analysis several groups that might be using stimulants adequately but are otherwise included in the group of non-affected individuals treated with ADHD medication, such as: a) previously diagnosed patients who responded to treatment and did not present anymore full ADHD diagnostic criteria when assessed in the studies; [48] b) subthreshold cases of ADHD who might have impairment and treatment indication;[83] and c) individuals with other diagnoses that are also indications for stimulant use (e.g., narcolepsy or resistant depression).[84] Nonetheless, our findings support the presence of over/inadequate treatment in different countries, raising concerns on stimulant overuse/ misuse, as recently suggested by others.[85]

The high heterogeneity observed in this meta-analysis, anticipated in our protocol,[31] indicates that our findings should be considered with caution. However, rather than the heterogeneity per se, it is more informative to focus on the reasons for heterogeneity. Our sensitivity meta-regression analyses identified that quality of the study, country and study design were significant covariates with important impact on heterogeneity for samples with children and adolescents with ADHD. In fact, these findings are congruent with the literature in several ways. Previous investigations suggest that ADHD medication use is predicted by sociodemographic variables and different practice parameters for ADHD prescriptions among countries.

Galera et al. observed that being male, with a mother with low education levels or being immigrant increases the hazard risk ~2 fold for ADHD medication use.[86] Wallach-Kildemoes et al. described the impact of different prescribing practices on rates of patients with ADHD treated in Denmark.[87] In our analysis including all samples (n = 29) of children and adolescents with ADHD independently of the diagnostic procedure (DSM/ICD criteria and diagnosis only reported by caregivers), as expected, the diagnostic method was a very influential covariate on our estimates. It is important to highlight that even larger meta-analyses on ADHD prevalence, with more than one hundred studies, observed similar high levels of heterogeneity.[2,88,89] Moreover, as in our study, methodological variables, as study design and diagnostic method, were found as the most important covariates explaining heterogeneity in those epidemiological studies.

Rather than a reductionist vision focusing only on either ADHD pharmacological overtreatment/misuse or under-treatment, we suggest that "*the two sides of the coin"* should be considered. The data presented in this study shows clearly that both ADHD pharmacological overtreatment/misuse and ADHD pharmacological undertreatment occurs concomitantly across the different countries with available data. However, it is important to appreciate that undertreatment and overtreatment are not uncommon in medicine. In fact, this dichotomy dates back to the initial use of antibiotics throughout nowadays.[90] More specifically, in psychiatry, studies on depression already demonstrated the diversity of clinical practices, with mixtures of both overtreatment of patients that do not fulfill diagnostic criteria and undertreatment of moderate and severe cases of the disorder,[91] apparently a worrisome paradox with multiple associated factors.[92]

Our study should be considered in light of its limitations. First, it is important to note that even though the data collected constitute the most comprehensive evidence available in the literature and response/completion rates observed are acceptable, it does not constitute a world representative sample. Moreover, differences in patterns of medication use exist even within countries.[86,93] Second, the funnel plots of our main analyses present a scattered pattern. However, the Eggers' tests were non-significant, and non-statistical methods were also extensively implemented against publication bias, an approach even more important in meta-analysis with a small number of studies.[94] Third, a relatively limited number of studies was included in our analyses. In addition, they presented substantial heterogeneity. Both issues reduce our external validity. However, heterogeneity was expected from the beginning, and it was also found in the three previous epidemiological ADHD meta-analyses that relied on worldwide samples,[2,88,89] even when the number of studies was over one hundred. Fourth, most of the selected studies were from developed countries, with USA samples being dominant. This finding most certainly inflates the treatment rates due to the exclusion of a large proportion of the world population with significant financial, cultural, and health access barriers to ADHD treatment. Fifth, we excluded studies on populations under five years from the main analyses, since treatment with medication in that age range is controversial and guidelines consensually do not recommend medication as first-line treatments. Sixth, several of the included studies performed medication assessment through only questioning the patient/caregiver on ADHD medication use, without using confirmatory methods. However, the medication assessment method was not a significant variable in meta-regression analyses. In addition, some studies assessed only lifetime ADHD or did not provide sufficient data to inform on

the approach used in the assessment (e.g., lifetime, current, past year diagnosis), making the evaluation of temporality between the presence of the disorder and use of medication a challenge. However, this issue was far less pronounced in studies included in our main analyses. Seventh, most non-ADHD samples did not allow differentiation between overtreatment and misuse. However, the prevalence of nonmedical use of medication is a reality mostly among adult and older adolescent populations. Finally, our data include the evidence on the pharmacological treatment of ADHD, and it does not address a potential more global under-treatment of ADHD, including non-pharmacological interventions.

Despite these limitations, our meta-analysis provides evidence for a substantial under-treatment of children and adolescents affected by ADHD in different countries. This is a relevant public health issue worldwide, since ADHD undertreatment is associated with known negative outcomes in education, health care, and productivity systems. At the same time, we found evidence of overtreatment/misuse in individuals without a formal ADHD diagnosis. This practice might expose individuals to undesirable side effects of medications, increased risk of medication misuse, and unmeasured costs for the health care system. Our findings indicate that, more than disputes between supporters and detractors of medication treatment for ADHD, additional evidence-based medical and parental education on ADHD is needed worldwide, as part of public health policies.

Table 1: Characteristics of studies in children and adolescent included in the meta-analysis.

Study	*Sample description*	*Country*	*Design*	*Diagnosis*	*Age*	*Response/ Completion rates (%)*	*Controls*		*ADHD*		*NOS*		
							Treatment Negative	*Treatment Positive*	*Treatment Negative*	*Treatment Positive*	*selection (up to 4)*	*comparability (up to 2)*	*total*
Angold et al., 2000	Great Smoky Mountains Study, 1992-1996	USA	Retrospective	DSM	9-16	71	1179	86	34	58	3	2	5
Barbaresi et al., 2002	Rochester Epidemiology Project, 1976-1982	USA	Retrospective, Administrative	DSM	NS	NS	5045	10	41	264	4	1	5
Bauermeister et al., 2003	Puerto Rico Service Use Study, 1999-2000	USA	Retrospective	DSM	4-17	90	1513	6	132	11	3	2	5
Bird et al., 2008	New York (South Bronx) and Boricua Youth Study (Puerto Rico)	USA	Prospective	DSM	5-13	85	2263	42	155	20	3	1	4
Bussing et al., 2005	North Central Florida public school, 1998-1999	USA	Prospective	DSM	5-11	55	61	0	92	67	4	1	5
Concannon et al., 2005	Northern Sydney, 2000	Australia	Cross Sectional	Question	10-12	65	-	-	128	150	1	0	1
Danielson et al., 2018	National Survey of Children's Health (NSCH), 2016	USA	Cross Sectional	Question	2-17	41	-	-	1618	2640	2	0	2
Efron et al., 2019	Longitudinal Study of Australian Children (LSAC), 2004-2015	Australia	Prospective	Question	14-15	71	-	-	19	72	2	0	2
Epstein-Ngo et al., 2015	Midwestern United States public schools, 2009-2013	USA	Cross Sectional	Question	NS	68	-	-	581	179	1	1	2
Froehlich et al., 2007	National Health and Nutrition Examination Survey (NHANES) 2001-2004	USA	Cross Sectional	DSM	8-15	79	-	-	143	79	4	1	2

Hailpern et al., 2014	National Health and Nutrition Survey (NHANES) 1999–2004	USA	Cross Sectional	Question	12-18	NS	4524	0	272	111	3	0	5
Jensen et al., 1999	Epidemiology of Child and Adolescent Mental Disorders (MECA) Study (1992)	USA	Cross Sectional	DSM	9-17	85	904	8	53	8	4	1	3
Knopf et al., 2012	German Health and Examination Survey for Children and Adolescents (KiGGS), 2003-2006	Germany	Cross Sectional	Question	0-17	67	12682	3	512	142	2	1	5
Merikangas et al., 2013	National Comorbidity Survey Adol. Suppl. (NCS-A), 2001-2004	USA	Cross Sectional	DSM	13-18	83	5953	93	355	82	3	1	3
Montiel et al., 2008	Maracaibo, Venezuela	Venezuela	Cross Sectional	DSM	4-12	88	75	4	148	6	3	1	4
Reich et al., 2006	Missouri twins sample, 1996-2001	USA	Cross Sectional	DSM	7-17	65	273	9	20	21	4	1	4
Russel et al., 2019	Millennium Cohort Study, 2014-2015	England	Cross Sectional	Question	14	61	-	-	104	141	2	0	5
Sayal et al., 2010	British Child and Adolescent Mental Health Survey (B-CAMHS) 2004	England	Cross Sectional	DSM/ICD	5-16	76	-	-	123	53	2	1	2
Sawyer et al., 2002	Australian National Survey of Mental Health and Well-Being, Feb-May 1998	Australia	Cross Sectional	DSM	6-17	70	3149	16	345	52	3	1	3
Sawyer et al., 2016	Australian National Child and Adolescent Mental Health Survey. 2013–2014	Australia	Cross Sectional	DSM	4-17	55	5854	22	374	55	4	1	4

Sciberras et al., 2016	Children's Attention Project, Melbourne, Australia, 2011-2015	Australia	Prospective	DSM	6-8	60	212	0	156	21	4	0	5
Schmitz et al., 2006	Public schools in Porto Alegre, 2002-2005	Brazil	Cross Sectional	DSM	6-18	93	-	-	97	3	4	1	4
St Amour et al., 2018	Heart Behavioural and Environmental Assessment Team	Canada	Cross Sectional	Question	10-14	31	1863	50	50	49	2	1	5
Szatmari et al., 1989	The Ontario Child Health Study (OCHS) 1966-1979	Canada	Cross Sectional	DSM	4-16	NS	2542	2	149	8	4	0	3
Szobot et al., 2007	Canoas, 2004	Brazil	Cross Sectional	DSM	15-20	70	-	-	41	0	4	0	4
Toomey et al., 2011	National Survey of Children's Health (NSCH) 2007	USA	Cross Sectional	Question	6-17	47	-	-	1666	3463	1	0	4
Tremmery et al., 2007	Study of Attention Disorders in Maastricht (SAM) 1999-2000	Netherlands	Prospective	DSM	9	32	236	2	35	10	3	1	1
Visser et al., 2007	National Survey of Children's Health (NSCH) 2003	USA	Cross Sectional	Question	4-17	55	-	-	2711	3786	1	0	4
Walls et al., 2017	National Survey of the Diagnosis and treatment of Attention-Deficit/Hyperactivity Disorder and Tourette Syndrome (NS-DATA) 2014	USA	Cross Sectional	Question	8-17	11	-	-	712	1689	1	0	1

"NS" = not stated (papers do not supply a range or mean age for those samples); "NOS" = Newcastle Ottawa Scale.

Figure 1: Search and screening flowchart.

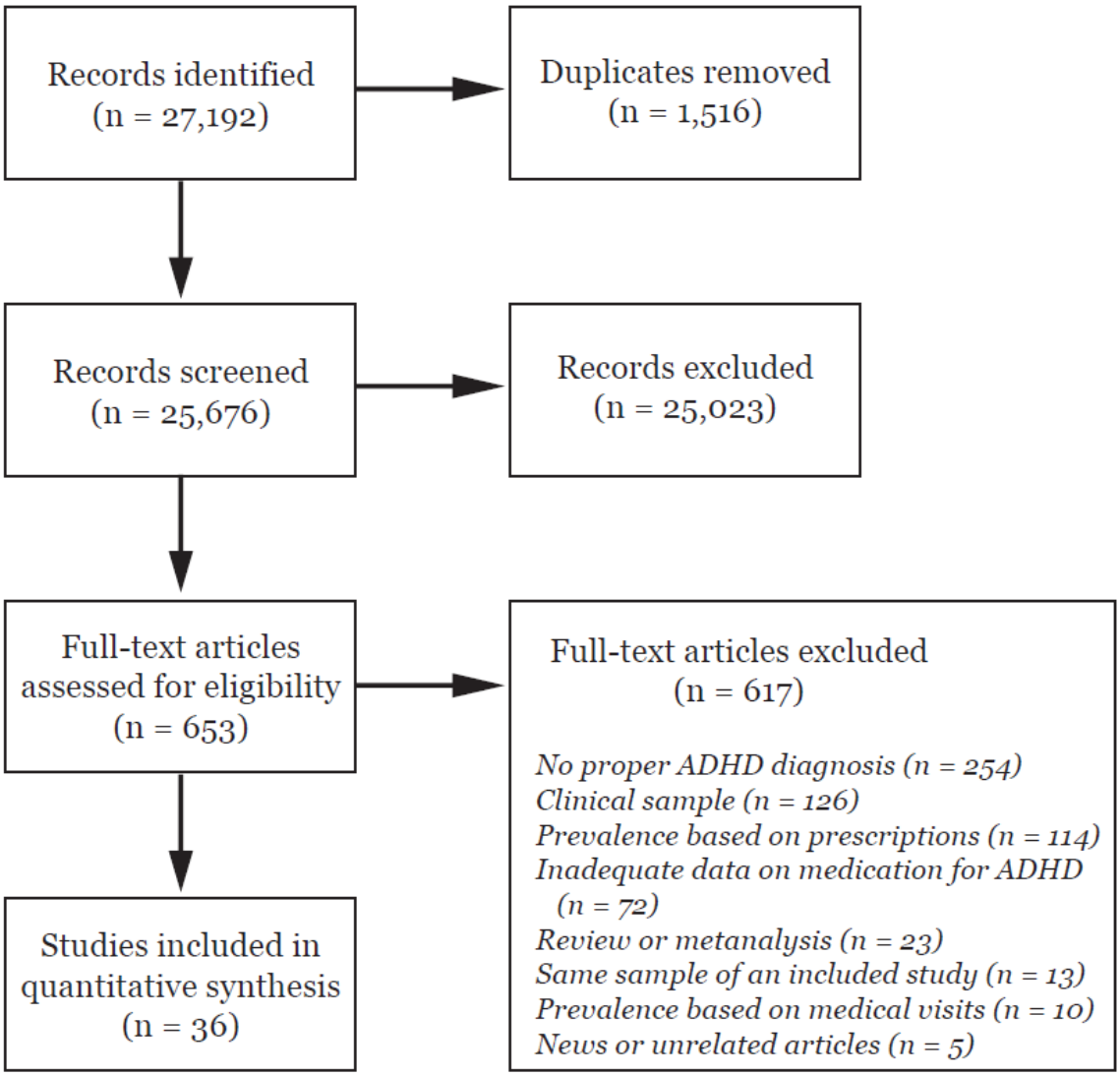


Figure 2: Forest plot showing the meta-analysis results of ADHD medication use among children and adolescents diagnosed with ADHD according to the DSM/ICD criteria

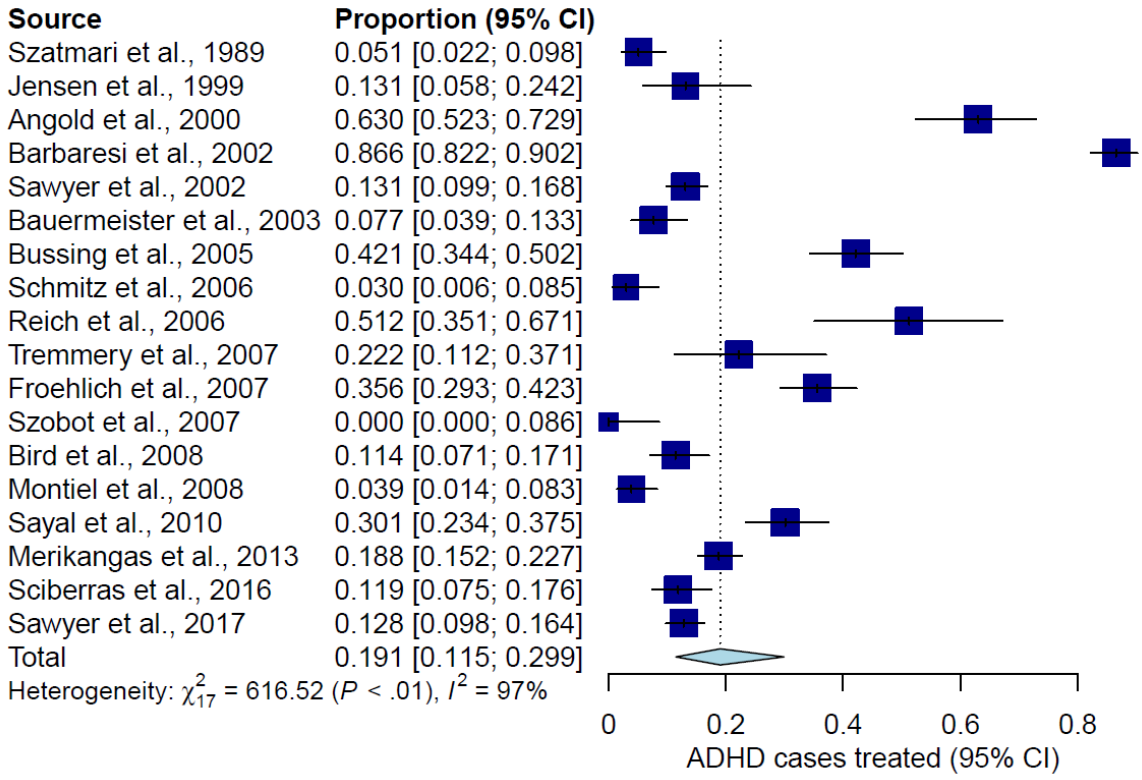
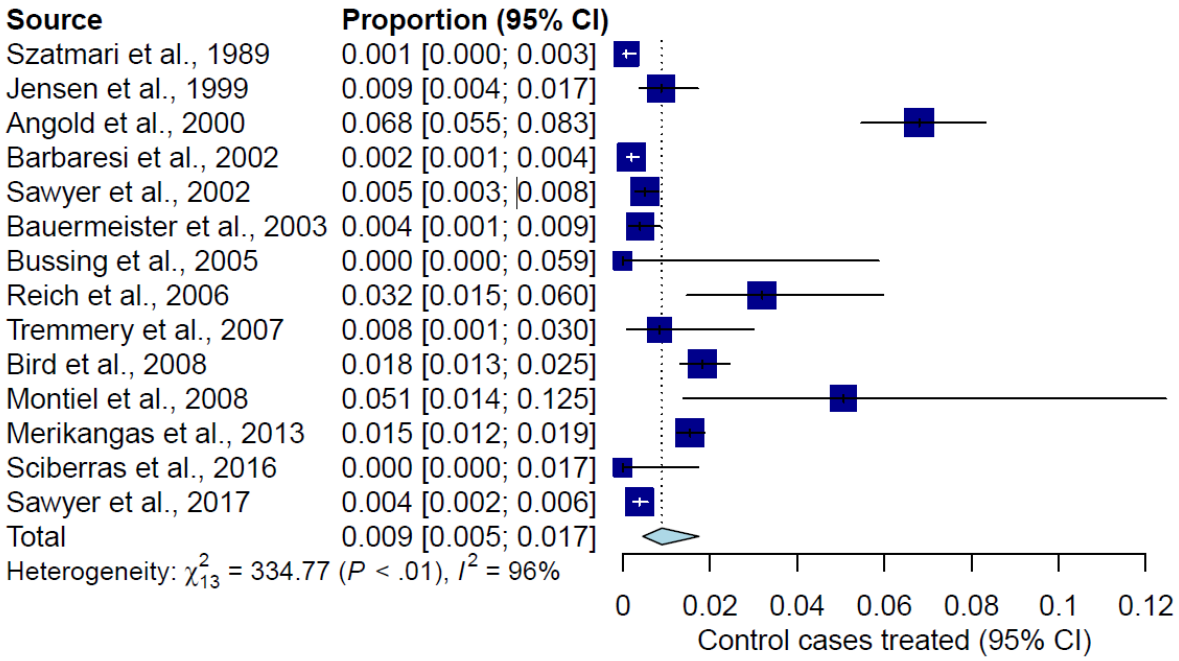


Figure 3: Forest plot showing the meta-analysis results of the rates of ADHD medication use among children and adolescents without a DSM/ICD diagnosis of ADHD



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8. CONCLUSÃO

8.1 Discussão de resultados dos estudos

Pela primeira vez na literatura, realizamos uma análise de redes completa em diferentes populações, agregando análises de estabilidade das redes formadas e comparações estatísticas destas redes à literatura atual. Primeiramente, todas as nossas análises demonstraram agrupamentos de sintomas condizentes com as dimensões de desatenção e de hiperatividade/impulsividade típicas do TDAH. Contudo, notamos uma baixa concordância entre os índices de força dos sintomas nos diferentes contextos amostrais, bem como maior inter-relação do sintoma “falar em excesso” com os sintomas típicos de impulsividade, quando comparados aos sintomas de hiperatividade ao qual “falar em excesso” é identificado. Tais achados condizem com estudos psicométricos prévios (127), corroborando a relevância da heterogeneidade sintomática do TDAH e reforçam o quanto pode ser difícil a simplificação de critérios diagnósticos do TDAH.

Com os testes de qualidade implementados, observamos a importância de efetuar análises de estabilidade das redes formadas pelos sintomas, especialmente à luz da notória heterogeneidade do TDAH. Tais análises indicaram que somente a força dos sintomas atingiu níveis adequados de estabilidade, portanto limitando a avaliação dos demais índices de centralidade. Mesmo limitados a um índice de centralidade, inter-relações entre sintomas podem ser identificadas. De acordo com o contexto amostral, sintomas diferentes apresentam maior força dentre os demais. Estes achados podem ser aplicados no futuro para desenvolver instrumentos diagnósticos refinados que usem destas particularidades de redes de sintomas. Estudos baseados em amostragens maiores podem atingir níveis de estabilidade aceitáveis em todos os índices de centralidade, enriquecendo as análises e a interpretação de seus achados.

Em nossas comparações de diferentes redes, sintomas informados por pais e professores em uma mesma amostra populacional não apresentaram diferenças em sua estrutura e nas forças globais de suas redes. Ao comparar amostras clínicas e comunitárias, contudo, podemos perceber que as forças globais das redes formadas diferem, mas que a estrutura das redes se mantém estatisticamente invariáveis. E, por fim, ao comparar amostras de crianças/adolescentes com amostras de adultos, tanto a estrutura quanto a força global dos sintomas foram diferentes. Estes achados

corroboram as evidências de alta heterogeneidade do TDAH em diferentes contextos sociais, especialmente correlacionados às diferenças de origens amostrais e estágios desenvolvimentais dos indivíduos.

Partindo do conhecimento da heterogeneidade do TDAH, da observação das dificuldades diagnósticas e das diferenças etiológicas e psicopatológicas presentes no transtorno, chegamos então ao impacto destes achados no reconhecimento e tratamento do transtorno. Realizamos, então, pela primeira vez na literatura, uma revisão sistemática e metanálise de toda a literatura disponível, independente de linguagem, tamanho amostral ou data, para, enfim, estimar a prevalência de tratamento de TDAH dentre populações apropriadamente diagnosticadas e não diagnosticadas com o transtorno.

Avaliando estudos abrangendo crianças e adolescentes que usaram métodos diagnósticos validados, estimamos que 19,1% (Intervalo de confiança de 95% [IC 95%]: 11,5 - 29,9) das crianças e adolescentes diagnosticados com TDAH recebem tratamento farmacológico e que 0,9% (IC 95%: 0,5 - 1,7) das crianças e adolescentes que possuem diagnóstico negativo também recebem tratamento farmacológico para o TDAH. Encontramos estudos heterogêneos conforme o esperado, e observou-se que a heterogeneidade encontrada foi influenciada principalmente pela avaliação da qualidade, pelo país e pelo desenho dos estudos incluídos.

Ao analisarmos os achados diferenciados por seus países e por estudos cuja metodologia foi mais criteriosa, tanto no diagnóstico positivo e negativo de TDAH quanto nos critérios de farmacoterapia, encontramos as seguintes relações entre subtratamento e sobretratamento do transtorno: nos Estados Unidos da América, para cada criança que está fazendo uso de medicações para tratamento do TDAH e que não possui o diagnóstico de TDAH, existem 3 crianças com o diagnóstico que não recebem a medicação (1 para 3). Na Austrália, a relação de sobre tratados para subtratados é de 1 para 11 e na Holanda é de 1 para 2.

As análises realizadas demonstram uma alta heterogeneidade em ambas as populações alvo, de indivíduos diagnosticados ou não-diagnosticados. Não foi possível localizar um estudo em particular cuja exclusão reduziu significativamente a heterogeneidade das análises. Dentre estudos em nossa análise primária, a característica de estudo mais impactante sobre a heterogeneidade encontrada foi a localização geográfica do estudo (redução importante de heterogeneidade na Europa

e Oceania quando sub analisados separadamente, em ambas as amostras). Enquanto as meta-regressões indicaram que as covariáveis qualidade de estudo, país e desenho do estudo foram significativas no impacto sobre a heterogeneidade entre estudos de indivíduos diagnosticados (responsáveis por 23,5%, 15% e 33,7% da heterogeneidade encontrada, respectivamente). Quando avaliamos a metanálise de todos os estudos incluídos, independentemente de métodos diagnósticos utilizados, notamos que esta variável torna-se a mais importante. Estes achados são congruentes com os encontrados na literatura. Estudos indicam uma importante associação entre taxa de tratamento de TDAH com fatores socioeconômicos como sexo, educação materna e nacionalidade estrangeira. (125) Podemos notar diferenças importantes em práticas clínicas e taxas de tratamento de TDAH mesmo em um país com um sistema de saúde universal e de amplo acesso. (126) Por fim, as grandes metanálises de TDAH, que também demonstram altos níveis de heterogeneidade, já indicavam que diferenças em desenhos de estudos e métodos diagnósticos seriam as covariáveis mais importantes para explicar a heterogeneidade dentre estes estudos. (2, 130, 131)

Nossos dados demonstram claramente a existência concomitante dos fenômenos de subtratamento e sobretratamento do Transtorno de Déficit de Atenção/Hiperatividade e que tais fenômenos estão presentes difusamente por países culturalmente distintos, embora a variabilidade de países seja pequena para que possamos inferir uma estimativa global. O subtratamento do TDAH tem implicações relevantes para a saúde pública mundial, visto que está associado a diversos desfechos negativos que impactam sistemas econômicos, educacionais e de saúde. O sobretratamento, por sua vez, pode acarretar impactos econômicos e de saúde na figura de efeitos adversos medicamentosos, riscos de abuso de substâncias, contribuindo para as controvérsias (leigas ou não) relacionadas ao diagnóstico e manejo apropriado do TDAH. Entendemos, por fim, que ao invés de debater a favor ou contra o uso de medicações no tratamento do TDAH, seria de maior benefício estimular a educação sobre o TDAH baseada em evidências, tanto entre profissionais médicos quanto entre pais e pacientes, a fim de otimizar diagnósticos e terapias do transtorno globalmente.

8.2 Limitações dos estudos

Algumas limitações do estudo de análise de redes devem ser destacadas. Primeiro, a baixa estabilidade das medidas de centralidade não-significativas fornecidas pelos modelos criados pode ser consequência de tamanho amostral pequeno. Segundo, optamos por truncar a variável SNAP para melhor comparar as amostras que usaram diferentes informativos de sintomas, o que contribuiu para a redução da estabilidade da amostra, porém não impactando as análises de forma estatisticamente significativa. Terceiro, as análises realizadas não consideraram os sintomas de comorbidades dos pacientes e as relações destes com os sintomas de TDAH, o que pode influenciar as medidas de centralidade e inter-relações de sintomas encontrados. Contudo, as amostras de crianças e adolescentes comparadas, clínica e comunitária, possuíam padrões distintos de comorbidades e mesmo de instrumentos informativos de sintomas e, as avaliações de estrutura de rede foram estatisticamente equivalentes, o que minimiza a relevância de controle de comorbidades na construção de rede de sintomas. Por fim, as redes de sintomas informados por pais e professores foram criadas a partir de uma amostra clínica de crianças e adolescentes, cuja gravidade e prejuízo esperado é maior que o encontrado em amostras comunitárias, diferença que pode interferir nos achados das comparações de redes.

Semelhantemente, algumas limitações da metanálise de taxas de tratamento para TDAH devem ser levadas em consideração. Primeiro, apesar de buscar toda a literatura disponível da forma mais abrangente possível, não podemos considerar esta como uma amostra representativa mundialmente. Notamos diferenças nas taxas de tratamento de pacientes mesmo a nível nacional, exemplificadoras do impacto socioeconômico sobre a heterogeneidade do tratamento do TDAH. (129, 132) Segundo, os gráficos de funil das análises principais apresentam um padrão disperso, o que poderia indicar viés de publicação. Porém, foram aplicadas técnicas estatísticas (teste de Egger não significativo) e técnicas não estatísticas (relacionadas ao processo de pesquisa e seleção de estudos publicados ou não publicados) que demonstram-se mais importantes que as demais, especialmente em metanálises com um pequeno número de estudos incluídos. (133) Terceiro, o número de artigos incluídos nesta metanálise é relativamente pequeno e as análises apresentam importantes taxas de heterogeneidade, reduzindo a validade externa dos achados. Contudo, tal heterogeneidade foi prevista a priori e, trabalhos epidemiológicos prévios, com inclusão de centenas de estudos, também demonstraram taxas de heterogeneidade consideráveis. (2, 130, 131) Quarto, a maioria dos estudos incluídos

são provenientes de países desenvolvidos, com predomínio de amostras dos Estados Unidos da América. Tal característica tende a inflar as taxas de tratamento encontradas, visto que exclui uma parcela imensa da população mundial com barreiras financeiras, culturais e de acesso a sistemas de saúde, impeditivos do tratamento farmacológico. Quinto, estudos cuja população era composta de indivíduos menores de 5 anos foram excluídas, visto que o tratamento nesta faixa etária é controverso e geralmente a terapia farmacológica não é recomendada como primeira linha em alguns *guidelines*. Sexto, muitos dos estudos incluídos avaliaram o uso de medicação através de questionamento simples para pais/cuidadores dos indivíduos, sem maiores métodos confirmatórios. Esta covariável, porém, não foi significativa em nossas subanálises. Sétimo, a maioria dos estudos não fornecia informações suficientes para se diferenciar sobretratamento e abuso de medicações de TDAH. Contudo, o uso não medicinal de medicações para TDAH é observado geralmente em amostras de adultos ou adolescentes tardios, que por sua vez foram incluídos no material suplementar e não compõem a amostra da análise principal deste estudo. Por fim, cabe salientar que esta metanálise compreende o tratamento farmacológico do TDAH e não inclui taxas de sub ou sobretratamento mais abrangentes, incluindo tratamentos não farmacológico do transtorno.

8.3 Perspectivas futuras e considerações finais

Observamos um grande campo para desenvolver os presentes trabalhos. A perspectiva futura no campo da análise de redes gira em torno de lançar mão de amostras mais robustas que possam manter estabilidade de todos os índices de centralidade e, também, construir redes integrando mais variáveis de interesse, como comorbidades, características demográficas e informação de prejuízo às redes formadas, podem estabelecer redes mais ricas, nos informando as inter-relações entre fatores ainda não avaliados em conjunto. Já do ponto de vista da epidemiologia de tratamento do TDAH, estudos populacionais disseminados a nível global podem nos fornecer medidas mais precisas de sub e sobretratamento, auxiliando entes públicos na tomada de decisão sobre maior controle de dispensação de medicamentos para TDAH e sobre a custo-efetividade de incorporar tais tratamentos aos sistemas de saúde universalizados.

A heterogeneidade do TDAH permeia tanto a clínica quanto a terapia do transtorno em diferentes sentidos. Neste trabalho, observamos que amostras distintas de indivíduos acometidos pelo TDAH demonstram heterogeneidade sintomatológica mesmo quando novos instrumentos psicométricos são aplicados. O conjunto de diferenças clínicas e psicossociais dentre os afetados pelo transtorno, a que chamamos heterogeneidade, implica em dificuldades diagnósticas e terapêuticas, refletindo em variações importantes de taxas de tratamento globalmente. Esforços em identificar os fatores de heterogeneidade e reduzir sua relevância podem aumentar a precisão de instrumentos diagnósticos e aumentar a acurácia da terapêutica atual, contribuindo substancialmente para a saúde pública mundial.

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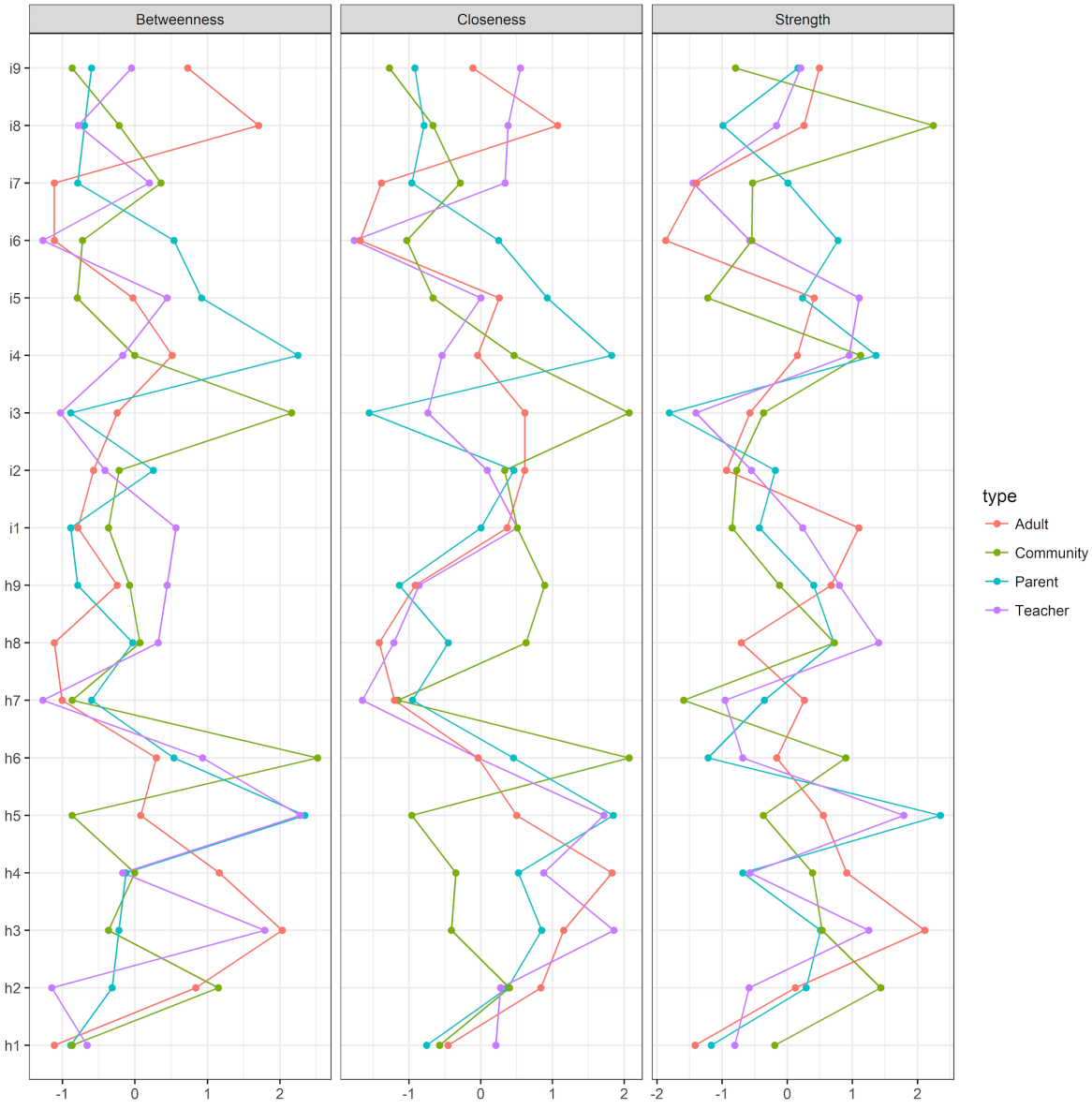
10. APÊNDICES

8.1 Suplementos do Artigo 1

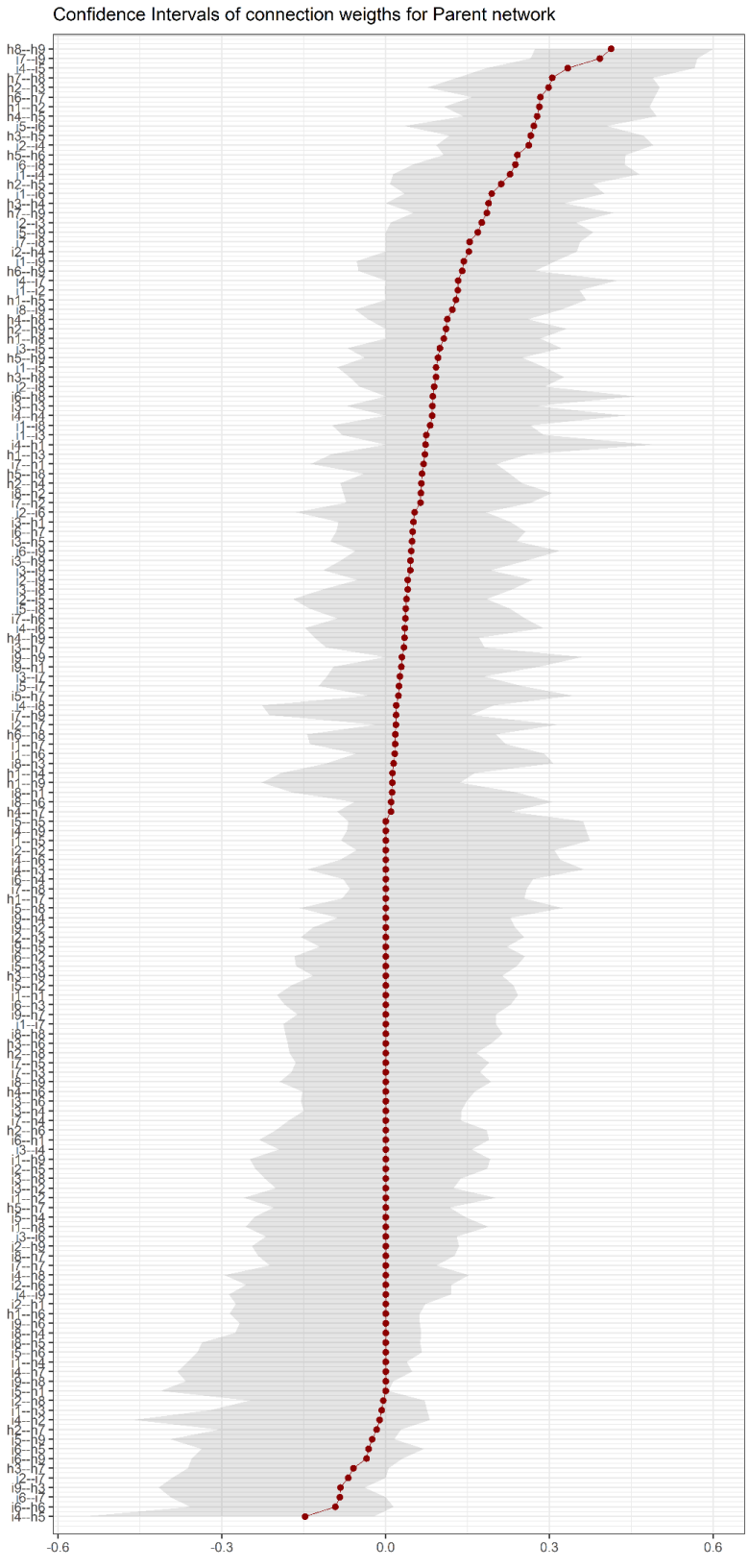
Table of contents:

Figure 1: Centrality indices of all networks, in Z-Scores



(*) Values presented as Z-Scores. (Costantini et al., 2015)

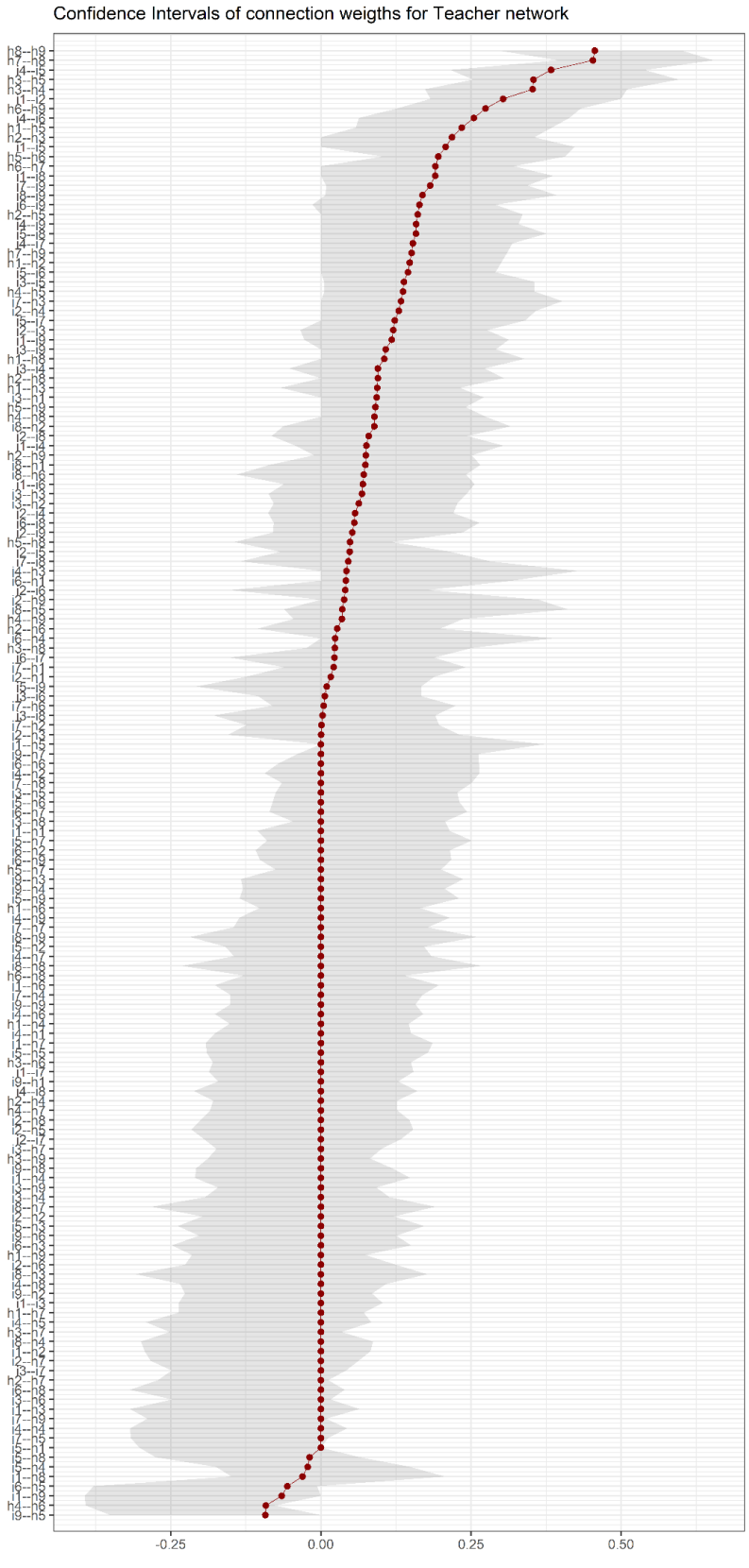
Figure 2: Confidence interval of connection weights in Parent network



(*) ordered by connection weight.

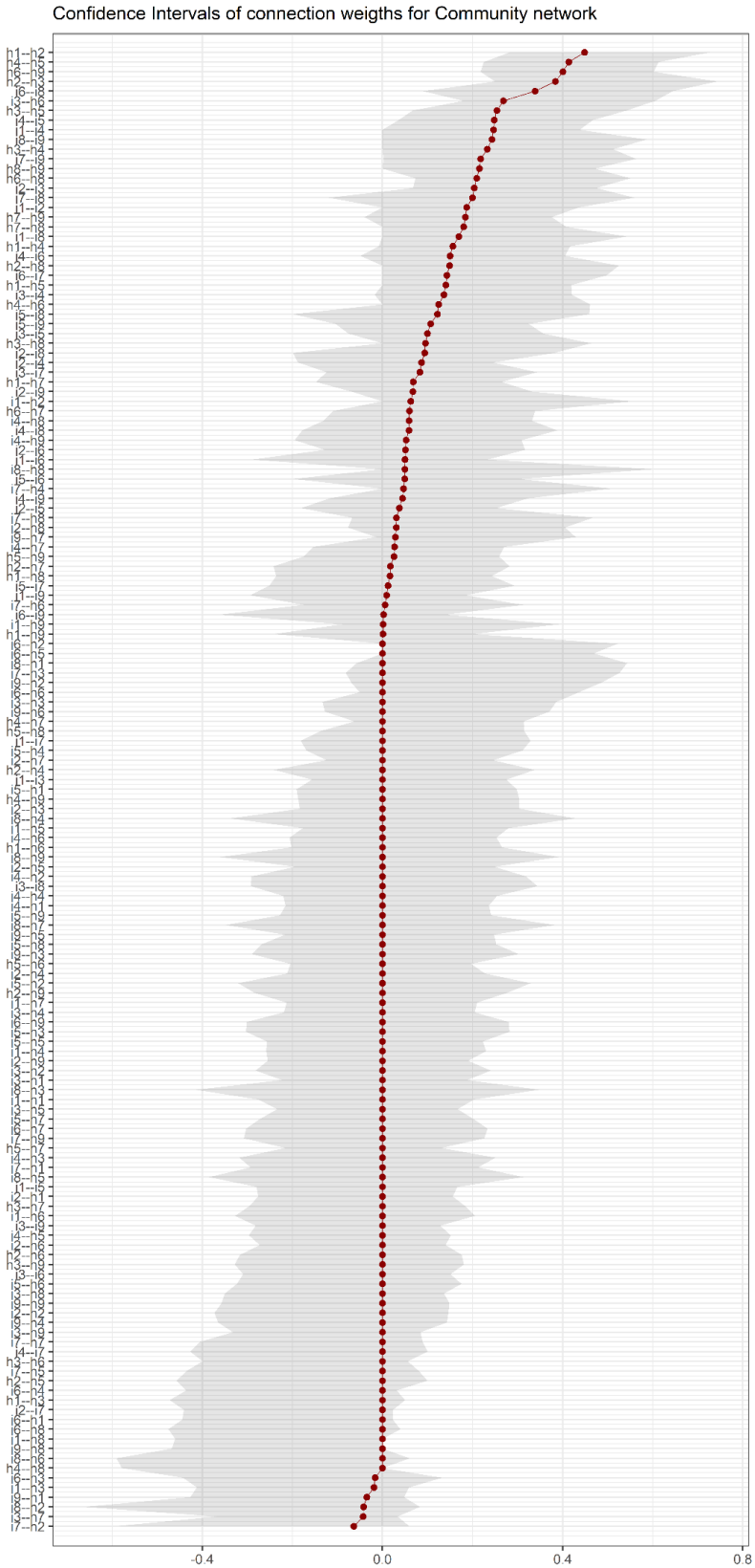
Connection weights are represented as a dot. The Confidence Interval for each connection is represented in gray.

Figure 3: Confidence interval of connection weights in Teacher network



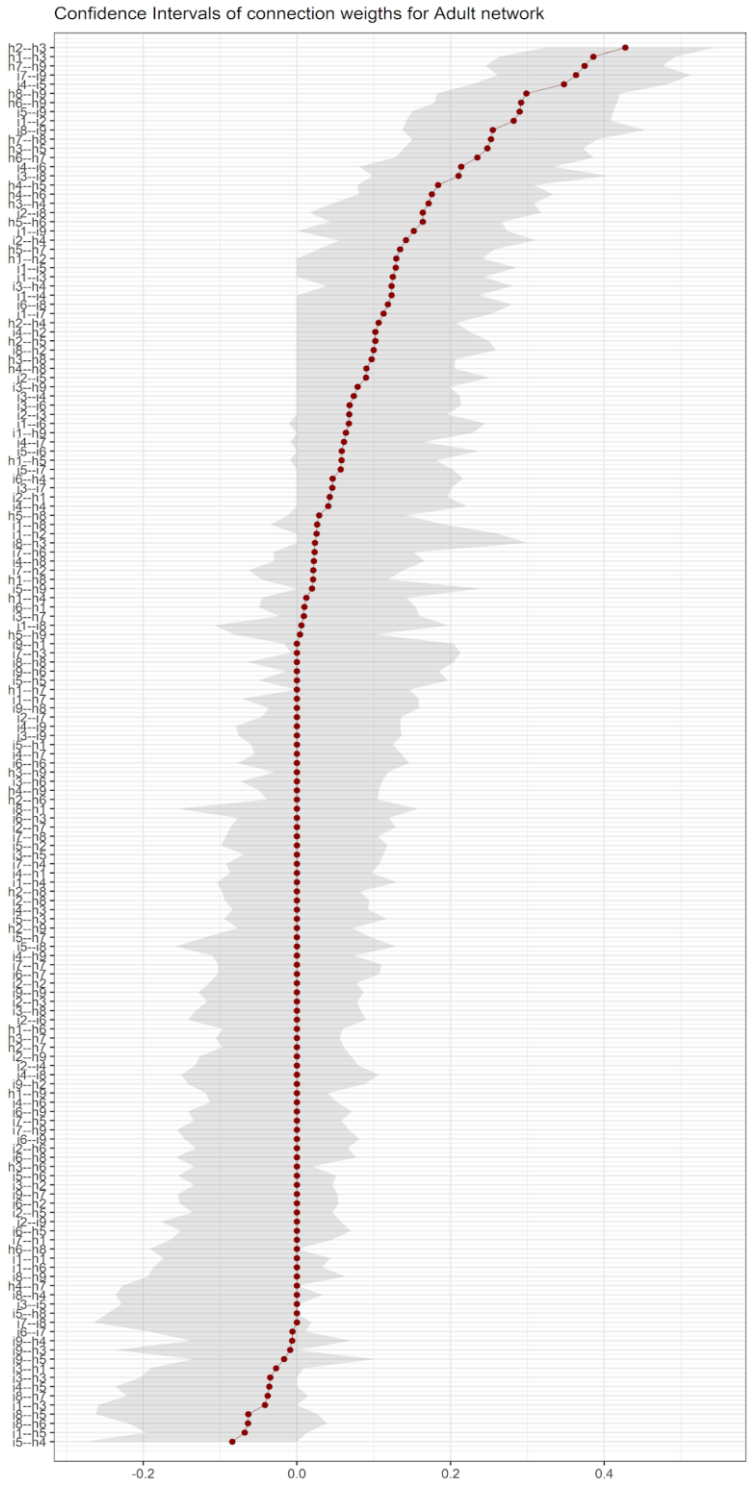
(*) Symptoms ordered by connection weight. Connection weights are represented as a dot. The Confidence Interval for each connection is represented in gray.

Figure 4: Confidence interval of connection weights in Community network



(*) Symptoms ordered by connection weight. Connection weights are represented as a dot. The Confidence Interval for each connection is represented in gray.

Figure 5: Confidence interval of connection weights in Adult network



(*) Symptoms ordered by connection weight. Connection weights are represented as a dot. The Confidence Interval for each connection is represented in gray.

Figure 6: Ten connections with highest weight in each network

Rank	Network			
	Parent	Teacher	Community	Adults
1st	im2 - im3	im2 - im3	h1 - h2	h2 - h3
2nd	im1 - im3	im1 - im2	h4 - h5	h1 - h3
3rd	i4 - i5	i4 - i5	h6 - im3	im1 - im3
4th	im1 - im2	h3 - h5	h2 - h3	i7 - i9
5th	h2 - h3	h3 - h4	i6 - i8	i4 - i5
6th	h6 - im1	i1 - i2	h3 - h5	im2 - im3
7th	h1 - h2	h6 - im3	i4 - i5	h6 - im3
8th	i5 - i6	i4 - i6	i1 - i4	i5 - i9
9th	h3 - h5	h1 - h5	i8 - i9	i1 - i2
10th	i2 - i4	h2 - h3	h3 - h4	i8 - i9

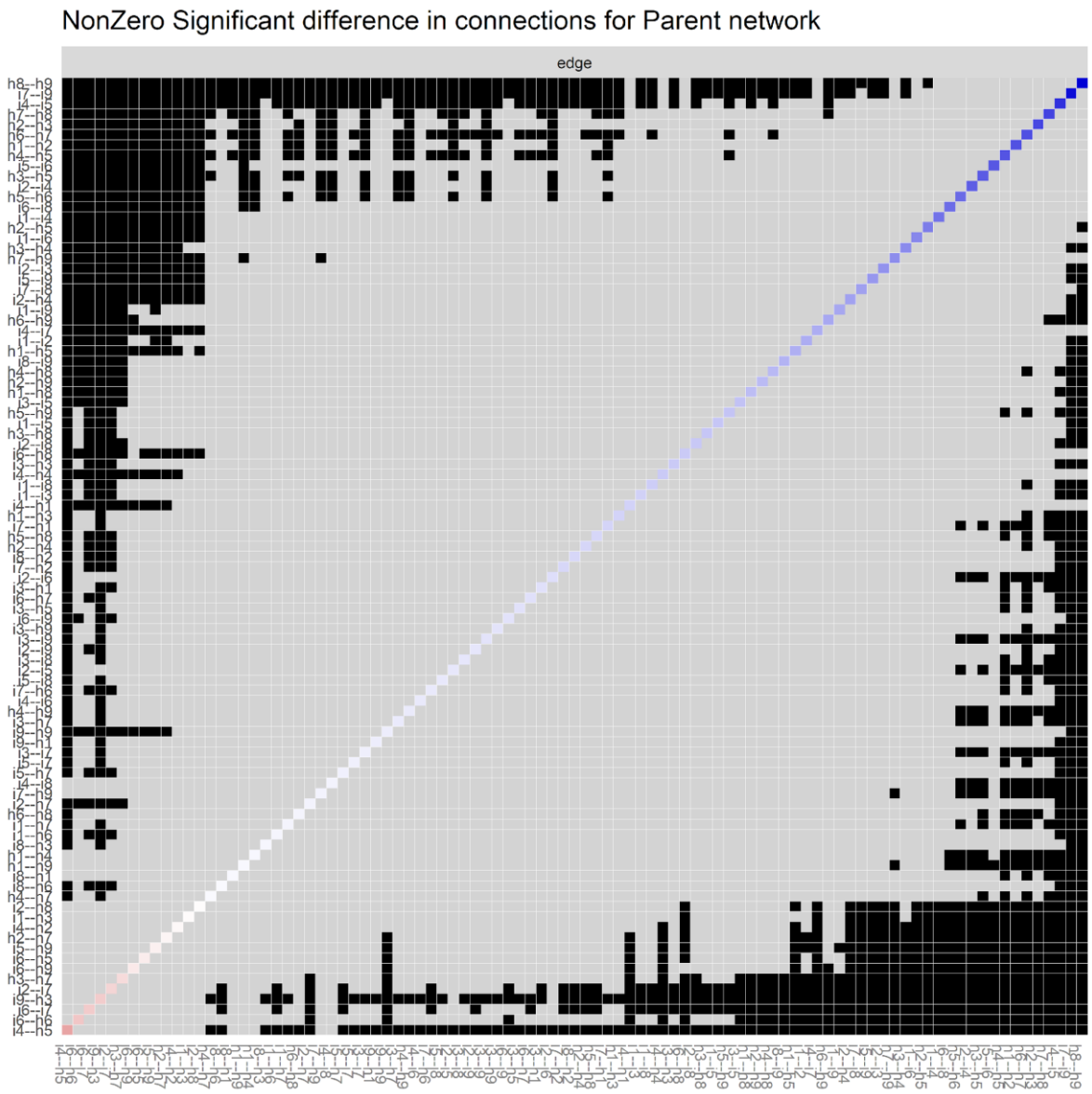
Present in four networks

i4 - i5	*Does not follow through instructions and Difficulty organizing tasks*
h2 - h3	*Gets up and Runs about*

Present in three networks

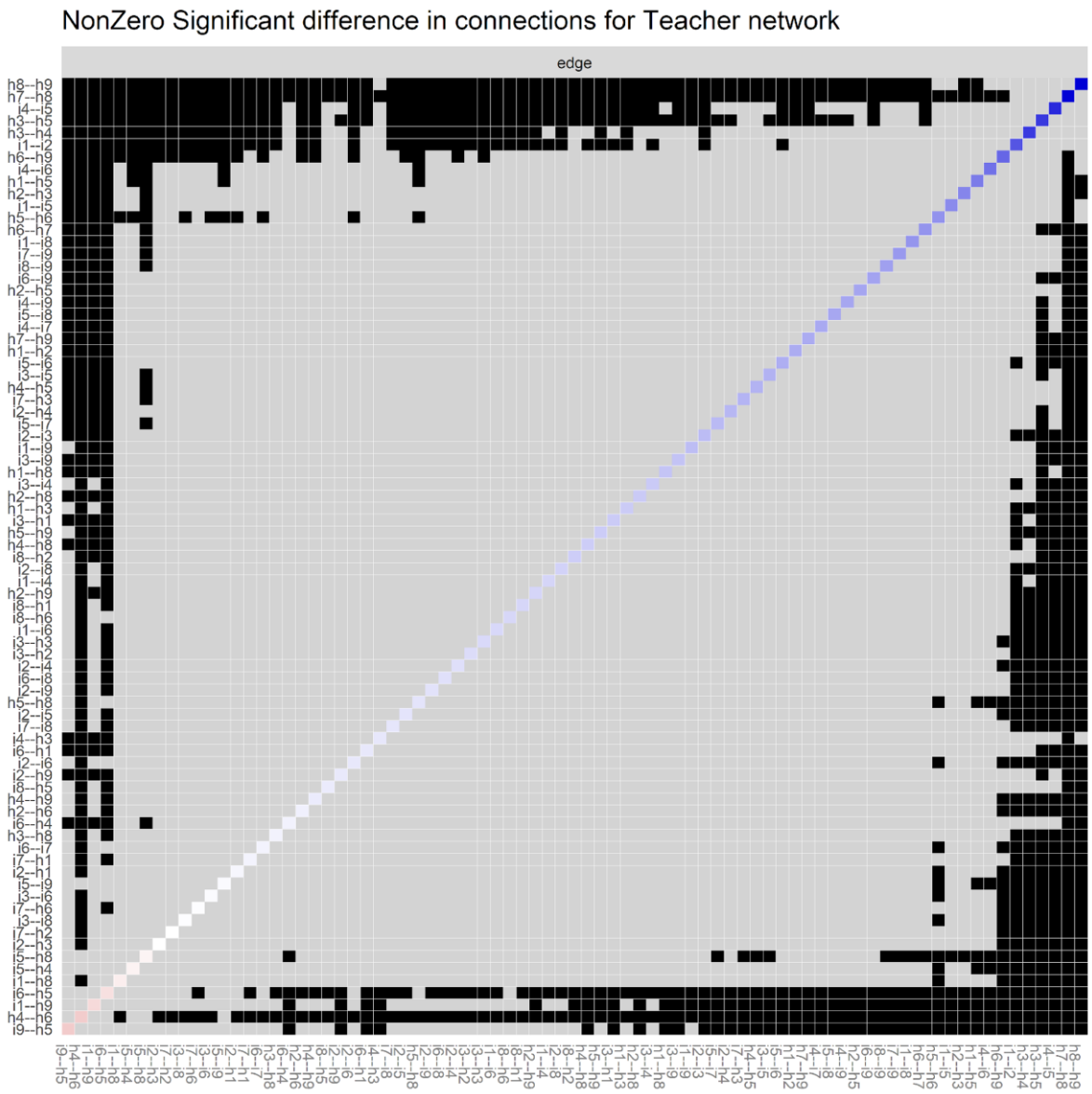
im2 - im3	*Difficulty waiting turn and Interrupts or intrudes*
h3 - h5	*Runs about and On the go*
h6 - im3	*Talks excessively and Interrupts or intrudes*

Figure 7: NonZero significant difference between connections in Parent network



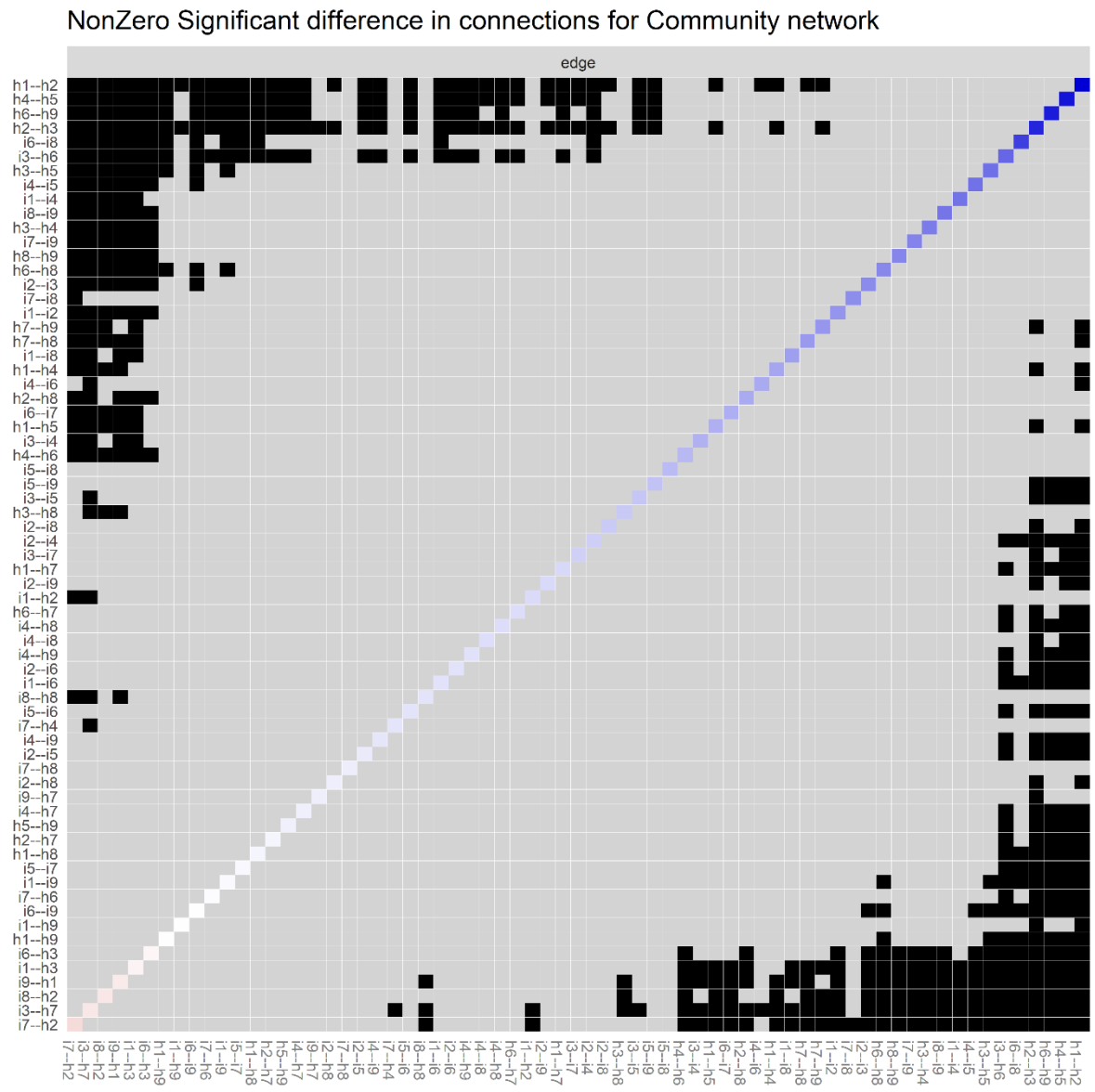
(*) A black box indicates a significant difference in weights between connections

Figure 8: NonZero significant difference between connections in Teacher network



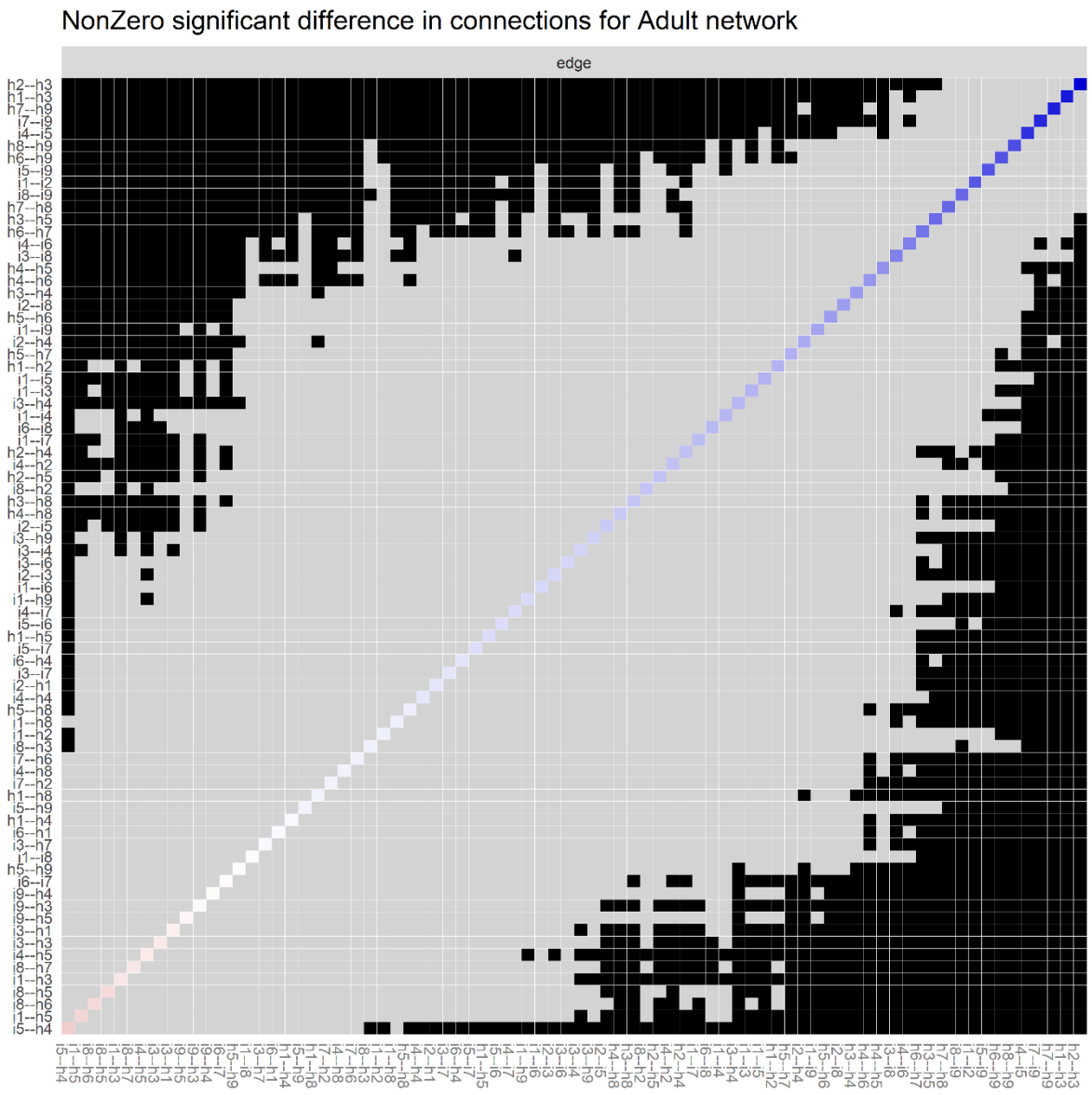
(*) A black box indicates a significant difference in weights between connections

Figure 9: NonZero significant difference between connections in Community network



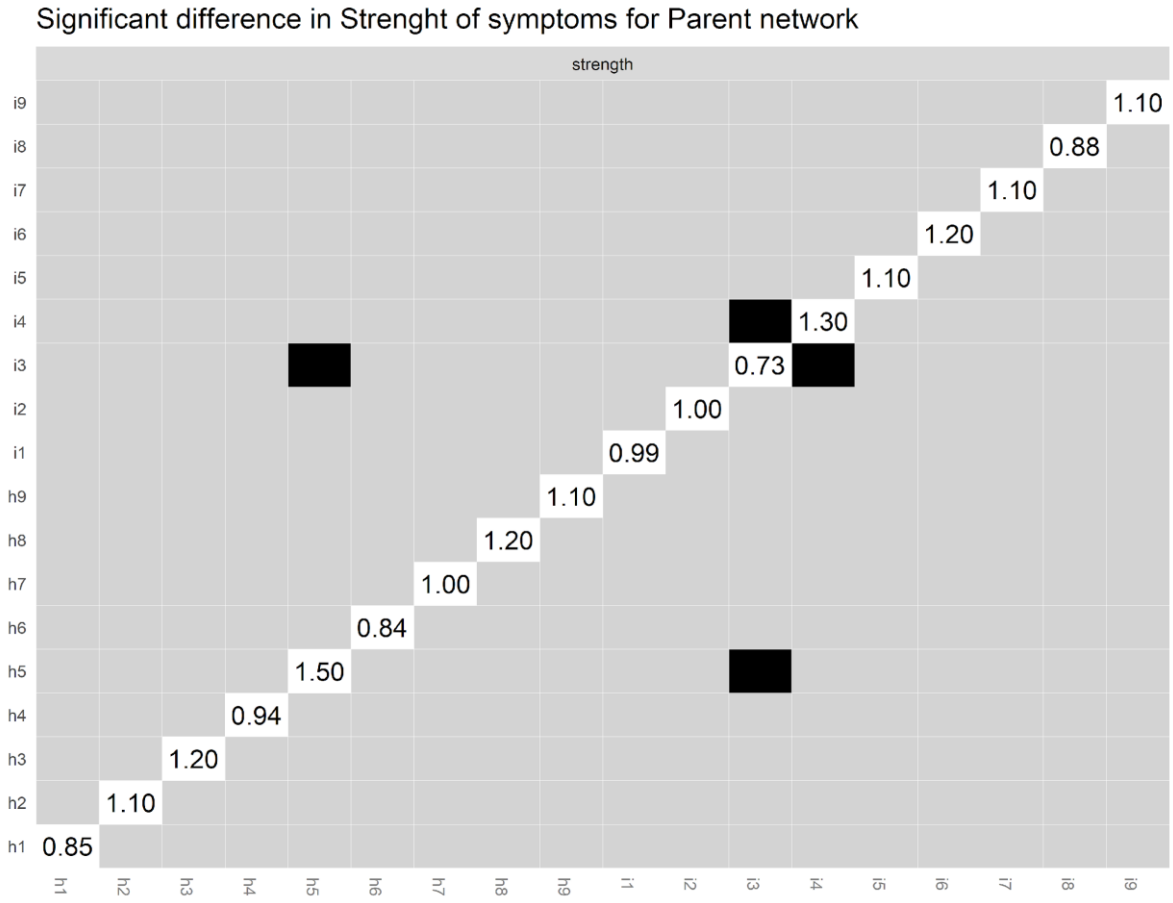
(*) A black box indicates a significant difference in weights between connections

Figure 10: NonZero significant difference between connections in Adult network



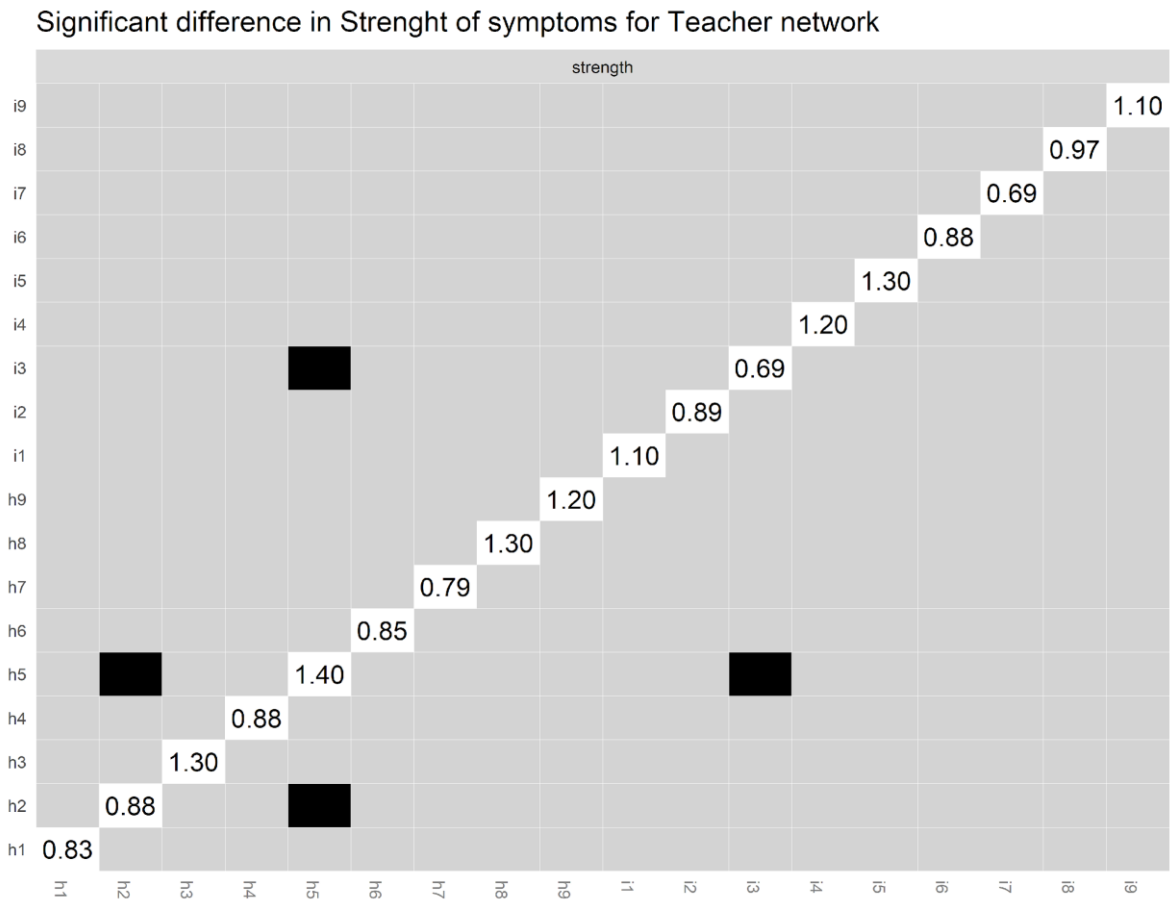
(*) A black box indicates a significant difference in weights between connections

Figure 11: Significant difference in Strength of symptoms in Parent network



(*) A black box indicates significant difference between symptom strength

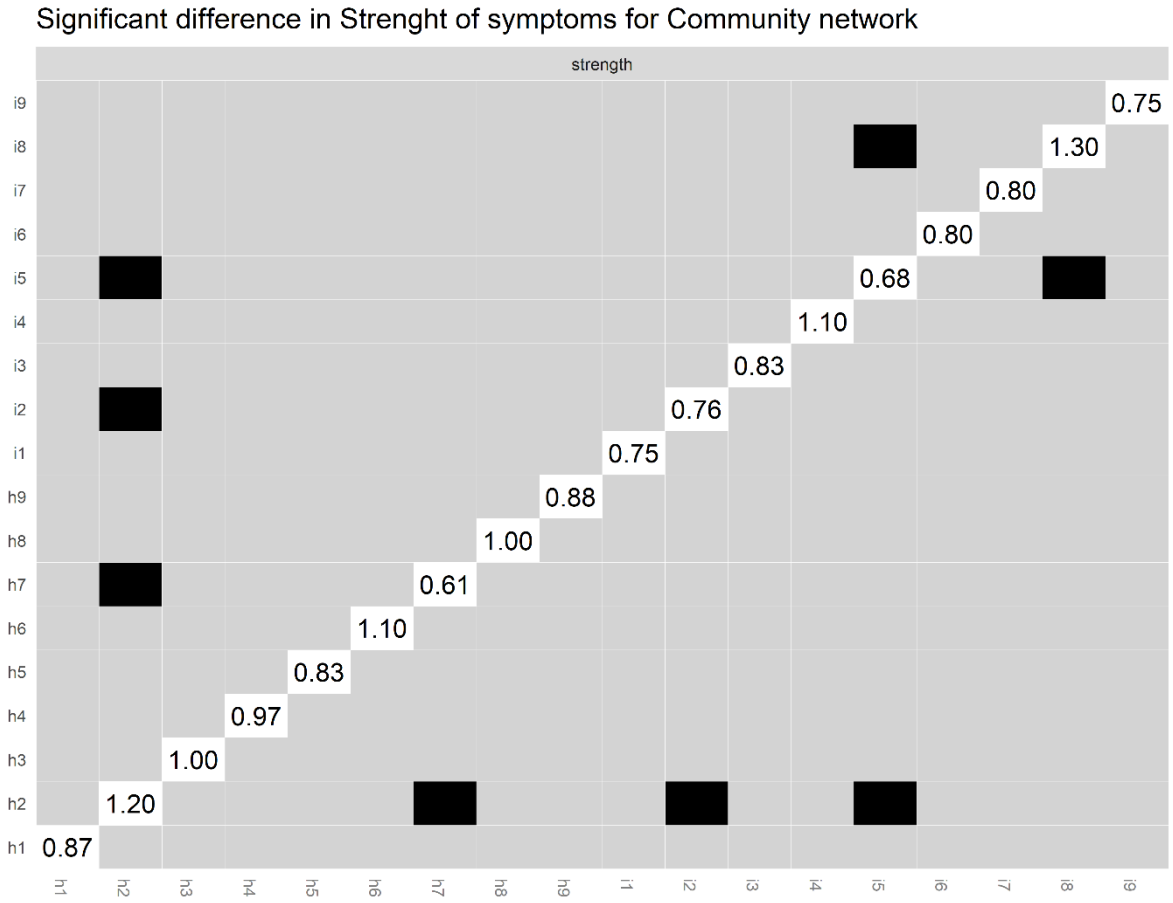
Figure 12: Significant difference in Strength of symptoms in Teacher network



(*) A black box indicates significant difference between symptom strength

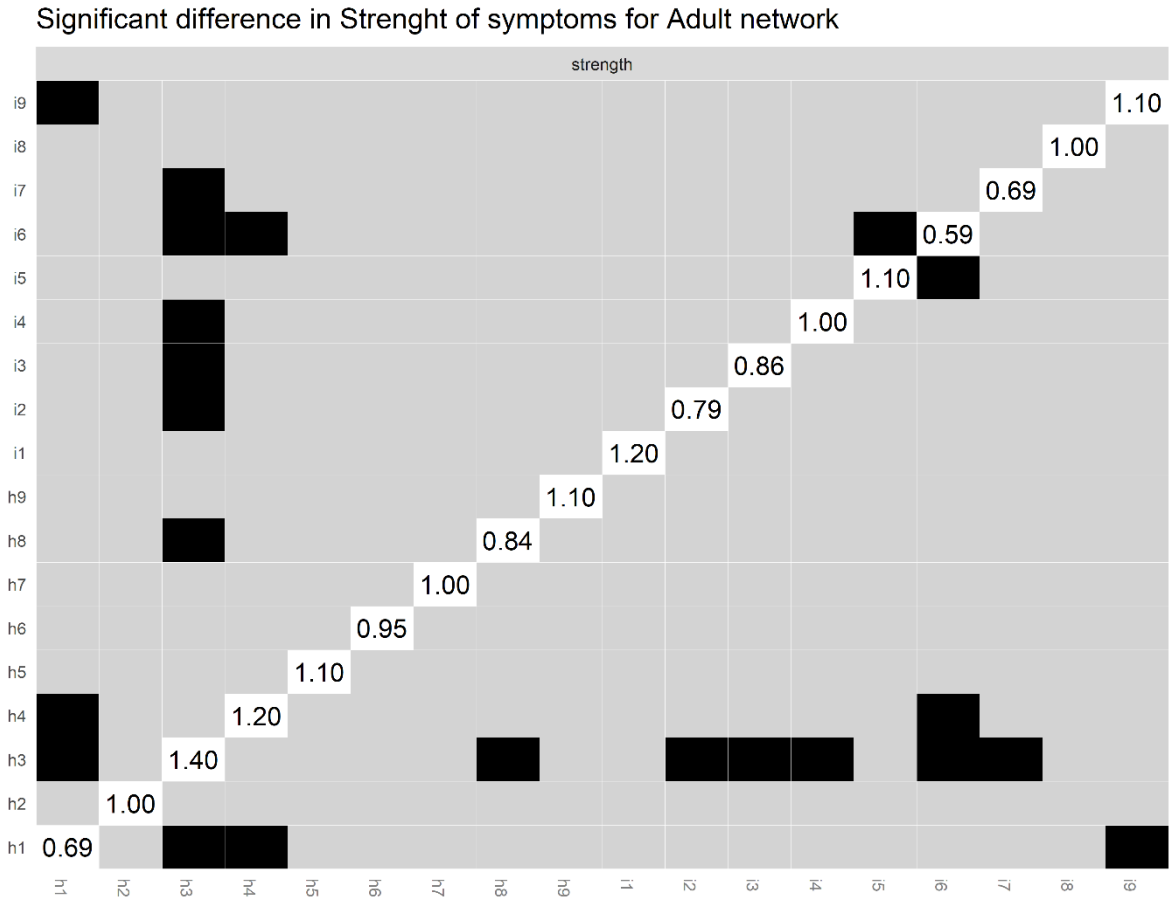
(Epskamp, Borsboom, & Fried, 2018)

Figure 13: Significant difference in Strength of symptoms in Community network



(*) A black box indicates significant difference between symptom strength

Figure 14: Significant difference in Strength of symptoms in Adult network



(*) A black box indicates significant difference between symptom strength

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Epskamp, S., Borsboom, D., & Fried, E. I. (2018). Estimating psychological networks and their accuracy: A tutorial paper. *Behavior Research Methods*, *50*(1), 195–212. https://doi.org/10.3758/s13428-017-0862-1

8.2 Suplementos do Artigo 2

Table of contents:

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	7
2	Hypothesis statement	7
3	Description of study outcome(s)	9
4	Type of exposure or intervention used	7
5	Type of study designs used	8
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	8
8	Search strategy, including time period included in the synthesis and key words	7
9	Effort to include all available studies, including contact with authors	8
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	Suppl. page 17
12	Use of hand searching (eg, reference lists of obtained articles)	8
13	List of citations located and those excluded, including justification	Suppl. Table S4
14	Method of addressing articles published in languages other than English	Suppl Page 17
15	Method of handling abstracts and unpublished studies	8
16	Description of any contact with authors	8
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Page 8 and Suppl. page 20
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Suppl. page 17
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9
22	Assessment of heterogeneity	10
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9-10
24	Provision of appropriate tables and graphics	Table 1 and Figures 1-3

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Page 12 and Suppl Figures S7-S20
28	Indication of statistical uncertainty of findings	12
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-12
30	Justification for exclusion (eg, exclusion of non-English language citations)	Suppl. Table S4
31	Assessment of quality of included studies	11
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	15-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	13-14
34	Guidelines for future research	18
35	Disclosure of funding source	2

Table S1: Diagnostic tools accepted in the meta-analysis

Diagnostic tool	**Reference**
Child and Adolescent Psychiatric Assessment (CAPA)	Angold A, Costello EJ. The Child and Adolescent Psychiatric Assessment (CAPA). Journal of the American Academy of Child and Adolescent Psychiatry 2000;39(1):39-48 doi: 10.1097/00004583-200001000-00015.
Child Symptom Inventory-4	Gadow KD, Sprafkin JN. *Child symptom inventory 4: Screening and norms manual*: Checkmate Plus, 2002.
Composite international diagnostic interview (CIDI)	Robins LN, Wing J, Wittchen HU, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Archives of general psychiatry 1988;45(12):1069-77.
Development and Well-being Assessment (DAWBA)	Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. Journal of child psychology and psychiatry, and allied disciplines 2000;41(5):645-55.
Diagnostic Interview Schedule for Children (DISC)	Shaffer D, Fisher P, Lucas CP, et al. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. Journal of the American Academy of Child and Adolescent Psychiatry 2000;39(1):28-38 doi: 10.1097/00004583-200001000-00014.
Schedule for Affective Disorders and Schizophrenia for School-age children ADHD module (K-SADS)	Kaufman J, Birmaher B, Brent D, 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 1997;36(7):980-8 doi: 10.1097/00004583-199707000-00021.
Mini-International Neuropsychiatric Interview-Plus (MINI-Plus)[7]	Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 1998;59 Suppl 20:22-33;quiz 34-57.
Amsterdam Diagnostisch Interview voor Kinderen (ADIKA)	Kortenbout Van der Sluijs M, Levita Dd, Manen Rv, et al. Amsterdam Diagnostisch Interview voor Kinderen en Adolescenten (ADIKA)[Amsterdam Diagnostic Interview for Children and Adolescents]. Lisse: Swets en Zeitlinger 1993.
Diagnostic Interview for Children and Adolescents (DICA)	Welner Z, Reich W, Herjanic B, et al. Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). Journal of the American Academy of Child and Adolescent Psychiatry 1987;26(5):649-53 doi: 10.1097/00004583-198709000-00007.

Ontario Child Health Study (OCHS) Hyperactivity Scale	Boyle MH, Offord DR, Racine Y, et al. Evaluation of the revised Ontario Child Health Study scales. Journal of child psychology and psychiatry, and allied disciplines 1993;34(2):189-213
Structured Clinical Interview for DSM-III-R (SCID)	Williams JB, Gibbon M, First MB, et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Archives of general psychiatry 1992;49(8):630-6.
Strengths and difficulties questionnaire (SDQ)	Stone LL, Otten R, Engels RC, et al. Psychometric properties of the parent and teacher versions of the strengths and difficulties questionnaire for 4- to 12-year-olds: a review. Clinical child and family psychology review 2010;13(3):254-74 doi: 10.1007/s10567-010-0071-2.
Rating scales	**Reference**
ADHD Rating Scale (DuPaul)	DuPaul G, Power T, Anastopoulos A, et al. ADHD rating scale II: checklists, norms, and clinical interpretation. Guilford, New York, 1998.
Adult ADHD Investigator System Report Scale (AISRS)	Spencer TJ, Adler LA, Meihua Q, et al. Validation of the adult ADHD investigator symptom rating scale (AISRS). Journal of attention disorders 2010;14(1):57-68 doi: 10.1177/1087054709347435.
Adult ADHD Self-Report Scale (ASRS-v1.1)	Adler L, Kessler R, Spencer T. Adult ADHD Self-Report Scale-v 1.1 (ASRS-v1. 1) Symptom Checklist. New York, NY, 2004.
Adult ADHD Self-Report Scale-Screening (ASRS-S)	Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychological medicine 2005;35(2):245-56.
Brief Psychiatric Rating Scale for Children (BPRS-C)	Gale J, Pfefferbaum B, Suhr M, et al. The Brief Psychiatric Rating Scale for Children: A Reliability Study. Journal of Clinical Child Psychology 1986;15(4):341 – 45.
Conners, Loney, and Milich Scale (CLAM)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' ADHD/DSM IV scales (CADS)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' parent rating scale (CPRS-R)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' teacher rating scale (CTRS-R)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' Abbreviated rating scale (ABRS)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' Abbreviated symptom questionnaire (ASQ)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' Global Index for Parents (CGI parents)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners' Global Index for Teachers (CGI teacher)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.

Conners' hyperkinetic index	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners'-Wells Adolescent Self-Report of Symptoms Scale	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Conners Adult ADHD Rating Scales (CAARS)	Conners CK. Conners' rating scales revised: Multi-Health Systems, Incorporated, 2001.
Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB HKS)	Brühl B, Döpfner M, Lehmkuhl G. Der Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS)–Prävalenz hyperkinetischer Störungen im Elternurteil und psychometrische Kriterien. Kindheit und Entwicklung 2000;9(2):115-25
Conners rating scale (parent) (IOWA)	Loney J, Milich R. Hyperactivity, inattention, and aggression in clinical practice. Advances in developmental and behavioral pediatrics 1982;3(1):113-47
Conners rating scale (teacher) (IOWA)	Pelham Jr WE, Milich R, Murphy DA, et al. Normative data on the IOWA Conners teacher rating scale. Journal of Clinical Child Psychology 1989;18(3):259-62.
Parental Account of Children's Symptoms (PACS)	Taylor E, Schachar R, Thorley G, et al. Conduct disorder and hyperactivity: I. Separation of hyperactivity and antisocial conduct in British child psychiatric patients. The British journal of psychiatry : the journal of mental science 1986;149:760-7
Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV)	Swanson JM, Kraemer HC, Hinshaw SP, et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40(2):168-79 doi: 10.1097/00004583-200102000-00011.
Swanson, Kotkin, Atkins, MFlynn, Pelham Scale (SKAMP)	Wigal SB, Gupta S, Guinta D, et al. Reliability and validity of the SKAMP rating scale in a laboratory school setting. Psychopharmacology bulletin 1998;34(1):47.
Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors (SWAN)	Swanson JM, Schuck S, Porter MM, et al. Categorical and Dimensional Definitions and Evaluations of Symptoms of ADHD: History of the SNAP and the SWAN Rating Scales. The International journal of educational and psychological assessment 2012;10(1):51-70.
Teacher Self Control Rating Scale (TSCRS)	Kendall PC, Zupan BA, Braswell L. Self-control in children: Further analyses of the Self-Control Rating Scale. Behavior Therapy 1981;12(5):667-81.
The ADD/H Comprehensive Teacher Rating Scale (ACTeRS)	Ullmann RK, Sleator EK, Sprague R. The ADD/H Comprehensive Teacher Rating Scale (ACTeRS). Odessa, FL: Psychological Assessment Resources 1991.
Vanderbilt ADHD Teacher Rating Scale (VARTRS)	Wolraich ML, Lambert W, Doffing MA, et al. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. Journal of pediatric psychology 2003;28(8):559-68

Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)	Wolraich ML, Lambert W, Doffing MA, et al. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. Journal of pediatric psychology 2003;28(8):559-68
Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)	Rosler M, Retz W, Retz-Junginger P, et al. Attention deficit hyperactivity disorder in adults. Benchmarking diagnosis using the Wender-Reimherr adult rating scale. Der Nervenarzt 2008;79(3):320-7 doi: 10.1007/s00115-007-2375-0.

Search syntax for Medline, since inception until April 2020:

1 "minimal brain disorder" OR "minimal brain dysfunction"
2 "overactive n3 child n3 syndrome"
3 adhd OR ADHD OR addh OR ADD
4 attention AND deficit AND (disorder* OR syndrome*) AND (hyperactiv* OR hyperkinetic*)
5 (hyperkinetic* OR hyperactivit*) AND (disorder OR syndrome)
6 (MH "Attention Deficit Disorder with Hyperactivity)
7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
8 Amphetamine* OR Amfetamine* OR Dextroamphetamine* OR Dexamphetamine* OR "Mixed amphetamine salts" OR Lisdexamfetamine* OR Methylphenidate OR Atomoxetine OR Clonidine OR guanfacine OR stimulant* OR psychostimulant* OR Elvanse OR Venvanse OR Adderall OR Dexedrine OR Detrostat OR Vyvanse OR ProCentra OR Dyanavel OR Evekeo OR Zenzedi OR Desoxyn OR Metadate OR Concerta OR Daytrana OR Ritalin OR Methylin OR Quillivant OR Focalin OR Biphentin OR Phenida OR Ritalina OR Hynidate OR Addwize OR Inspiral OR Attenade OR Medikinet OR Equasym OR Penid OR Tranquilyn OR Rubifen OR Aptensio OR Strattera OR Tomoxetin OR Attentrol OR Axepta OR Atoken OR Attentin OR Kapvay OR Intuniv
9 "pharmacological treatment*" OR (drug* AND treatment*) OR pharmacotherapy OR (psychotropic AND (drug* OR medicat*)) OR (MH "Psychotropic Drugs")
10 S8 OR S9
11 (cohort AND (study OR studies)) OR "cohort analy*" OR ("follow up" AND (study OR studies)) OR (observational AND (study OR studies)) OR longitudinal OR retrospective OR (epidemiological AND (study OR studies)) OR ("cross section" AND (study OR studies)) OR "cross sectional" OR "follow up" OR (MH "Health Care Surveys")
12 incidence OR prevalence OR occur* OR frequenc* OR proportion* OR rate* OR number* OR percent* OR episode* OR epidemiolo* OR distribut* OR demograph* OR survey* OR trend*
13 (MH "Epidemiologic Methods")
14 (MH "Incidence")
15 (MH "Prevalence")
16 (MH "Demography")
17 (MH Epidemiology+)
18 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
19 S7 AND S10 AND S18
20 S7 and S10

Search syntax for CINAHL, since inception until April 2020:
("minimal brain disorder" OR "minimal brain dysfunction") OR (overactive AND child AND syndrome) OR (adhd OR ADHD OR addh OR ADD) OR (attention AND deficit AND (disorder* OR syndrome*) AND (hyperactiv* OR hyperkinetic*)) OR ((hyperkinetic* OR hyperactivit*) AND (disorder OR syndrome)) OR ("Attention Deficit Hyperactivity Disorder")
AND
(Amphetamine* OR Amfetamine* OR Dextroamphetamine* OR Dexamphetamine* OR "Mixed amphetamine salts" OR Lisdexamfetamine* OR Methylphenidate OR Atomoxetine OR Clonidine OR guanfacine OR stimulant* OR psychostimulant* OR Elvanse OR Venvanse OR Adderall OR Dexedrine OR Detrostat OR Vyvanse OR ProCentra OR Dyanavel OR Evekeo OR Zenzedi OR Desoxyn OR Metadate OR Concerta OR Daytrana OR Ritalin OR Methylin OR Quillivant OR Focalin OR Biphentin OR Phenida OR Ritalina OR Hynidate OR Addwize OR Inspiral OR Attenade OR Medikinet OR Equasym OR Penid OR Tranquilyn OR Rubifen OR Aptensio OR Strattera OR Tomoxetin OR Attentrol OR Axepta OR Atoken OR Attentin OR Kapvay OR Intuniv) OR ("pharmacological treatment*" OR (drug* AND treatment*) OR pharmacotherapy OR (psychotropic AND (drug* OR medicat*)) OR ("Psychotropic Drugs")
AND
((cohort AND (study or studies)) OR "cohort analy*" OR (follow up AND (study or studies)) OR (observational AND (study or studies)) OR longitudinal OR retrospective OR (epidemiological AND (study OR studies)) OR ("cross section" AND (study OR studies)) OR "cross sectional" OR "follow up") OR (incidence OR prevalence OR occur* OR frequenc* OR proportion* OR rate* OR number* OR percent* OR episode* OR epidemiolo* OR distribut* OR demograph* OR survey* OR trend*) OR (epidemiology) OR (incidence) OR (prevalence) OR (demography)

Search syntax for PsychInfo, since inception until April 2020:
(“minimal brain disorder" OR "minimal brain dysfunction" OR (overactive AND child AND syndrome) OR adhd OR ADHD OR addh OR ADD OR (attention AND deficit AND (disorder* OR syndrome*) AND (hyperactiv* OR hyperkinetic*)) OR ((hyperkinetic* OR hyperactivit*) AND (disorder OR syndrome)) OR (DE "Attention Deficit Disorder”) OR (DE “Attention Deficit Disorder with Hyperactivity”))
AND
(Amphetamine* OR Amfetamine* OR Dextroamphetamine* OR Dexamphetamine* OR "Mixed amphetamine salts" OR Lisdexamfetamine* OR Methylphenidate OR Atomoxetine OR Clonidine OR guanfacine OR stimulant* OR psychostimulant* OR Elvanse OR Venvanse OR Adderall OR Dexedrine OR Detrostat OR Vyvanse OR ProCentra OR Dyanavel OR Evekeo OR Zenzedi OR Desoxyn OR Metadate OR Concerta OR Daytrana OR Ritalin OR Methylin OR Quillivant OR Focalin OR Biphentin OR Phenida OR Ritalina OR Hynidate OR Addwize OR Inspiral OR Attenade OR Medikinet OR Equasym OR Penid OR Tranquilyn OR Rubifen OR Aptensio OR Strattera OR Tomoxetin OR Attentrol OR Axepta OR Atoken OR Attentin OR Kapvay OR Intuniv OR ("pharmacological treatment*") OR (drug* AND treatment*) OR pharmacotherapy OR (psychotropic AND (drug* OR medicat*)))
AND
((cohort AND (study OR studies)) OR "cohort analy*" OR (follow up AND (study OR studies)) OR (observational AND (study OR studies)) OR longitudinal OR retrospective OR (epidemiological AND (study OR studies)) OR ("cross section" AND (study OR studies)) OR "cross sectional" OR "follow up" OR incidence OR prevalence OR occur* OR frequenc* OR proportion* OR rate* OR number* OR percent* OR episode* OR epidemiolo* OR distribut* OR demograph* OR survey* OR trend* OR (DE "Epidemiology”))
15 S7 AND S10 AND S14

Search syntax for EMBASE, since inception until April 2020:
("minimal brain disorder" OR "minimal brain dysfunction" OR (overactive NEAR/3 child NEAR/3 syndrome) OR (attention NEAR/3 deficit NEAR/3 (disorder* OR syndrome*) NEAR/6 (hyperactiv* OR hyperkinetic*)) OR ((hyperkinetic* OR hyperactivit*) NEAR/3 (disorder or syndrome)) OR "attention deficit disorder")
((cohort NEAR/1 (study or studies)) or "cohort analy*" or (follow up NEAR/1 (study or studies)) or (observational NEAR/1 (study or studies)) or longitudinal or retrospective or (epidemiological NEAR/1 (study or studies)) or ("cross section" NEAR/1 (study or studies)) or "cross sectional" or "follow up" or (incidence or prevalence or occur* or frequenc* or proportion* or rate* or number* or percent* or episode* or epidemiolo* or distribut* or demograph* or survey* or trend*) OR "health care survey" OR incidence OR prevalence OR demography OR epidemiology)
(Amphetamine* or Amfetamine* or Dextroamphetamine* or Dexamphetamine* or "Mixed amphetamine salts" or Lisdexamfetamine* or Methylphenidate or Atomoxetine or Clonidine or guanfacine or stimulant* or psychostimulant* or Elvanse or Venvanse or Adderall or Dexedrine or Detrostat or Vyvanse or ProCentra or Dyanavel or Evekeo or Zenzedi or Desoxyn or Metadate or Concerta or Daytrana or Ritalin or Methylin or Quillivant or Focalin or Biphentin or Phenida or Ritalina or Hynidate or Addwize or Inspiral or Attenade or Medikinet or Equasym or Penid or Tranquilyn or Rubifen or Aptensio or Strattera or Tomoxetin or Attentrol or Axepta or Atoken or Attentin or Kapvay or Intuniv or ((pharmacological OR drug*) NEAR/3 treatment*) OR pharmacotherapy OR (psychotropic NEAR/3 (drug* OR medicat*)) OR "psychotropic agent")

Search syntax for Web of Science, since inception until April 2020:
TOPIC: ("minimal brain disorder" OR "minimal brain dysfunction" OR (overactive NEAR/3 child NEAR/3 syndrome) OR adhd OR ADHD OR addh OR ADD OR (attention NEAR/3 deficit NEAR/3 (disorder* OR syndrome*) NEAR/6 (hyperactiv* OR hyperkinetic*)) OR ((hyperkinetic* OR hyperactivit*) NEAR/3 (disorder OR syndrome)))
AND
TOPIC: (((pharmacologic* OR drug*) NEAR/3 treatment*) OR pharmacotherapy OR (psychotropic NEAR/3 (drug* OR medicat*)) OR Amphetamine* OR Amfetamine* OR Dextroamphetamine* OR Dexamphetamine* OR ("Mixed amphetamine salts") OR Lisdexamfetamine* OR Methylphenidate OR Atomoxetine OR Clonidine OR guanfacine OR stimulant* OR psychostimulant* OR Elvanse OR Venvanse OR Adderall OR Dexedrine OR Detrostat OR Vyvanse OR ProCentra OR Dyanavel OR Evekeo OR Zenzedi OR Desoxyn OR Metadate OR Concerta OR Daytrana OR Ritalin OR Methylin OR Quillivant OR Focalin OR Biphentin OR Phenida OR Ritalina OR Hynidate OR Addwize OR Inspiral OR Attenade OR Medikinet OR Equasym OR Penid OR Tranquilyn OR Rubifen OR Aptensio OR Strattera OR Tomoxetin OR Attentrol OR Axepta OR Atoken OR Attentin OR Kapvay OR Intuniv)
AND
TOPIC: ((cohort NEAR/1 (study OR studies)) OR "cohort analy*" OR (“follow up” NEAR/1 (study OR studies)) OR (observational NEAR/1 (study OR studies)) OR longitudinal OR retrospective OR (epidemiological NEAR/1 (study OR studies)) OR ("cross section" NEAR/1 (study OR studies)) OR "cross sectional" OR "follow up" OR incidence OR prevalence OR occur* OR frequenc* OR proportion* OR rate* OR number* OR percent* OR episode* OR epidemiolo* OR distribut* OR demograph* OR survey* OR trend*)

Search syntax for Scopus, since inception until April 2020:
("minimal brain disorder" OR "minimal brain dysfunction" OR (overactive W/3 child W/3 syndrome) OR adhd OR ADHD OR addh OR ADD OR (attention W/3 deficit W/3 (disorder* OR syndrome*) W/6 (hyperactiv* OR hyperkinetic*)) OR ((hyperkinetic* OR hyperactivit*) W/3 (disorder OR syndrome))) AND ((pharmacological AND (drug* OR treatment*)) OR pharmacotherapy OR (psychotropic W/3 (drug* OR medicat*)) OR Amphetamine* OR Amfetamine* OR Dextroamphetamine* OR Dexamphetamine* OR "Mixed amphetamine salts" OR Lisdexamfetamine* OR Methylphenidate OR Atomoxetine OR Clonidine OR guanfacine OR stimulant* OR psychostimulant* OR Elvanse OR Venvanse OR Adderall OR Dexedrine OR Detrostat OR Vyvanse OR ProCentra OR Dyanavel OR Evekeo OR Zenzedi OR Desoxyn OR Metadate OR Concerta OR Daytrana OR Ritalin OR Methylin OR Quillivant OR Focalin OR Biphentin OR Phenida OR Ritalina OR Hynidate OR Addwize OR Inspiral OR Attenade OR Medikinet OR Equasym OR Penid OR Tranquilyn OR Rubifen OR Aptensio OR Strattera OR Tomoxetin OR Attentrol OR Axepta OR Atoken OR Attentin OR Kapvay OR Intuniv) AND ((cohort W/1 (study OR studies)) OR "cohort analy*" OR (follow up W/1 (study OR studies)) OR (observational W/1 (study OR studies)) OR longitudinal OR retrospective OR (epidemiological W/1 (study OR studies)) OR ("cross section" W/1 (study OR studies)) OR "cross sectional" OR "follow up" OR incidence OR prevalence OR occur* OR frequenc* OR proportion* OR rate* OR number* OR percent* OR episode* OR epidemiolo* OR distribut* OR demograph* OR survey* OR trend*)

Search syntax for other databases, since inception until April 2020:
For these searches, the following keywords were used, since only simple searches could be undertaken: “ADHD”, “prevalence”, “survey”, “trend”, “pharmacological”, “medication”, “epidemiology”, “attention deficit”

- Prospero
- Cochrane Library
- Campbell Collection of Systematic reviews
- FDA U.S. Food and Drug Administration
- Dept. of Health
- Proquest: Dissertations and Thesis: UK and Ireland.
- Google (using time limits of 24 hours/past week) to pick up in press articles
- Evidence search
- CRD – Centers for Reviews and Dissemination
- NICE
- Medlar
- Open Grey
- Grey literature in Public Health
- Oaister
- Zetoc
- NTIS – National Technical Information Service
- Trip – Turning Research into Practice
- Grey literature Report
- NICHSR (Natl Info Center on Health Services Research and Health Care Technology)
- RePORT (Research Portfolio Online Reporting Tools)
- CADTH checklist
- ETHOS (Electronic Theses Online Service)
- DART – Europe E-Theses portal
- WHO
- Public Health England

Description of data extraction procedures:

CRMM and RM performed the searches. All abstracts were uploaded to Covidence software (https://www.covidence.org/). Two independent reviewers (among CRMM, RM, LT, FC, MS, or JA) screened each study through title and abstract. Two independent reviewers (CRMM, RM, LT, GCAM, JZ, and FC) carefully assessed the full text of selected references. A third senior researcher (LAR or SC) evaluated and resolved any disagreement whenever necessary. For studies reported in languages other than English, two reviewers with fluency in the language conducted the revision, and, if needed, a translator was contacted. After inclusion, two independent reviewers (CRMM, RM, and GCAM) extracted the data, through a double-checking process. Discrepancies in this process were resolved between the reviewers. Papers referring to the same study were linked in the reference list, and data were extracted from: 1) the first (earlier) publication; 2) the paper reporting the largest sample size; or 3) the publication with the most complete data (in this order).

Description of quality assessment procedures:

We assessed the quality of studies using a modified version of the Newcastle–Ottawa scale (NOS),[30] composed by two domains: selection of the study groups, accounting for the representativeness and proper definition of the cases and controls (rated 0 to 4) and comparability, referring to the control for covariate factors in the study (rated 0 to 2), as the exposure domain of the NOS was deemed not suitable for prevalence studies. The modified version of the NOS and its domains are described in detail in the supplemental material, Tables S2 and S3. Each study could receive from zero (low quality, high risk of bias) to six points (high quality, low risk of bias). Two authors independently assessed and scored each included study. In a second step, results were compared, and a third author (CRMM) acted as an arbitrator in case of discrepancies

Table S2: Newcastle-Ottawa Scale for Case-Control studies, modified version

	Selection (criterion met = 1 point)				Comparability (Up to 2 points)	
	1) Definition	2) Representativeness	3) Controls	4) Definition of Controls		Total

1) Is the case definition adequate?

a) yes, with independent validation (1 point) - >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records

b) yes, e.g. record linkage or based on self-reports - e.g. ICD (International Classification of Diseases) codes in database or self-report with no reference to primary record or no description

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases (1 point)

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls (1 point)

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint) (1 point)

b) no description of source

5) Comparability of cases and controls on the basis of the design or analysis

a) study controls for ___ (select the most important factor) (1 point)

b) study controls for any additional factor (This criterion could be modified to indicate specific control for a second important factor.) (1 point)

Table S3: Newcastle-Ottawa Scale for Cohort studies, modified version

	Selection (criterion met = 1 point)				Comparability (Up to 2 points)	
	1) Representativeness	2) Selection Non-exposed	3) Ascertainment of Exposure	4) Outcome not present		Total

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community (1 point)

b) somewhat representative of the average _____ in the community (1 point)

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort (1 point)

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure to (e.g.) implants

a) secure record (e.g. surgical records) (1 point)

b) structured interview (1 point)

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes (1 point) - In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death; that is a statement of no history of disease or incident earns a star

b) no

5) Comparability of cohorts on the basis of the design or analysis

a) study controls for ___ (select the most important factor) (1 point)

b) study controls for any additional factor (This criterion could be modified to indicate specific control for a second important factor.) (1 point)

Description of deviations from the published protocol:

We decided to exclude studies based on health insurance and medical registry data, although they were included in the published protocol since they clearly represent clinical samples of treatment-seeking individuals. When identified in the studies, the ADHD Not Otherwise Specified (ADHD-NOS) and ADHD Unspecified (ADHD-U) cases were excluded from the analysis, since including these cases would either deflate treatment rates of individuals diagnosed with ADHD or inflate treatment rates of undiagnosed individuals. Samples of only preschoolers and adults were not included in our main analysis since treatment recommendations in preschoolers differ from those in school-aged children, and there are peculiar characteristics of the few studies with adult samples (i.e., university samples of adults, where recognition of ADHD, misuse, and overuse of stimulants is more frequent). However, all data and analyses on these populations are reported in the Supplementary material. Additionally, we decided to retain studies reporting on medication for ADHD and not only those reporting specifically stimulants and/or atomoxetine, but we provided subgroup analyses for this specific group in the supplemental material. Finally, we deemed appropriate to focus our main analysis on studies with a diagnosis based on DSM and/or ICD criteria, since studies where the diagnosis was made based on the answer to only one question about previous diagnosis include treatment-seeking populations, thus presenting potentially inflated rates of treatment. However, for transparency, these findings are also reported in the supplemental material.

Table S4: List of excluded references during full-text screening, with reason for exclusion

Excluided References	**Reasons for exclusion**
Abbas, S.; Ihle, P.; Adler, J. B. Et al. Predictors of non-drug psychiatric/psychotherapeutic treatment in children and adolescents with mental or behavioural disorders. Eur Child Adolesc Psychiatry. 2017 Apr;26(4):433-444. doi: 10.1007/s00787-016-0900-z	Clinical sample
Acquazzino, M. A.; Miller, M.; Myrvik, M.; Newby, R.; Scott, J. P. Attention Deficit Hyperactivity Disorder in Children With Sickle Cell Disease Referred for an Evaluation. J Pediatr Hematol Oncol. 2017 Jul;39(5):350-354. doi: 10.1097/MPH.0000000000000847.	Without or inadequate data on medication for ADHD
Aduen, P. A.; Kofler, M. J.; Sarver, D. E.; Wells, E. L.; Soto, E. F.; Cox, D. J. ADHD, depression, and motor vehicle crashes: A prospective cohort study of continuously-monitored, real-world driving. J Psychiatr Res. 2018 Jun;101:42-49. doi: 10.1016/j.jpsychires.2018.02.026	Clinical sample
Advokat, Claire D.; Guidry, D.; Martino, L. Licit and illicit use of medications for Attention-Deficit Hyperactivity Disorder in undergraduate college students. J Am Coll Health. 2008 May-Jun;56(6):601-6. doi: 10.3200/JACH.56.6.601-606.	No proper ADHD diagnosis
Ahmad, M.; Masood, I.; Umer, D. et al. Evaluating the use of central nervous system stimulants among medical and non-medical students. Value Health 2017;2 0(9):A898-A899. DOI: 10.1016/j.jval.2017.08.2752	No proper ADHD diagnosis
Akici, A.; Gelal, A.; Demircan, D.; Tiskaoglu, R.; Topcus, I.; Yilmaz, H. Assessment of Methylphenidate Prescriptions Written for the Treatment of Attention-Deficit/Hyperactivity Disorder. Klinik Psikofarmakol Bülteni. Mar 2013; 23(1):1. DOI: 10.5455/bcp.20121001010745	No proper ADHD diagnosis
Al Ghriwati, N.; Langberg, J. M.; Gardner, W. et al. Impact of Mental Health Comorbidities on the Community-Based Pediatric Treatment and Outcomes of Children with Attention Deficit Hyperactivity Disorder. J Dev Behav Pediatr. 2017 Jan;38(1):20-28. doi: 10.1097/DBP.0000000000000359.	Clinical sample
Alabede, H.; Agarwal, M.; Cawley, P. Can i have your attention? an audit of best practice and patient satisfaction in ADHD assessment and management. Eur J Pediatr (2016) 175:1393–1880. DOI 10.1007/s00431-016-2785-8	Clinical sample
Albert, M.; Rui, P.; Ashman, J. J. Physician Office Visits for Attention-deficit/Hyperactivity Disorder in Children and Adolescents Aged 4-17 Years: United States, 2012-2013 NCHS Data Brief Jan 2017. PMID:28135186	Prevalence based on prescriptions
Alessi-Severini, Silvia; Biscontri, Robert G.; Collins, David M.; Sareen, Jitender; Enns, Murray W. Ten years of antipsychotic prescribing to children: a Canadian population-based study. Can J Psychiatry. 2012 Jan;57(1):52-8. DOI: 10.1177/070674371205700109	Without or inadequate data on medication for ADHD

Alexander, G. C.; Garfield, C.; Dorsey, R. et al. U.S. trends in the diagnosis and treatment of attention deficithyperactivity disorder, 2000-2010. Acad Pediatr. 2012 Mar-Apr;12(2):110-6. doi: 10.1016/j.acap.2012.01.003.	Prevalence based on prescriptions
Al-Haggar, M.; El-Baz, R.; Youseff, H.; Othman, N.; Ali, R. Overview on attention deficit hyperactivity disorder among children from Delta regions of Egypt (a 10 years-study). J Pediatr Neuro, 2006;4(1). DOI: 10.1055/s-0035-1557298	Clinical sample
Al-Haidar, F. A. Co-morbidity and treatment of attention deficit hyperactivity disorder in Saudi Arabia. East Mediterr Health J, Nov 2003;9(5-6). PMID: 16450529	Clinical sample
Ali, M. M.; Teich, J.; Lynch, S.; Mutter, R. Utilization of Mental Health Services by Preschool-Aged Children with Private Insurance Coverage. Adm Policy Ment Health. 2018 Sep;45(5):731-740. doi: 10.1007/s10488-018-0858-x.	No proper ADHD diagnosis
Alqahtani, Mohammed M. J. How do parents view psychological assessment and intervention for their children with ADHD in Saudi Arabia? Asia Pac J Couns Psychother, 2017;8(1). DOI: 10.1080/21507686.2016.1260612	Clinical sample
Altomare, C.; Garofalo, A.; Vulnera, M. Prescription monitoring methylphenidate and atomoxetine in the treatment of Attention Deficit Hyperactivity Disorder. Giornale Italiano di Farmacia Clinica. 2016. DOI10.1721/2344.25128	Prevalence based on prescriptions
Amiri, S.; Ghoreishizadeh, M. A.; Sadeghi-Bazargani, H. et al. Prevalence of Adult Attention Deficit Hyperactivity Disorder (Adult ADHD): Tabriz.Iran J Psychiatry. 2014 Apr;9(2):83-8.; PMID:25632285	Without or inadequate data on medication for ADHD
Amor, L.B.; Sikirica, V.; Cloutier, M. et al. Combination and switching of stimulants in children and adolescents with attention deficit/hyperactivity disorder in Quebec. J Can Acad Child Adolesc Psychiatry. 2014 set; 23(3): 157–166. PMID: 25320609	Prevalence based on prescriptions
Anderson, J. Reported Diagnosis and Prescription Utilization Related to Attention Deficit Hyperactivity Disorder in Children Ages 5-17, 2008-2015. Agency for Healthcare Research and Quality, Aug 2018. PMID: 30395426	Clinical sample
Anderson, K. N.; Ailes, E. C.; Danielson, M. et al. Attention-Deficit/Hyperactivity Disorder Medication Prescription Claims Among Privately Insured Women Aged 15-44 Years - United States, 2003-2015. J Atten Disord. 2018 Mar 1:1087054718759753. doi: 10.1177/1087054718759753	Prevalence based on prescriptions
Anderson, K. N.; Dutton, A. C.; Broussard, C. S. et al. ADHD Medication Use During Pregnancy and Risk for Selected Birth Defects: National Birth Defects Prevention Study, 1998-2011. J Atten Disord, Mar 2018. doi: 10.1177/1087054718759753	Clinical sample

Appelbaum, Kenneth L. Stimulant use under a prison treatment protocol for attention-deficit/hyperactivity disorder. J Correct Health Care. 2011 Jul;17(3):218-25. doi: 10.1177/1078345811401356	Clinical sample
Aragonès, E.; Lluís, J. P,; Ramos-Quiroga, J.A.; López-Cortacans, G.; Caballero, A.; Bosch, R. Prevalence in adults of attention deficit hyperactivity disorder using the medical records of primary care. Rev Esp Salud Publica. 2010 Jul-Aug;84(4):417-22. PMID: 21141268	Prevalence based on prescriptions
Aras, Ş.; Taş, F. V.; Ünlü, G. Alterations in medication in a child and adolescent psychiatric outpatient clinic. Klinik Psikofarmakoloji Bülteni. Jul, 27 2005; 15(3):127-133.	Clinical sample
Aras, S.; Tas, F. Varol; Unlu, G. Medication prescribing practices in a child and adolescent psychiatry outpatient clinic. Child Care Health Dev. Oct, 26 2006. https://doi.org/10.1111/j.1365-2214.2006.00703.x	No proper ADHD diagnosis
Arat, A.; Östberg, V.; Burström, B.; Hjern, A. ADHD medication in offspring of immigrants—Does the income level of the country of parental origin matter?. BMC Psychiatry. 2018 Jan 8;18(1):3. doi: 10.1186/s12888-017-1572-z.	Prevalence based on prescriptions
Arbuckle, T. E.; Davis, K.; Boylan, K.; Fisher, M.; Fu, J. Processed data for CHMS 2007–2009: Bisphenol A, phthalates and lead and learning and behavioral problems in Canadian children 6–19 years of age. Data Brief. 2016,Jun 22. doi: 10.1016/j.dib.2016.06.017	Clinical sample
Arim, R. G.; Miller, A. R.; Guèvremont, A.; Lach, L. M.; Brehaut, J. C.; Kohen, D. E. Children with neurodevelopmental disorders and disabilities: a population-based study of healthcare service utilization using administrative data. Dev Med Child Neurol. 2017 Dec;59(12):1284-1290. doi: 10.1111/dmcn.13557.	No proper ADHD diagnosis
Arria, A. M.; Caldeira, K. M.; O'Grady, K. E. et al. Nonmedical use of prescription stimulants among college students: associations with attention-deficit-hyperactivity disorder and polydrug use. Pharmacotherapy. 2008 Feb; 28(2): 156–169 .doi: 10.1592/phco.28.2.156	No proper ADHD diagnosis
Arria, A. M.; Caldeira, K. M.; Vincent, K. B. Et al. Do college students improve their grades by using prescription stimulants nonmedically? Addict Behav. 2017 Feb; 65: 245–249. Published online 2016 Jul 19. doi: 10.1016/j.addbeh.2016.07.016	No proper ADHD diagnosis
Arria, A. M.; Geisner, I. M.; Cimini, M. D. et al. Perceived academic benefit is associated with nonmedical prescription stimulant use among college students. Addict Behav. 2018 Jan;76:27-33. doi: 10.1016/j.addbeh.2017.07.013.	No proper ADHD diagnosis
Asheim, H.; Nilsen, K. B.; Johansen, K.; Furu, K.. Prescribing of stimulants for ADHD in Nordland County. Tidsskr Nor Laegeforen. 2007 Sep 20;127(18):2360-2. PMID: 17895938	No proper ADHD diagnosis
Asheim, H.; Nilsen, K. B.; Stordahl, H.; Johansen, K. Prescription of central nervous system stimulants. Tidsskr Nor Laegeforen, 2001 Mar 20. PMID:11332376	No proper ADHD diagnosis

Bachmann, C. J.; Philipsen, A.; Hoffmann, F. ADHD in Germany: Trends in Diagnosis and Pharmacotherapy. Dtsch Arztebl Int. 2017 Mar 3;114(9):141-148. doi: 10.3238/arztebl.2017.0141.	Prevalence based on prescriptions
Bachmann, C. J.; Philipsen, A.; Hoffmann, F. ADHD in Germany: trends in diagnosis and pharmacotherapy-a country-wide analysis of health insurance data on attention-deficit/ hyperactivity disorder (ADHD) in children, adolescents and adults from 2009-2014. Dtsch Arztebl Int. 2017, mar 03; 114(9):141-148. DOI: 10.3238/arztebl.2017.0141	Prevalence based on prescriptions
Bachmann, C. J.; Wijlaars, L. P.; Kalverdijk, L. J. et al. Trends in ADHD medication use in children and adolescents in five western countries, 2005-2012. Eur Eur Neuropsychopharmacol. 2017 May;27(5):484-493. doi: 10.1016/j.euroneuro.2017.03.002	No proper ADHD diagnosis
Bahmanyar, S.; Sundström, A.; Kaijser, M.; von Knorring, A; Kieler, H. Pharmacological treatment and demographic characteristics of pediatric patients with Attention Deficit Hyperactivity Disorder, Sweden. Eur Neuropsychopharmacol. 2013 Dec;23(12):1732-8. doi: 10.1016/j.euroneuro.2013.07.009	Prevalence based on prescriptions
Baldursson, G.; Magnusson, P.; Gudmundsson, O. O. Medication use and treatment characteristics of children referred to the outpatient ADHD-clinic at the Department of Child and Adolescent Psychiatry, the National University Hospital. Laknabladid 2000-May.	Clinical sample
Barbaresi, W. J.; Katusic, S. K.; Colligan, R. C. Et al. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: results from a population-based study. J Dev Behav Pediatr. 2006 Feb;27(1):1-10. doi: 10.1097/DBP.0000000000000099	Without or inadequate data on medication for ADHD
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Bird, H.R.; Shrout, P.E.; Duarte, C.S.; Shen, S.; Bauermeister, J.J.; Canino, G. Longitudinal Mental Health Service and Medication Use for ADHD Among Puerto Rican Youth in Two Contexts. J Am Acad Child Adolesc Psychiatry, 2008; 47(8): 879-889. DOI: 10.1097/CHI.0b013e318179963c	Same sample of an included study
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Carballo, J. J.; Garcia-Nieto, R.; Perez-Rodriguez, M. M. et al. Longitudinal trends in diagnosis at child and adolescent mental health centres in Madrid, Spain. Eur Child Adolesc Psychiatry. 2013 Jan. doi: 10.1007/s00787-012-0322-5.	Without or inadequate data on medication for ADHD
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Centers for Disease, Control; Prevention. Mental health in the United States. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder--United States, 2003. MMWR September 2, 2005 / 54(34);842-847.	Same sample of an included study
Cesar, E. L. R.; Wagner, G. A.; Castaldeli-Maia, J. M.; Silveira, C. M.; de Andrade, A. G.; de Oliveira, L. G. Prescribed use of methylphenidate hydrochloride and its correlates among Brazilian college students. Rev Psiq Clín. Oct, 16 2012. DOI: 10.1590/S0101-60832012000600001	No proper ADHD diagnosis
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Chang, Z.; D'Onofrio, B. M.; Quinn, P. D.; Lichtenstein, P.; Larsson, H. Archival Report: Medication for Attention-Deficit/Hyperactivity Disorder and Risk for Depression: A Nationwide Longitudinal Cohort Study. Biol Psychiatry. 2016 Dec 15;80(12):916-922. doi: 10.1016/j.biopsych.2016.02.018.	Prevalence based on prescriptions
Chang, Z.; Quinn, P. D.; Hur, K.; Gibbons, R. D.; Sjolander, A.; Larsson, H.; D'Onofrio, B. M. Association Between Medication Use for. JAMA Psychiatry. 2017 Jun 1;74(6):597-603. doi: 10.1001/jamapsychiatry.2017.0659. JAMA Psychiatry. 2017 Jun 1. doi: 10.1001/jamapsychiatry.2017.0659.	No proper ADHD diagnosis
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Charach, A.; Cao, H.; Schachar, R.; To, T. Correlates of methylphenidate use in Canadian children: a cross-sectional study. Can J Psychiatry. Can J Psychiatry. 2006 Jan;51(1):17-26. DOI:10.1177/070674370605100105	No proper ADHD diagnosis
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Crystal, S.; Bilder, S.; Simmel, C. Increasing mental health diagnosing and treatment among U.S. Medicaid Youth, 2001-2010. Pharmacoepidemiol Drug Saf 2016; 25(Suppl. 3). DOI: 10.1002/pds.4070	Prevalence based on medical visits
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Dalsgaard, S.; Kvist, A. P.; Leckman, J. F.; Nielsen, H. S.; Simonsen, M. Gender and injuries predict stimulant medication use. J Child Adolesc Psychopharmacol. 2014 Jun 1; 24(5): 253–259. doi: 10.1089/cap.2013.0101	Prevalence based on prescriptions
Dalsgaard, S.; Kvist, A. P.; Leckman,.; Mortensen, P. B; Nielsen, Nielsen, H. S.; Simonsen, M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry. 2015 Aug;2(8):702-709. doi: 10.1016/S2215-0366(15)00271-0.	Prevalence based on prescriptions
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Darim, N. P.; Da Silva, P. F. ADHD prevalence according to schools of a Brazilian country town. ADHD Atten Def Hyp Disord (2017) 9(Suppl 1):S1–S55. DOI 10.1007/s12402-017-0224-y	No proper ADHD diagnosis
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DeBar, L. L.; Lynch, F. L.; Boles, M. Healthcare use by children with attention deficit/hyperactivity disorder with and without psychiatric comorbidities. J Behav Health Serv Res. 2004 Jul-Sep;31(3):312-23. PMID: 15263869	Prevalence based on prescriptions
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Department of Health, Education; Welfare, Washington D. C. Report of the Conference on the Use of Stimulant Drugs in the Treatment of Behaviorally Disturbed Young School Children (Washington, D.C., January 11-12, 1971).	Review or metanalysis
DeSantis, A. D.; Webb, E. M.; Noar, S. M. Illicit use of prescription ADHD medications on a college campus: a multimethodological approach. J Am Coll Health. 2008 Nov-Dec;57(3):315-24. doi: 10.3200/JACH.57.3.315-324.	No proper ADHD diagnosis
Desantis, A.; Noar, S. M.; Webb, E. M. Nonmedical ADHD stimulant use in fraternities. J Stud Alcohol Drugs. 2009 Nov;70(6):952-4. DOI:10.15288/jsad.2009.70.952	No proper ADHD diagnosis
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Dey, A. N.; Bloom, B. Summary health statistics for U.S. children: National Health Interview Survey, 2003. Vital Health Stat 10. 2005 Mar;(223):1-78. PMID:15792295	Without or inadequate data on medication for ADHD
Dey, A. N.; Schiller, J. S.; Tai, D. A. Summary health statistics for U.S. children: National Health Interview Survey, 2002. Vital Health Stat 10. 2004 Mar. PMID: 15791897	Without or inadequate data on medication for ADHD

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DuPaul, G. J.; Pinho, T. D.; Pollack, B. L.; Gormley, M. J.; Laracy, S. D. First-Year College Students with ADHD And/or LD: Differences in Engagement, Positive Core Self-Evaluation, School Preparation, and College Expectations. J Learn Disabil. 2017 May/Jun;50(3):238-251. doi: 10.1177/0022219415617164.	Without or inadequate data on medication for ADHD
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Dupont, R. L.; Coleman, J. J.; Bucher, R. H.; Wilford, B B. Characteristics and motives of college students who engage in nonmedical use of methylphenidate. Am J Addict. 2008 May-Jun;17(3):167-71. doi: 10.1080/10550490802019642.	No proper ADHD diagnosis
Dvorsky, M. R. Longitudinal relations between ADHD symptoms and substance use across the transition to college and evaluation of promotive and protective factors. Virginia Commonwealth University, 2018. US ProQuest Information & Learning 2018	No proper ADHD diagnosis
Edelsohn, G. A.; Ghuman, J.; Martin, V.; Hutchison, S. L.; Karpov, I.; Parthasarathy, M.; Castelnovo, K. Psychotropic medication utilization in medicaid-eligible children ages 0-2 years: Longitudinal view. J Am Acad Child Adolesc Psychiatry. 2017. DOI:10.1016/j.jaac.2017.09.057	Clinical sample
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Emadeldin, M.; Moussa, S.; Refaat, O.; Amer, D.; Khoweild, A.; Goueli, T. Child impairment and parental burden in pediatric psychiatric outpatient clinics in Cairo. Acad Child Adolesc Psychiatry. Oct, 2016. Doi: 10.1016/j.jaac.2016.09.297	Clinical sample
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Epstein, J. N.; Langberg, J. M.; Lichtenstein, P. K. et al. Attention-deficit/hyperactivity disorder outcomes for children treated in community-based pediatric settings. Arch Pediatr Adolesc Med. 2010 Feb;164(2):160-5. doi: 10.1001/archpediatrics.2009.263.	Clinical sample
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Evans, W. N.; Morrill, M. S.; Parente, S. T. Measuring inappropriate medical diagnosis and treatment in survey data: The case of ADHD among school-age children. J Health Econ. 2010 Sep;29(5):657-73. doi: 10.1016/j.jhealeco.2010.07.005	Prevalence based on prescriptions
Evren, C. Comorbidity of attention deficit-hyperactivity disorder and substance use disorder. Dusunen Adam. Jun, 2018. DOI: 10.5350/DAJPN20183102001	Review or metanalysis
Eysbouts, Y.; Poulton, A.; Salmelainen, P. Stimulant medication in pre-school children in New South Wales. J Paediatr Child Health. Feb, 2011. doi:10.1111/j.1440-1754.2011.02107.x	No proper ADHD diagnosis
Faber, A.; de Jong-van den Berg, L. T.; van den Berg, P. B.; Tobi, H. Psychotropic co-medication among stimulant-treated children in The Netherlands. J Child Adolesc Psychopharmacol. 2005 Feb;15(1):38-43.	No proper ADHD diagnosis
Faber, A.; Kalverdijk, L. J.; De Jong-Van Den Berg, L. T. W.; Hugtenburg, J. G.; Minderaa, R. B.; Tobi, H. Co-morbidity and patterns of care in stimulant-treated children with ADHD in the Netherlands. Eur Child Adolesc Psychiatry. 2010 Feb;19(2):159-66. doi: 10.1007/s00787-009-0075-y	No proper ADHD diagnosis
Faber, A.; Kalverdijk, L. J.; De Jong-Van Den Berg, L. T. W.; Hugtenburg, J. G.; Minderaa, R. B.; Tobi, H. Parents report on stimulant-treated children in The Netherlands: Initiation of treatment and follow-up care. J Child Adolesc Psychopharmacol. 2006 Aug;16(4):432-40.	No proper ADHD diagnosis

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Fairman, K. A.; Peckham, A. M.; Sclar, D. A. Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. J Atten Disord. 2017 Feb 1:1087054716688534. doi: 10.1177/1087054716688534	Prevalence based on medical visits
Fairman, K.A; Peckham, A.M.; Sclar, D.A. Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. J Atten Disord, 2017. Published online Feb 1. DOI: 10.1177/1087054716688534	Prevalence based on medical visits
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Fallesen, P.; Wildeman, C. The Effect of Medical Treatment of Attention Deficit Hyperactivity Disorder (ADHD) on Foster Care Caseloads Evidence from Danish Registry Data. J Health Soc Behav. 2015 Sep;56(3):398-414. doi: 10.1177/0022146515595046.	No proper ADHD diagnosis
Farbstein, I.; Mansbach-Kleinfeld, I.; Auerbach, J. G.; Ponizovsky, A. M.; Apter, A. The Israel survey of mental health among adolescents: Prevalence of attention-deficit/hyperactivity disorder, comorbidity, methylphenidate use, and help-seeking patterns. Isr Med Assoc J. 2014 Sep;16(9):568-73. PMID: 25351015	Without or inadequate data on medication for ADHD
Feldman, H. M.; Blum, N. J.; Gahman, A. E.; Shults, J. Diagnosis of attention-deficit/hyperactivity disorder by developmental pediatricians in academic centers: A DBPNet study. Acad Pediatr. 2015 May-Jun;15(3):282-8. doi: 10.1016/j.acap.2014.09.004.	Without or inadequate data on medication for ADHD
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Feuer, A. J.; Thai, A.; Demmer, R. T.; Vogiatzi, M. Association of Stimulant Medication Use With Bone Mass in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. JAMA Pediatr. 2016 Dec 5;170(12):e162804. doi: 10.1001/jamapediatrics.2016.2804	No proper ADHD diagnosis
Fiks, A. G.; Ross, M. E.; Mayne, S. L.. et al. Preschool ADHD Diagnosis and Stimulant Use Before and After the 2011 AAP Practice Guideline. Pediatrics Dec 2016;138(6). DOI: 10.1542/peds.2016-2025	No proper ADHD diagnosis
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Flood, E.; Gajria, K.; Sikirica, V. et al. Research paper: The Caregiver Perspective on Paediatric ADHD (CAPPA) survey: Understanding sociodemographic and clinical characteristics, treatment use and impact of ADHD in Europe. J Affect Disord. 2016, aug; 200, 222-234. DOI: 10.1016/j.jad.2016.04.011	Clinical sample
Fogelman, Y.; Kahan, E. Methylphenidate use for attention deficit hyperactivity disorder in northern Israel - A controversial issue. Isr Med Assoc J. 2001 Dec;3(12):925-7. PMID: 11794916	No proper ADHD diagnosis
Fogelman, Y.; Vinker, S.; Guy, N.; Kahan, E. Prevalence of and change in the prescription of methylphenidate in Israel over a 2-year period. CNS Drugs. 2003;17(12):915-9. DOI: 10.2165/00023210-200317120-00005	No proper ADHD diagnosis
Fontanella, C. A.; Hiance, D. L.; Phillips, G. S.; Bridge, J. A.; Campo, J. V. Trends in psychotropic medication use for Medicaid-enrolled preschool children. J Child Fam Stud. 2013, may; 23(4). DOI: 10.1007/s10826-013-9761-y	No proper ADHD diagnosis
Forrester, M. B. Adult atomoxetine ingestions reported to Texas Poison Control Centers, 2003-2005. Ann Pharmacother. 2006 Dec;40(12):2136-41. DOI: 10.1345/aph.1H430.	No proper ADHD diagnosis
Forrester, M. B. Methylphenidate abuse in Texas, 1998-2004. J Toxicol Environ Health A. 2006 Jun;69(12):1145-53.. DOI: 10.1080/15287390500360273.	No proper ADHD diagnosis
Forster, M.; Gower, A. L.; Borowsky, I. W.; McMorris, B. J. Associations between adverse childhood experiences, student-teacher relationships, and non-medical use of prescription medications among adolescents. Addict Behav. 2017 May;68:30-34. doi: 10.1016/j.addbeh.2017.01.004.	No proper ADHD diagnosis
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Fossos-Wong, N.; Kilmer, J. R.; Lee, C. M. et al. Alcohol and substance use patterns among nonmedical prescription stimulant users attending college. Alcohol Clin Exp Res. 2018.	No proper ADHD diagnosis
Franke, A. G.; Bonertz, C.; Christmann, M.; Huss, M.; Fellgiebel, A.; Hildt, E.; Lieb, K. Non-Medical Use of Prescription Stimulants and Illicit Use of Stimulants for Cognitive Enhancement in Pupils and Students in Germany. Pharmacopsychiatry. 2011 Mar;44(2):60-6. doi: 10.1055/s-0030-1268417.	No proper ADHD diagnosis
Frankenberger, W.; Lozar, B.; Dallas, P. The use of stimulant medication to treat Attention Deficit Hyperactive Disorder (ADHD) in elementary school children. Developmental Disabilities Bulletin. 1990; 18(1), 1-13.	No proper ADHD diagnosis
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Grobe, T. G. Regional differences of ADHD diagnosis rates in health insurance data from 2005 to 2015: Methodological considerations and results. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz, 2017; 60(12): 1336-1345. DOI: 10.1007/s00103-017-2640-8	Without or inadequate data on medication for ADHD
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Hales, Craig M.; Kit, Brian K.; Gu, Qiuping; Ogden, Cynthia L. Trends in prescription medication use among children and adolescents—United States, 1999-2014. JAMA: Journal of the American Medical Association, 2018; 319(19):2009-2020	No proper ADHD diagnosis
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Handwerk, M. L.; Smith, G. L.; Thompson, R. W.; Spellman, D. F.; Daly, D. L. Psychotropic medication utilization at a group-home residential facility for children and adolescents. J Child Adolesc Psychopharmacol, 2008; 18(5): 517-525	Clinical sample
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Harpaz-Rotem, I.; Rosenheck, R. A. Prescribing practices of psychiatrists and primary care physicians caring for children with mental illness. Child: Care, Health And Development, 2006; 32(2):225-237	Clinical sample
Harrison, Christine; Sofronoff, Kate. ARTICLES: ADHD and Parental Psychological Distress: Role of Demographics, Child Behavioral Characteristics, and Parental Cognitions. J Am Acad Child Adolesc Psychiatry, 2002; 41():703-711	Clinical sample
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Hartung, C. M.; Canu, W. H.; Cleveland, C. S. et al. Stimulant medication use in college students: comparison of appropriate users, misusers, and nonusers. Psychol Addict Behav. 2013 Sep;27(3):832-40. doi: 10.1037/a0033822.	No proper ADHD diagnosis
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Hinshaw, Stephen P.; Scheffler, Richard M.; Fulton, Brent D. *et al*. International variation in treatment procedures for ADHD: social context and recent trends. Psychiatric Services (Washington, D.C.) 2011;62(5):459-464	Review or metanalysis
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Hire, A. J.; Ashcroft, D. M.; Springate, D. A.; Steinke, D. T. ADHD in the United Kingdom: Regional and Socioeconomic Variations in Incidence Rates Amongst Children and Adolescents (2004-2013). J Atten Disord, 2015. Published online Nov 23. DOI: 10.1177/1087054715613441.	Without or inadequate data on medication for ADHD
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Hjern, A.; Weitoft, G. R.; Lindblad, F. Social adversity predicts ADHD-medication in school children - a national cohort study. Acta Paediatrica, 2010; 99(6):920-924	No proper ADHD diagnosis
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Hoagwood, K.; Kelleher, K. J.; Feil, M.; Comer, D. M.. Treatment services for children with ADHD: a national perspective. J Am Acad Child Adolesc Psychiatry, 2000; 39(2): 198-206	Prevalence based on prescriptions
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Hodgkins, Paul; Sasane, Rahul; Meijer, Willemijn M. Pharmacologic Treatment of Attention-Deficit/Hyperactivity Disorder in Children:	Prevalence based on prescriptions

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Holden, S. E.; Jenkins-Jones, S.; Poole, C. D.; Morgan, C. L.; Coghill, D.; Currie, C. J. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). Child Adolesc Psychiatry Ment Health, 2013; 7(1):34	Prevalence based on prescriptions
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Holley, Trina D. ADHD Prevalence Rates in a Hampton Roads School District. Thesis. Regent University, 2004.	No proper ADHD diagnosis
Hollingworth, Samantha A.; Nissen, Lisa M.; Stathis, Stephen S.; Siskind, Dan J.; Varghese, John M. N.; Scott, James G. Australian national trends in stimulant dispensing: 2002-2009. Aust N Z J Psychiatry, 2011;45(4):332-336	No proper ADHD diagnosis
Holowenko, H.; Pashute, K. ADHD in schools: A survey of prevalence and 'coherence' across a local UK population. Educ Psychol Pract. 2018, jun; 16(2):181-190. DOI: 10.1080/713666060	Prevalence based on prescriptions
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Hsia, Y. F.; Maclennan, K. Rise in psychotropic drug prescribing in children and adolescents during 1992-2001: a population-based study in the	No proper ADHD diagnosis

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Huang, K.; Wei, H.; Hsu, J. et al Risk of suicide attempts in adolescents and young adults with attention-deficit hyperactivity disorder: a nationwide longitudinal study. Br J Psychiatry. 2018 Apr;212(4):234-238. doi: 10.1192/bjp.2018.8.	Clinical sample
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Huemer, J.; Riegler, A.; Völkl-Kernstock, S. *et al*. The influence of reported ADHD and substance abuse on suicidal ideation in a non-clinical sample of young men. Neuropsychiatr, 2016;30(3):131-137. DOI: 10.1007/s40211-016-0198-6.	No proper ADHD diagnosis
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Ivis, F. J.; Adlaf, E. M. Prevalence of methylphenidate use among adolescents in Ontario. Can J Public Health, 1999; 90(5):309-312. PMID: 10570573.	No proper ADHD diagnosis
Jaber, Lutfi; Rigler, Shmuel; Shuper, Avinoam; Diamond, Gary. Changing Epidemiology of Methylphenidate Prescriptions in the Community: A Multifactorial Mode. J Atten Disord, 2017; 21(14):1143-1150. DOI: 10.1177/1087054714528044	No proper ADHD diagnosis
Jaber, Lutfi; Rigler, Shmuel; Shuper, Avinoam; Diamond, Gary. Changing Epidemiology of Methylphenidate Prescriptions in the Community: A Multifactorial Model. J Atten Disord, 2014; published online April 28. 21(14): 1143-1150. DOI: 10.1177/1087054714528044	No proper ADHD diagnosis
Jablonska, Beata; Kosidou, Kyriaki; Ponce de Leon, Antonio et al. Neighborhood Socioeconomic Characteristics and Utilization of ADHD Medication in Schoolchildren: A Population Multilevel Study in Stockholm County. J Atten Disord, 2016. Published online April 19.	No proper ADHD diagnosis
Jain, Roshini; Chang, Ch Chiech; Koto, Mpho; Geldenhuys, Alden; Nichol, Richard; Joubert, Gina. Non-medical use of methylphenidate among medical students of the University of the Free State. S Afr J Psychiatr, 2017. 23:1006. DOI: 10.4102/sajpsychiatry.v23.1006	No proper ADHD diagnosis
Janols, Lars-Olof; Liliemark, Jan; Klintberg, Karin; von Knorring, Anne-Liis. Central stimulants in the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents. A naturalistic study of the	No proper ADHD diagnosis

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Jick, H.; Kaye, J. A.; Black, C. Incidence and prevalence of drug-treated attention deficit disorder among boys in the UK. Br J Gen Pract. 2004 May;54(502):345-7. PMID: 15113516	Prevalence based on prescriptions
Johansen, M. E.; Matic, K.; McAlearney, A. S. Attention Deficit Hyperactivity Disorder Medication Use among Teens and Young Adults. J Adolesc Health, 2015; 57(2):192-197. DOI: 10.1016/j.jadohealth.2015.04.009.	No proper ADHD diagnosis
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Jonas, B. S.; Gu, Q.; Albertorio-Diaz, J. R. Psychotropic medication use among adolescents: United States, 2005-2010. NCHS Data Brief, 2013; 135: 1-8. PMID: 24314102.	No proper ADHD diagnosis
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Mineo, Ludovico; Sarraf, Yasmin; Ingram, Cody *et al*. Affective temperaments and stimulant medications misuse for neuroenhancement in graduate students J Subst Use, 2018; 23(2): 124-129. DOI: 10.1080/14659891.2017.1364307.	No proper ADHD diagnosis
Mitchell, B.; Carleton, B.; Smith, A.; Prosser, R.; Brownell, M.; Kozyrskyj, A. Trends in psychostimulant and antidepressant use by children in 2 Canadian provinces. Can J Psychiatry, 2008; 53(3): 152-159.	No proper ADHD diagnosis
Moggi, F. Are attention-deficit/hyperactivity disorder symptoms associated with a more severe course of substance use? A longitudinal study with young Swiss men. Eur Psychiatry, 2016; 33: S21. DOI: 10.1016/j.eurpsy.2016.01.828	Without or inadequate data on medication for ADHD
Mohr-Jensen, C.; Vinkel Koch, S.; Briciet Lauritsen, M.; Steinhausen, H. C. The validity and reliability of the diagnosis of hyperkinetic disorders in the Danish Psychiatric Central Research Registry. Eur Psychiatry, 2016; 35: 16-24. DOI: 10.1016/j.eurpsy.2016.01.2427.	Clinical sample
Moline, Scott; Frankenberger, William. Use of stimulant medication for treatment of attention-deficit/hyperactivity disorder: A survey of middle and high school students' attitudes. Psychol Sch, 2001; 38(6): 569-584. DOI:10.1002/pits.1044	No proper ADHD diagnosis
Morgan, Paul L.; Staff, Jeremy; Hillemeier, Marianne M.; Farkas, George; Maczuga, Steven, Racial and ethnic disparities in ADHD diagnosis from kindergarten to eighth grade. Pediatrics. 2013 Jul;132(1):85-93. DOI: 10.1542/peds.2012-2390	Clinical sample
Morrill, M. S. Special Education Financing and ADHD Medications: A Bitter Pill to Swallow. J Policy Anal Manage. 2018, feb; 37(2). DOI: 10.1002/pam.22055	Clinical sample
Morrow, R. C.; Morrow, A. L.; Haislip, G. Methylphenidate in the United States, 1990 through 1995. Am J Public Health, 1998; 88(7): 1121. DOI: 10.2105/ajph.88.7.1121	No proper ADHD diagnosis
Morrow, R. L.; Garland, E. J.; Wright, J. M.; Maclure, M.; Taylor, S.; Dormuth, C. R. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. CMAJ. 2012 Apr 17; 184(7): 755–762. doi: 10.1503/cmaj.111619	Prevalence based on prescriptions
Mowlem, F. D.; Rosenqvist, M. A.; Martin, J.; Lichtenstein, P.; Asherson, P.; Larsson, H. Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. Eur Child Adolesc Psychiatry. 2019 Apr;28(4):481-489. doi: 10.1007/s00787-018-1211-3.	Without or inadequate data on medication for ADHD

Mulvihill, Katrina Josefa. The prevalence of prescription stimulant abuse and motivations in a sample of community college students. ProQuest Dissertations Publishing, 2013.	No proper ADHD diagnosis
Newlove-Delgado, T.; Ford, T. J.; Hamilton, W.; Stein, K.; Ukoumunne, O. C. Prescribing of medication for attention deficit hyperactivity disorder among young people in the Clinical Practice Research Datalink 2005-2013: analysis of time to cessation. Eur Child Adolesc Psychiatry, 2017; 27(1):29-35. DOI: 10.1007/s00787-017-1011-1.	Prevalence based on prescriptions
Norum, J.; Olsen, A. I.; Nohr, F. I.; Heyd, A.; Totth, A. Medical treatment of children and youths with attention-deficit/hyperactivity disorder (ADHD): a Norwegian Prescription Registry Based Study. Glob J Health Sci, 2014; 6(4): 155-162. DOI: 10.5539/gjhs.v6n4p155.	No proper ADHD diagnosis
Nyarko, K. A.; Grosse, S. D.; Danielson, M. L.; Holbrook, J. R.; Visser, S. N.; Shapira, S. K. Treated Prevalence of Attention-Deficit/Hyperactivity Disorder Increased from 2009 to 2015 Among School-Aged Children and Adolescents in the United States. J Child Adolesc Psychopharmacol, 2017; 27(8):731-734. DOI: 10.1089/cap.2016.0196.	Prevalence based on prescriptions
Oehrlein, E. M.; Burcu, M.; Safer, D. J.; Zito, J. M. National Trends in ADHD Diagnosis and Treatment: Comparison of Youth and Adult Office-Based Visits. Psychiatr Serv. 2016 Sep 1;67(9):964-9. doi: 10.1176/appi.ps.201500269.	Prevalence based on prescriptions
Okumura, Y.; Usami, M.; Okada, T. *et al*. Prevalence, incidence and persistence of ADHD drug use in Japan. Epidemiol Psychiatr Sci, 2018; 28: 1-5. DOI: 10.1017/S2045796018000252.	No proper ADHD diagnosis
Okumura, Yasuyuki; Fujita, Junichi; Matsumoto, Toshihiko. Trends of psychotropic medication use among children and adolescents in Japan data from the national insurance claims database between 2002 and 2010. Seishin Shinkeigaku Zasshi, 2014; 116(11): 921-935. PMID: 25702498	No proper ADHD diagnosis
Olfson, M.; Blanco, C.; Wang, S.; Greenhill, L. L.Trends in office-based treatment of adults with stimulants in the United States. J Clin Psychiatry. 2013 Jan;74(1):43-50. doi: 10.4088/JCP.12m07975.	Prevalence based on prescriptions
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Olfson, M.; Marcus, S. C.; Weissman, M. M.; Jensen, P. S. National Trends in the Use of Psychotropic Medications by Children. J Am Acad Child Adolesc Psychiatry. 2002; 41(5): 514-521. DOI: 10.1097/00004583-200205000-00008	No proper ADHD diagnosis
Olfson, Mark; Gameroff, Marc J.; Marcus, Steven C.; Jensen, Peter S. National Trends in the Treatment of Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 2003; 160(6):1071-1077. DOI: 10.1176/appi.ajp.160.6.1071	No proper ADHD diagnosis

Olfson, Mark; Huang, Cecilia; Gerhard, Tobias *et al*. New research: Stimulants and Cardiovascular Events in Youth With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry, 2012; 51(2): 147–156. DOI: 10.1016/j.jaac.2011.11.008	Clinical sample
Olubokun, Jibowu. Attention Deficit Hyperactivity Disorder-A Pre Audit Study of the Pattern of Drug Treatment in a Specialist Community Child and Adolescent Mental Health Service in the UK. International Journal of Criminology and Sociology, 2015; 4: 136-140. DOI: http://dx.doi.org/10.6000/1929-4409.2015.04.14.	No proper ADHD diagnosis
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Oner, Ozgur; Turkcapar, Hakan; Isli, Fatma *et al*. Attention deficit hyperactivity disorder treatment practice in Turkey. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology 2016; 26(3):265. DOI: 10.5455/bcp.20151202103706	No proper ADHD diagnosis
Oner, Ozgür; Yilmaz, Esra Safak; Karada X011f, Hasan *et al*. ADHD Medication Trends in Turkey: 2009-2013. Journal of Attention Disorders, 2014. Published online Feb 19. 21(14): 1192-1197. DOI: 10.1177/1087054714523129	No proper ADHD diagnosis
Ornoy, A.; Ovadia, M.; Rivkin, D.; Milshtein, E.; Barlev, L.. Prevalence of ADHD among 7-9-Year-Old Children in Israel. A Comparison between Jewish and Arab Populations. Isr J Psychiatry Relat Sci. 2016;53(2):3-8. PMID: 28079031	No proper ADHD diagnosis
Ott, R.; Biller-Andorno, N. Neuroenhancement among Swiss students--a comparison of users and non-users. Pharmacopsychiatry, 2014; 47(1):22-28. DOI: 10.1055/s-0033-1358682.	No proper ADHD diagnosis
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Pagsberg, A. K.; Thomsen, P. H. Off-label prescription of psychopharmacological drugs for children and adolescents. Ugeskr Laeger, 2017; 179(35). PMID: 28874238	No proper ADHD diagnosis
Palli, S. R.; Kamble, P. S.; Chen, H.; Aparasu, R. R. Persistence of stimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol, 2012; 22(2):139-148. DOI: 10.1089/cap.2011.0028.	Prevalence based on prescriptions
Panther, S. G.; Knotts, A. M.; Odom-Maryon, T.; Daratha, K.; Woo, T.; Klein, T. A. Off-label prescribing trends for ADHD medications in very young children. J Pediatr Pharmacol Ther, 2017; 22(6):423-429. DOI: 10.5863/1551-6776-22.6.423.	Clinical sample
Pastor, P. N.; Reuben, C. A. Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004-2006. Vital Health Stat 10. 2008 Jul;(237):1-14. PMID: 18998276	No proper ADHD diagnosis

Pastor, P. N.; Reuben, C. A. Racial and ethnic differences in ADHD and LD in young school-age children: parental reports in the National Health Interview Survey. Public Health Rep. 2005 Jul-Aug;120(4):383-92. DOI: 10.1177/003335490512000405	No proper ADHD diagnosis
Pastor, P.; Reuben, C.; Duran, C.; Hawkins, L. Association between diagnosed ADHD and selected characteristics among children aged 4-17 years: United States, 2011-2013. NCHS Data Brief, 2015; (201):201. PMID: 25974000.	Without or inadequate data on medication for ADHD
Pastor, Patricia N.; Reuben, Cynthia A. Attention Deficit Disorder and Learning Disability: United States, 1997-98. Vital Health Stat 10. 2002; (206):1-12. PMID: 15789507	Without or inadequate data on medication for ADHD
Pastor, Patricia N.; Simon, Alan E.; Reuben, Cynthia A. ADHD: Insurance and Mental Health Service Use. Clin Pediatr (Phila), 2017; 56(8): 729-736. DOI: 10.1177/0009922816673401.	Without or inadequate data on medication for ADHD
Patel, A.; Medhekar, R.; Ochoa-Perez, M. *et al*. Care Provision and Prescribing Practices of Physicians Treating Children and Adolescents With ADHD. Psychiatr Serv, 2017; 68(7): 681-688. DOI: 10.1176/appi.ps.201600130.	Prevalence based on prescriptions
Pauly, V.; Frauger, E.; Lepelley, M.; Boucherie, Q.; Mallaret, M.; Micallef, J. Patterns and profiles of methylphenidate use in adults: A cohort study from the regional French health insurance database. Fundam Clin Pharmacol, 2018; 32:10. DOI:10.1111/fcp.12370.	No proper ADHD diagnosis
Penberthy, J. Kim; Hook, Joshua N.; Breton, Marc D.; Runyon, Carolyn F.; Kovatchev, Boris P. Retrospective analysis of ADHD diagnoses in an outpatient pediatric clinic. Journal of Ethics in Mental Health, 2012 ;7:1-5.	Clinical sample
Penfold, R.; Alagar, L.; Enns, M.; Chipperfield, S.; Strutt, C.; Bowen, S. Patterns of Regional Mental Illness Disorder Diagnoses and Service Use in Manitoba - A Population-Based Study. Manitoba Centre for Health Policy, 2004	No proper ADHD diagnosis
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Pennap, D.; Zito, J. M.; Santosh, P. J.; Tom, S. E.; Onukwugha, E.; Magder, L. S. Patterns of early mental health diagnosis and medication treatment in a medicaid-insured birth cohort. JAMA Pediatr. 2018 Jun 1;172(6):576-584. doi: 10.1001/jamapediatrics.2018.0240.	Clinical sample
Pennap, Dinci; Burcu, Mehmet; Safer, Daniel J.; Zito, Julie M. Hispanic Residential Isolation, ADHD Diagnosis and Stimulant Treatment among Medicaid-Insured Youth. Ethn Dis. 2017 Apr 20;27(2):85-94. doi: 10.18865/ed.27.2.85.	Clinical sample
Perwien, A.; Hall, J.; Swensen, A.; Swindle, R. Stimulant treatment patterns and compliance in children and adults with newly treated	Prevalence based on prescriptions

attention-deficit/hyperactivity disorder. J Manag Care Pharm. 2004 Mar-Apr;10(2):122-9. DOI: 10.18553/jmcp.2004.10.2.122	
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Piovani, D.; Clavenna, A.; Cartabia, M.; Bonati, M. Psychotropic medicine prescriptions in Italian youths: a multiregional study. Eur Child Adolesc Psychiatry, 2016; 25(3): 235-245. DOI: 10.1007/s00787-015-0726-0.	No proper ADHD diagnosis
Polyzoi, M.; Ahnemark, E.; Medin, E.; Ginsberg, Y. Estimated prevalence and incidence of diagnosed ADHD and health care utilization in adults in Sweden – A longitudinal population-based register study.Neuropsychiatr Dis Treat, 2018; 14: 1149-1161. DOI:10.2147/NDT.S155838	Clinical sample
Ponizovsky, Alexander M.; Marom, Eli; Fitoussi, Israel. Trends in attention deficit hyperactivity disorder drugs consumption, Israel, 2005-2012 Pharmacoepidemiol Drug Saf, 2014; 23(5): 534-538. DOI:10.1002/pds.3604	No proper ADHD diagnosis
Pottegard, A.; Bjerregaard, B. K.; Glintborg, D.; Hallas, J.; Moreno, S. I. The use of medication against attention deficit hyperactivity disorder in Denmark: A drug use study from a national perspective. European Journal Of Clinical Pharmacology, 2012; 68(10):1443-1450. DOI:10.1007/s00228-012-1265-y	No proper ADHD diagnosis
Pottegård, Anton; Hallas, Jesper; Hernández, Díaz; Zoëga, Helga. Children's relative age in class and use of medication for ADHD: a Danish Nationwide Study. J Child Psychol Psychiatry, 2014; 55(11): 1244-1250. OI:10.1111/jcpp.12243	No proper ADHD diagnosis
Poulin, C. From attention-deficit/hyperactivity disorder to medical stimulant use to the diversion of prescribed stimulants to non-medical stimulant use: Connecting the dots. Addiction. 2007 May;102(5):740-51. DOI: 10.1111/j.1360-0443.2007.01758.x	Without or inadequate data on medication for ADHD
Poulton, Alison S.; Armstrong, Bruce; Nanan, Ralph K. Perinatal Outcomes of Women Diagnosed with Attention-Deficit/Hyperactivity Disorder: An Australian Population-Based Cohort Study. CNS Drugs 2018;32(4):377-386. DOI:10.1007/s40263-018-0505-9	Review or metanalysis
Preen, D. B.; Calver, J.; Sanfilippo, F. M.; Bulsara, M.; Holman, C. D. Patterns of psychostimulant prescribing to children with ADHD in Western Australia: variations in age, gender, medication type and dose prescribed. Aust N Z J Public Health, 2007; 31(2): 120-126. PMID: 17461001	Prevalence based on prescriptions
Prescribing study reveals undertreatment of ADHD, depression, and anxiety among youth. Brown University Child & Adolescent Psychopharmacology Update. 2018;20(4):1-4	News or unrelated article
Pringsheim, T.; Stewart, D. G.; Chan, P.; Tehrani, A. The Pharmacoepidemiology of Psychotropic Medication Use in Canadian	No proper ADHD diagnosis

Children From 2012 to 2016. J Am Acad Child Adolesc Psychiatry, 2018; 57(10): S162. DOI:10.1016/j.jaac.2018.09.099	
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Prosser, B.; Reid, R. Changes in use of psychostimulant medication for ADHD in South Australia (1990-2006). Aust N Z J Psychiatry, 2009; 43(4): 340-347. DOI:10.1080/00048670902721129	Prevalence based on prescriptions
Prosser, Brenton; Lambert, Matthew C.; Reid, Robert. Psychostimulant prescription for ADHD in new South Wales: a longitudinal perspective. J Atten Disord, 2015; 19(4): 284-292. DOI:10.1177/1087054714553053	Prevalence based on prescriptions
Prosser, Brenton; Reid, Robert. Psychostimulant use for children with ADHD in Australia. J Emot Behav Disord, 1999; 7(2): 110-117. DOI:10.1177/106342669900700206	Without or inadequate data on medication for ADHD
Rabiner, David L.; Anastopoulos, Arthur D.; Costello, Jane; Hoyle, Rick H.; Swartzwelder, H. Scott. Adjustment to college in students with ADHD. J Atten Disord, 2008; 11(6): 689-699. DOI: 10.1177/1087054707305106	No proper ADHD diagnosis
Raghavan, R.; McMillen, J. C. Use of multiple psychotropic medications among adolescents aging out of foster care. Psychiatr Serv. 2008 Sep; 59(9): 1052–1055. doi: 10.1176/appi.ps.59.9.1052	Clinical sample
Raman, S. R.; Man, K. K. C.; Bahmanyar, S. *et al*. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. The Lancet Psychiatry, 2018; 5(10): 824-835. DOI:10.1016/S2215-0366(18)30293-1	No proper ADHD diagnosis
Rasmussen, L.; Ormhøj, S. S.; Gasse, C.; Pottegård, A. Use of attention-deficit/hyperactivity disorder medication among older adults in Denmark. Pharmacoepidemiol Drug Saf, 2017; 26: 493. DOI:10.1002/pds.4275	Without or inadequate data on medication for ADHD
Rasmussen, L.; Wallach-Kildemoes, H.; Zoëga, H.; Bilenberg, N.; Hallas, J.; Pottegård, A. Assessing the quality of treatment with attention-deficit/hyperactivity disorder medication in Denmark. Pharmacoepidemiol Drug Saf, 2017; 26: 331. DOI:10.1002/pds.4275	No proper ADHD diagnosis
Reale, L.; Zanetti, M.; Cartabia, M.; Fortinguerra, F.; Bonati, M. Two-years of activity of the Lombardy Region's ADHD Registry: An analysis of the diagnostic and therapeutic pathways of care. Ricerca e Pratica. 2014, set; 30(5):198-211.	Clinical sample
Reid, Robert; Hakendorf, Paul; Prosser, Brenton. Use of psychostimulant medication for ADHD in South Australia. J Am Acad Child Adolesc Psychiatry, 2002; 41(8): 906-913. DOI: 10.1097/00004583-200208000-00008	No proper ADHD diagnosis

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Retief, M.; Verster, C. Prevalence and correlates of non-prescribed stimulant and related drug use in a sample of South African undergraduate medical students. S Afr J Psychiatr, 2016; 22(1):795. DOI: 10.4102/sajpsychiatry.v22i1.795.	No proper ADHD diagnosis
Riegler, A,; Völkl-Kernstock, S.; Lesch, O.; Walter, H.; Skala, K. Attention deficit hyperactivity disorder and substance abuse: An investigation in young Austrian males. J Affect Disord. 2017 Aug 1;217:60-65. doi: 10.1016/j.jad.2017.03.072.	No proper ADHD diagnosis
Rimvall, Martin; Elberling, Hanne; Rask, Charlotte; Helenius, Dorte; Skovgaard, Anne; Jeppesen, Pia. Predicting ADHD in school age when using the Strengths and Difficulties Questionnaire in preschool age: a longitudinal general population study, CCC2000. Eur Child Adolesc Psychiatry, 2014; 23(11): 1051-1060. DOI:10.1007/s00787-014-0546-7	Prevalence based on prescriptions
rnoy, A.; Rivkin, D.; Barlev, L. CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): ACCESSIBILITY AND AVAILABILITY OF SERVICES IN ISRAEL. Harefuah, 2018; 157(4): 219-224. PMID: 29688638	Without or inadequate data on medication for ADHD
Robison, L. M.; Sclar, D. A.; Skaer, T. L.; Galin, R. S. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990-1995. Clin Pediatr (Phila). 1999 Apr;38(4):209-17. DOI: 10.1177/000992289903800402	Prevalence based on prescriptions
Robison, L. M.; Sclar, D. A.; Skaer, T. L.; Galin, R. S. Treatment modalities among US children diagnosed with attention-deficit hyperactivity disorder: 1995-99. Int Clin Psychopharmacol. 2004 Jan;19(1):17-22. PMID: 15101565	Prevalence based on prescriptions
Robison, L. M.; Skaer, T. L.; Sclar, D. A. Is attention-deficit hyperactivity disorder (ADHD) diagnosed in adults? An examination of US office-based physician visits, 1995-2000. International Journal of Pharmaceutical Medicine. 2005, dec; 18(6):337-341. DOI: 10.2165/00124363-200418060-00003	Prevalence based on prescriptions
Robison, L. M.; Skaer, T. L.; Sclar, D. A.; Galin, R. S. Is attention deficit hyperactivity disorder increasing among girls in the US? Trends in diagnosis and the prescribing of stimulants. CNS Drugs. 2002;16(2):129-37. DOI: 10.2165/00023210-200216020-00005	Prevalence based on prescriptions
Robison, Linda M.; Sclar, David A.; Skaer, Tracy L. Trends in ADHD and stimulant use among adults: 1995-2002. Psychiatric Services, 2005;56(12):1497-1497. DOI:10.1176/appi.ps.56.12.1497	Prevalence based on prescriptions
Rodríguez G., C. T.; González M., M. I.; Arroba B., M. L.; Cabello B. L. Prevalence of attention deficit disorder with hyperactivity in children from an urban area. Pediatria de Atencion Primaria 2017;19(76):311-320.	Clinical sample

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Roesler, Michael; Retz, Wolfgang; Yaqoobi, Khalid; Burg, Eva; Retz-Junginger, Petra. Attention deficit/hyperactivity disorder in female offenders: prevalence, psychiatric comorbidity and psychosocial implications. Eur Arch Psychiatry Clin Neurosci, 2009; 259(2): 98-105. DOI:10.1007/s00406-008-0841-8	Clinical sample
Romano, E.; Baillargeon, R. H.; Fortier, I.; Wu, H. X.; Robaey, P.; Zoccolillo, M.; Tremblay, R. E. Individual change in methylphenidate use in a national sample of children aged 2 to 11 years. Can J Psychiatry. 2005; 50(3): 144-152. DOI: 10.1177/070674370505000303.	No proper ADHD diagnosis
Romano, E.; Baillargeon, R. H.; Wu, H. X.; Robaey, P.; Tremblay, R. E. Prevalence of methylphenidate use and change over a two-year period: A nationwide study of 2- to 11-year-old Canadian children. Journal of Pediatrics, 2002;141(1):71-75. DOI:10.1067/mpd.2002.125399	No proper ADHD diagnosis
Ross, L.;, Sapre V.; Stanislaus C.; Poulton, A. High Dose Stimulant Medication for the Management of Attention Deficit/Hyperactivity Disorder (ADHD): A Retrospective Cohort Study	Clinical sample
Rowland, A. S.; Skipper, B. J.; Umbach, D. M. et al. The Prevalence of ADHD in a Population-Based Sample. J Atten Disord. 2015 Sep;19(9):741-54. doi: 10.1177/1087054713513799.	Without or inadequate data on medication for ADHD
Rowland, A. S.; Umbach, D. M.; Catoe, K. E. et al. Studying the epidemiology of attention-deficit hyperactivity disorder: screening method and pilot results. Can J Psychiatry. 2001 Dec;46(10):931-40. DOI: 10.1177/070674370104601005	Without or inadequate data on medication for ADHD
Rowland, A. S.; Umbach, D. M.; Stallone, L.; Naftel, A. J.; Bohlig, E. M.; Sandler, D. P. Prevalence of medication treatment for attention deficit-hyperactivity disorder among elementary school children in Johnston County, North Carolina. Am J Public Health. 2002 February; 92(2): 231–234. PMID: 11818297	Without or inadequate data on medication for ADHD
Roy, E.; Nolin, M. A.; Traore, I.; Leclerc, P.; Vasiliadis, H. M. Nonmedical use of prescription medication among adolescents using drugs in Quebec. Can J Psychiatry, 2015; 60(12): 556-563. DOI: 10.1177/070674371506001206	No proper ADHD diagnosis
Ruiz, B.; Centeno, G. A.; Camargo, A. P.; Fernández, R.; Palanca, I.; Avendaño, C. Utilization study for ADHD pediatric population in specialized health care. A longitudinal study 2011-2015 Jornal?? , 2016; 119:18. DOI:10.1111/bcpt.12546	Clinical sample
Rushton, J. L.; Whitmire, J. T. Pediatric stimulant and selective serotonin reuptake inhibitor prescription trends: 1992 to 1998. Arch Pediatr Adolesc Med, 2001; 155(5): 560-565. PMID: 11343498	No proper ADHD diagnosis

Rydell, M.; Lundstrom, S.; Gillberg, C.; Lichtenstein, P.; Larsson, H. Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample. J Child Psychol Psychiatr, 2018; 59(8): 863-871. DOI:10.1111/jcpp.12882	Without or inadequate data on medication for ADHD
Safer, D. J. Recent Trends in Stimulant Usage. J Atten Disord, 2016; 20(6): 471-177. DOI: 10.1177/1087054715605915.	Review or metanalysis
Safer, D. J.; Krager, J. M. The increased rate of stimulant treatment for hyperactive inattentive students in secondary-schools. Pediatrics 1994;94(4):462-464. MID: 7936853	No proper ADHD diagnosis
Safer, D. J.; Zito, J. M.; Fine, E. M. Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics, 1996; 98(6): 1084-1088. PMID: 8951257	No proper ADHD diagnosis
Safer, Daniel J.; Malever, Michael. Stimulant Treatment in Maryland Public Schools. Pediatrics, 2000; 106(3):533. DOI: 10.1542/peds.106.3.533.	No proper ADHD diagnosis
Salmelainen, P. Trends in the prescribing of stimulant medication for the treatment of Attention Deficit Hyperactivity Disorder in adults in New South Wales. N S W Public Health Bull, 2004; 15(3):1-55	No proper ADHD diagnosis
Salmelainen, P. Trends in the prescribing of stimulant medication for the treatment of attention deficit hyperactivity disorder in children and adolescents in New South Wales. N S W Public Health Bull, 2002;13(1): 1-65. PMID: 12189396	No proper ADHD diagnosis
Sánchez Martínez, D. P.; Guillén Pérez, J. J. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in the Region of Murcia, Spain: Differences by gender, age and location of residence. An Pediatr (Barc), 2018; 88(4): 183-190. DOI:10.1016/j.anpedi.2017.02.014	No proper ADHD diagnosis
Sankaranarayanan, J.; Puumala, S. E.; Kratochvil, C. J. Diagnosis and treatment of adult attention-deficit/hyperactivity disorder at US ambulatory care visits from 1996 to 2003. Curr Med Res Opin. 2006 Aug;22(8):1475-91. DOI: 10.1185/030079906X112615	Prevalence based on prescriptions
Santesteban-Echarri, O.; Ramos-Olazagasti, M.A.; Eisenberg, R.E. et al. Parental warmth and psychiatric disorders among Puerto Rican children in two different socio-cultural contexts. J Psychiatr Res, 2017; 87: 30-36. DOI: 10.1016/j.jpsychires.2016.12.008	Same sample of an included study
Saucedo, R. S.; Pharm, X. L. B. S.; Hincapie-Castillo, J. M.; Zambrano, D.; Bussing, R.; Winterstein, A. G. Prevalence, time trends, and utilization patterns of psychotropic polypharmacy among pediatric medicaid beneficiaries, 1999–2010. Psychiatric Services 2018; 69(8): 919-926. DOI:10.1176/appi.ps.201700260	No proper ADHD diagnosis

Schmidt-Troschke, S. O.; Ostermann, T.; Melcher, D.; Schuster, R.; Erben, C. M.; Matthiessen, P. F. The use of methylphenidate in children: Analysis of prescription usage based in routine date of the statutory health insurance bodies concerning drug prescriptions. Gesundheitswesen, 2004; 66(6): 387-392. DOI: 10.1055/s-2004-813322.	No proper ADHD diagnosis
Schoeman, Renata; de Klerk, Manie. Adult attention deficit hyperactivity disorder: A database analysis of South African private health insurance S Afr J Psychiatr, 2017; 23: 1010. DOI: 10.4102/sajpsychiatry.v23.1010	News or unrelated article
Schubert, I.; Koester, I.; Lehmkuhl, G. The Changing Prevalence of Attention-Deficit/Hyperactivity Disorder and Methylphenidate Prescriptions A Study of Data From a Random Sample of Insurees of the AOK Health Insurance Company in the German State of Hesse, 2000-2007. Dtsch Arztebl Int. 2010, set; 107(36):615-21. DOI: 10.3238/arztebl.2010.0615	Prevalence based on prescriptions
Schubert, I.; Koster, I.; Adam, C.; Ihle, P.; Dopfner, M.; Lehmkuhl, G. Psychotropic Drugs for Children with the Claims Diagnosis "Attention Deficit/Hyperkinetic Disorder". A Drug Utilisation Study of Outpatient Care with Person-Related Data of the Statutory Health Insurance (Versichertenstichprobe AOK Hessen/KV Hessen, 1998-2001). Zeitschrift fur Gesundheitswissenschaften, 2003; 11(4): 306-324.	Clinical sample
Sclar, D. A.; Robison, L. M.; Castillo, L. V.; Bowen, K. A.; Schmidt, J. M.; Oganov, A. M. Attention deficit/hyperactivity disorder among adults in the United States: Trend in diagnosis and use of pharmacotherapy. Clinical Pediatrics. 2012, mar; 51(6):584-9. DOI: 10.1177/0009922812439621	Prevalence based on prescriptions
Sgro, M.; Roberts, W.; Grossman, S.; Barozzino, T. School board survey of attention deficit/hyperactivity disorder: Prevalence of diagnosis and stimulant medication therapy. Paediatr Child Health. 2000 Jan;5(1):19-23. DOI: 10.1093/pch/5.1.19	No proper ADHD diagnosis
Shin, Ju-Young; Lee, Shin Haeng; Shin, Sun Mi; Shin, Han Na; Park, Byung-Joo. Regulatory action and moderate decrease in methylphenidate use among ADHD diagnosed patients aged five and under in Korea. Regul Toxicol Pharmacol, 2015; 72(2): 244-248. DOI:10.1016/j.yrtph.2015.04.022	Clinical sample
Shyu, Y.; Yuan, S.; Lee, Sheng-Y. et al. Attention-deficit/hyperactivity disorder, methylphenidate use and the risk of developing schizophrenia spectrum disorders: A nationwide population-based study in Taiwan. Schizophr Res. 2015 Oct;168(1-2):161-7. doi: 10.1016/j.schres.2015.08.033.	Clinical sample
Silveira, R. R.; Lejderman, B.; Ferreira, P. E. M. S.; da Rocha, G. M. P. Patterns of non-medical use of methylphenidate among 5th and 6th year students in a medical school in southern Brazil. Trends Psychiatry Psychother. June 2014; 36(2):101-106. DOI: 10.1590/2237-6089-2013-0065	No proper ADHD diagnosis
Simeone, J. C. Evaluation of treatment patterns for medications utilized in the management of pediatric attention-deficit/hyperactivity disorder. Thesis. University of Rohde Island. 2010.	Prevalence based on prescriptions

Sinzig, J.; Blanz, S.; Schmidt, M. H.; Lehmkuhl, G. How many children and adolescents do receive a combined behavioral and psychopharmacological therapy? Prax Kinderpsychol Kinderpsychiatr. 2008;57(2):85-97.DOI: 10.13109/prkk.2008.57.2.85	Clinical sample
Smith, M. D. Investigation of the relationship between ADHD and bodyweight in a Canadian sample of children. US ProQuest Information & Learning 2017	No proper ADHD diagnosis
Smith, T. E.; DeSantis, A. D.; Martel, M. M. Gender Differences in Nonprescribed Psychostimulant Use in Young Adults. Subst Use Misuse. 2018 Mar 21;53(4):622-628. doi: 10.1080/10826084.2017.1355384	Without or inadequate data on medication for ADHD
Song, I.; Lee, M. S.; Lee, E. K.; Shin, J. Y. Patient and provider characteristics related with prescribing of ADHD medication: Nationwide health insurance claims database study in Korea. Asia Pac Psychiatry. 2018 Mar;10(1). doi: 10.1111/appy.12289.	Prevalence based on prescriptions
Song, M.; Dieckmann, N.; Nigg, J. Can we resolve varying ADHD prevalence estimates in the U.S.? A closer look at NSCH 2007 and 2008 and 2011-2012. ADHD Atten Def Hyp Disord (2017) 9(Suppl 1):S1–S55. DOI 10.1007/s12402-017-0224-y	Without or inadequate data on medication for ADHD
Speranza, N.; Goyeneche, N.; Ferreiro, D. et al. Uso de metilfenidato en niños y adolescentes usuarios de servicios de asistencia pública de Montevideo. Archivos de Pediatría del Uruguay 2008-12 2008;79(4):277-283	No proper ADHD diagnosis
Stegmann, B.; Rexroth, C. A.; Wenzel-Seifert, K.; Haen, E. Hyperkinetic disorders in childhood and adolescence- an analysis of KinderAGATE 2009-2012. Z Kinder Jugendpsychiatr Psychother. 2015 Mar;43(2):101-14. PMID: 25951625	Clinical sample
Stegmann, Benedikt; Rexroth, Christian A.; Wenzel-Seifert, Katharina; Haen, Ekkehard. Hyperkinetic disorders in childhood and adolescence- an analysis of KinderAGATE 2009-2012.Z Kinder Jugendpsychiatr Psychother, 2015; 43(2): 101-114. PMID: 25951625	Clinical sample
Steyn, F. Methylphenidate use and poly-substance use among undergraduate students attending a South African university. S Afr J Psychiatr. 2016 Mar 22;22(1):760. doi: 10.4102/sajpsychiatry.v22i1.760.	No proper ADHD diagnosis
Stuhec, M. The use of medication against attention deficit/hyperactivity disorder in Slovenia: A drug consumption study. Eur Neuropsychopharmacol. 2014, oct; 24(2):S717-S718. DOI: 10.1016/S0924-977X(14)71156-3	No proper ADHD diagnosis
Stuhec, M. The use of medication against attention deficit/hyperactivity disorder in Slovenia: A drug consumption study. European Neuropsychopharmacology October 2014;24():S717-S718. DOI: 10.1016/S0924-977X(14)71156-3	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I. Age-related pharmacotherapy of attention deficit hyperactivity disorder in adults in Slovenia from 2003 to 2015: A population-based study	Clinical sample

Eur Neuropsychopharmacol, 2017; 27: S748-S749. DOI: 10.1016/j.eurpsy.2017.01.002.	
Stuhec, M.; Locatelli, I. Age-related pharmacotherapy of attention deficit hyperactivity disorder in adults in Slovenia from 2003 to 2015: A population-based study. Eur Neuropsychopharmacol.2017, oct; 27:S748-S749. DOI: 10.1016/S0924-977X(17)31371-8	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I. Age-related pharmacotherapy of attention deficit hyperactivity disorder in Slovenia in children and adolescents: A population-based study. Eur Psychiatry, 2017; 42: 129-133. DOI:10.1016/j.eurpsy.2017.01.002	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I. Age-related pharmacotherapy of attention deficit hyperactivity disorder in Slovenia in children and adolescents: A population-based study. Eur Psychiatry. 2017 May;42:129-133. doi: 10.1016/j.eurpsy.2017.01.002.	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I. Attention deficit hyperactivity disorder pharmacotherapy in Slovenian adults: a population-based study. Int J Clin Phar.2018, feb; 40(2):341-344. DOI: 10.1007/s11096-018-0605-0	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I.; Svab, V. Trends in attention-deficit/hyperactivity disorder drug consumption in children and adolescents in Slovenia from 2001 to 2012: a drug use study from a national perspective. J Child Adolesc Psychopharmacol, 2015; 25(3): 254-259. DOI: 10.1089/cap.2014.0071.	No proper ADHD diagnosis
Stuhec, M.; Locatelli, I.; Svab, V. Trends in attention-deficit/hyperactivity disorder drug consumption in children and adolescents in Slovenia from 2001 to 2012: a drug use study from a national perspective. J Child Adolesc Psychopharmacol. 2015 Apr;25(3):254-9. doi: 10.1089/cap.2014.0071.	No proper ADHD diagnosis
Sundquist J.; Ohlsson H.; Sundquist K.; Kendler KS. Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. BMC Psychiatry. 2017 Jun 30;17(1):235. doi: 10.1186/s12888-017-1381-4.	Prevalence based on prescriptions
Tai, Y. M.; Gau, S. S. F.; Gau, C. S. Injury-proneness of youth with attention-deficit hyperactivity disorder: A national clinical data analysis in Taiwan. Res Dev Disabil. 2013 Mar;34(3):1100-8. doi: 10.1016/j.ridd.2012.11.027.	Clinical sample
Takahashi, K.; Miyatake, N.; Kurato, R.; Takahashi, N. Prevalence of attention deficit hyperactivity disorder and/or autism spectrum disorder and its relation to lifestyle in female college students. Environ Health Prev Med. 2016 Nov;21(6):455-459. DOI: 10.1007/s12199-016-0548-9	Without or inadequate data on medication for ADHD
Termorshuizen, F.; Selten, J. P.; Heerdink, E. R. Dispensing of psychotropic medication among 400,000 immigrants in The Netherlands. Soc Psychiatry Psychiatr Epidemiol. 2017; 52(8): 963–977. doi: 10.1007/s00127-017-1405-x	No proper ADHD diagnosis

Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy. 2006;26(10):1501-1510. doi:10.1592/phco.26.10.1501	No proper ADHD diagnosis
Truter, I. Methylphenidate: prescribing patterns in a South African primary care patient population. J Clin Pharm Ther. 2005 Feb;30(1):59-63. DOI: 10.1111/j.1365-2710.2004.00608.x.	No proper ADHD diagnosis
Truter, I. Prescribing patterns of methylphenidate and atomoxetine for patients with attention-deficit/hyperactivity disorder. Trop J Pharm Res. 2014,set; 13(7):1157. DOI: 10.4314/tjpr.v13i7.21	No proper ADHD diagnosis
Tuithof, M.; Ten Have, M.; van Dorsselaer, S.; de Graaf, R. Prevalence, persistency and consequences of ADHD in the Dutch adult population. Tijdschr Psychiatr. 2014;56(1):10-9. PMID: 24446222	Without or inadequate data on medication for ADHD
Tuttle, J. P.; Scheurich, N. E.; Ranseen, J. Prevalence of ADHD diagnosis and nonmedical prescription stimulant use in medical students. Acad Psychiatry. 2010 May-Jun;34(3):220-3. doi: 10.1176/appi.ap.34.3.220.	Without or inadequate data on medication for ADHD
Upadhyay, N.; Medhekar, R. A.; Fujimoto, K. et al. Physician peer-influence on prescribing psychotropic polypharmacy in the treatment of children and adolescents with mental disorders. J Am Acad Child Adolesc Psychiatry. 2017, oct; 56(10). DOI: 10.1016/j.jaac.2017.09.050	Without or inadequate data on medication for ADHD
Upadhyay N, Chen H, Mgbere O, Bhatara VS, Aparasu RR. The Impact of Pharmacotherapy on Substance Use in Adolescents With Attention-Deficit/Hyperactivity Disorder: Variations Across Subtypes. Subst Use Misuse. 2017;52(10):1266-1274. doi:10.1080/10826084.2016.1273955	Same sample of an included study
Valentine, J.; Zubrick, S.; Sly, P. National trends in the use of stimulant medication for attention deficit hyperactivity disorder. J Paediatr Child Health. 1996 Jun;32(3):223-7. PMID: 8827539	No proper ADHD diagnosis
van den Ban, E. F.; Souverein, P. C.; van Engeland, H.; Swaab, H.; Egberts, T. C. G.; Heerdink, E. R. Differences in ADHD medication usage patterns in children and adolescents from different cultural backgrounds in the Netherlands. Soc Psychiatry Psychiatr Epidemiol. 2015 Jul;50(7):1153-62. doi: 10.1007/s00127-015-1068-4.	Clinical sample
van der Maas, M.; Kolla, N. J.; Erickson, P. G.; Wickens, C. M.; Mann, R. E.; Vingilis, E. Examining the effect of social bonds on the relationship between ADHD and past arrest in a representative sample of adults. Crim Behav Ment Health. 2018 Apr;28(2):120-131. doi: 10.1002/cbm.2045.	Without or inadequate data on medication for ADHD
van der Schans, J.; Çiçek, R.; Vardar, S. et al. Methylphenidate use and school performance among primary school children: a descriptive study. BMC Psychiatry. 2017 Mar 29;17(1):116. doi: 10.1186/s12888-017-1279-1.	No proper ADHD diagnosis

Van Zyl, P. M.; Joubert, G.; Fechter, L. et al. Methylphenidate use among students living in junior on-campus residences of the University of the Free State. S Afr Fam Pract. 2017, mar; 59(3):1-5. DOI: 10.1080/20786190.2017.1292695	No proper ADHD diagnosis
Verdi, G.; Weyandt, L. L.; Zavras, B. M. Non-Medical Prescription Stimulant Use in Graduate Students: Relationship With Academic Self-Efficacy and Psychological Variables. J Atten Disord. 2016 Sep;20(9):741-53. doi: 10.1177/1087054714529816.	No proper ADHD diagnosis
Vingilis, E.; Erickson, P. G.; Toplak, M. E. et al. Attention Deficit Hyperactivity Disorder Symptoms, Comorbidities, Substance Use, and Social Outcomes among Men and Women in a Canadian Sample. Biomed Res Int. 2015;2015:982072. doi: 10.1155/2015/982072.	Without or inadequate data on medication for ADHD
Vingilis, E.; Mann, R. E.; Erickson, P. et al. Attention deficit hyperactivity disorder, other mental health problems, substance use, and driving: examination of a population-based, representative canadian sample. Traffic Inj Prev. 2014;15 Suppl 1:S1-9. doi: 10.1080/15389588.2014.926341.	Without or inadequate data on medication for ADHD
Vinker, S.; Vinker, R.; Elhayany, A. Prevalence of methylphenidate use among israeli children 1998-2004. Clin Drug Investig. 2006;26(3):161-7. DOI: 10.2165/00044011-200626030-00006	No proper ADHD diagnosis
Virk, J.; Liew, Z.; Olsen, J.; Nohr, E. A.; Catov, J. M.; Ritz, B. Pre-conceptual and prenatal supplementary folic acid and multivitamin intake, behavioral problems, and hyperkinetic disorders: A study based on the Danish National Birth Cohort (DNBC). Nutr Neurosci. 2018 Jun;21(5):352-360. doi: 10.1080/1028415X.2017.1290932.	Prevalence based on prescriptions
Visser, S. N.; Bitsko, R. H.; Danielson, M. L. et al. Treatment of attention deficit/hyperactivity disorder among children with special health care needs. J Pediatr. 2015 Jun;166(6):1423-30.e1-2. doi: 10.1016/j.jpeds.2015.02.018.	Clinical sample
Visser, S. N.; Blumberg, S. J.; Danielson, M. L..; Bitsko, R. H.; Kogan, M. D. State-based and demographic variation in parent-reported medication rates for attention-deficit/hyperactivity disorder, 2007-2008. Prev Chronic Dis. 2013;10:E09. doi: 10.5888/pcd9.120073.	Clinical sample
Visser, S. N.; Danielson, M. L.; Bitsko, R. H. et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry. 2014 Jan;53(1):34-46.e2. doi: 10.1016/j.jaac.2013.09.001.	Clinical sample
Visser, S. N.; Danielson, M. L.; Wolraich, M.L. et al. Vital Signs: National and State-Specific Patterns of Attention Deficit/Hyperactivity Disorder Treatment Among Insured Children Aged 2-5 Years - United States, 2008-2014. MMWR. 2016, may; 65(17). DOI: 10.15585/mmwr.mm6517e1	Clinical sample
Visser, S. N.; Kramer, D.; Snyder, A. B.; Sebian, J.; McGiboney, G.; Handler, A. Student-Perceived School Climate Is Associated With ADHD Medication Treatment Among Adolescents in Medicaid. J Atten Disord. 2019 Feb;23(3):234-245. doi: 10.1177/1087054715569601.	Prevalence based on prescriptions

Visser, S. N.; Zablotsky, B.; Holbrook, J. R.; Danielson, M. L.; Bitsko, R. H. Diagnostic Experiences of Children With Attention-Deficit/Hyperactivity Disorder. Natl Health Stat Report. 2015 Sep 3;(81):1-7. PMID: 26375578	Without or inadequate data on medication for ADHD
Vogel, S. W. N.; Bijlenga, D.; Benjamins, J. S.; Beekman, A. T. F.; Kooij, J. J. S.; Van Someren, E. J. W. Attention deficit hyperactivity disorder symptom severity and sleep problems in adult participants of the Netherlands sleep registry. Sleep Med. 2017 Dec;40:94-102. doi: 10.1016/j.sleep.2017.09.027.	Clinical sample
Vuori, M. A.; Martikainen, J. E.; Koski-Pirilä, A.; Saastamoinen, L. K. Recent Trends in Stimulant Medication Use Among Children in Finland. J Am Acad Child Adolesc Psychiatry. 2018;57(10):S173	Prevalence based on prescriptions
Walker, S.; Venter, A.; van der Walt, A.; Esterhuyse, K. G. F. Prevalence of attention-deficit/hyperactivity disorder (ADHD) symptomatology and psychiatric co-morbidity among adolescents diagnosed with ADHD in childhood. S Afr J Psychiatr. 2011, mar; 17(1). DOI:10.4102/sajpsychiatry.v17i1.261	Clinical sample
Wallach-Kildemoes, H.; Skovgaard, A. M.; Thielen, K.; Pottegård, A.; Mortensen, L. H. Social adversity and regional differences in prescribing of ADHD medication for school-age children. J Dev Behav Pediatr. 2015 Jun;36(5):330-41. doi: 10.1097/DBP.0000000000000170.	No proper ADHD diagnosis
Wang, L. J.; Lee, S. Y.; Yuan, S. S. et al. Prevalence rates of youths diagnosed with and medicated for ADHD in a nationwide survey in Taiwan from 2000 to 2011. Epidemiol Psychiatr Sci. 2017 Dec;26(6):624-634. doi: 10.1017/S2045796016000500.	Clinical sample
Wang LJ, Yang KC, Lee SY, et al. Initiation and Persistence of Pharmacotherapy for Youths with Attention Deficit Hyperactivity Disorder in Taiwan. PLoS One. 2016;11(8):e0161061. Published 2016 Aug 12. doi:10.1371/journal.pone.0161061	Clinical sample
Wang, L. J.; Shyu, Y. C.; Yuan, S. S. et al. Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing bipolar disorder: A nationwide population-based study in Taiwan. J Psychiatr Res. 2016 Jan;72:6-14. doi: 10.1016/j.jpsychires.2015.10.014.	Clinical sample
Warfield, M. E.; Adams, R. S.; Ritter, G. A.; Valentine, A.; Williams, T. V.; Larson, M. J. Health care utilization among children with chronic conditions in military families. Disabil Health J. 2018 Oct;11(4):624-631. doi: 10.1016/j.dhjo.2018.06.002.	Without or inadequate data on medication for ADHD
Warren, M.E.; Lapane, K. L. Overweight in children and adolescents in relation to attention-deficit/hyperactivity disorder: results from a national sample. Pediatrics. 2008 Jul;122(1):e1-6. doi: 10.1542/peds.2007-1955.	Clinical sample
Webb, J. R.; Valasek, M. A.; North, C. S. Prevalence of stimulant use in a sample of US medical students. Ann Clin Psychiatry. 2013 Feb;25(1):27-32. PMID: 23376867	No proper ADHD diagnosis
Weissenberger, S.; Ptacek, R.; Vnukova, M. et al. ADHD and lifestyle habits in Czech adults, a national sample. Neuropsychiatr Dis Treat. 2018; 14: 293–299. Published online 2018 Jan 15. doi: 10.2147/NDT.S148921	Without or inadequate data on

	medication for ADHD
Weller, L.; Fredrickson, D. D.; Burbach, C.; Molgaard, C. A.; Ngong, L. Chronic disease medication administration rates in a public school system. J Sch Health. 2004 May;74(5):161-5. PMID: 15283496	No proper ADHD diagnosis
Wendy A . W.; Marybeth J . M. Psychotropic Medication Use Among Children in the child welfare system. ssue Brief No. 59. Durham, NH Carsey Institute, University of New Hampshire. 2012	Prevalence based on prescriptions
Westover, A. N.; Nakonezny, P. A.; Halm, E. A.; Adinoff, B. Risk of amphetamine use disorder and mortality among incident users of prescribed stimulant medications in the Veterans Administration. Addiction. 2018 May;113(5):857-867. doi: 10.1111/add.14122.	No proper ADHD diagnosis
Weyandt, L. L.; Oster, D. R.; Gudmundsdottir, B. G.; DuPaul, G. J.; Anastopoulos, A. D. Neuropsychological functioning in college students with and without ADHD. Neuropsychology. 2017 Feb;31(2):160-172. doi: 10.1037/neu0000326.	Clinical sample
Whitely, M. The rise and fall of ADHD child prescribing in Western Australia: lessons and implications. Aust N Z J Psychiatry. 2012;46(5):400-403	Review or metanalysis
Whitely, M.; Lester, L.; Phillimore, J.; Robinson, S. Influence of birth month on the probability of Western Australian children being treated for ADHD. Med J Aust 2017; 206 (2): 85. || doi: 10.5694/mja16.00398	No proper ADHD diagnosis
Wilens, T.; Zulauf, C.; Martelon, M. et al. Nonmedical Stimulant Use in College Students: Association With Attention-Deficit/Hyperactivity Disorder and Other Disorders. J Clin Psychiatry. 2016 Jul;77(7):940-7. doi: 10.4088/JCP.14m09559.	No proper ADHD diagnosis
Winterstein, A. G.; Gerhard, T.; Shuster, J. et al. Utilization of pharmacologic treatment in youths with attention deficit/hyperactivity disorder in Medicaid database. Ann Pharmacother. 2008 Jan;42(1):24-31. DOI: 10.1345/aph.1K143	Clinical sample
Winterstein, A. G.; Soria-Saucedo, R.; Gerhard, T.; Correll, C. U.; Olfson, M. Differential Risk of Increasing Psychotropic Polypharmacy Use in Children Diagnosed With ADHD as Preschoolers. J Clin Psychiatry. 2017 Jul;78(7):e744-e781. doi: 10.4088/JCP.16m10884.	Clinical sample
Wolraich, M. L.; Lindgren, S.; Stromquist, A.; Milich, R.; Davis, C.; Watson, D. Stimulant medication use by primary care physicians in the treatment of attention deficit hyperactivity disorder. Pediatrics. 1990 Jul;86(1):95-101. PMID: 2359688	Clinical Sample
Wolraich, M. L.; McKeown, R. E.; Visser, S. N. et al. The prevalence of ADHD: its diagnosis and treatment in four school districts across two states. J Atten Disord. 2014 Oct;18(7):563-75. doi: 10.1177/1087054712453169.	Without or inadequate data on medication for ADHD
Wurdemann, E. ADHS (Aufmerksamkeitsdefizit- Hyperaktivitätsstörung) bei jungen Erwachsenen. Dissertation. Universität Bremen, 2010	Prevalence based on prescriptions

Xu, j.; Druss, B. G.; Lally, C.; Cummings, J. R.; Ji, X. Racial-Ethnic Differences in Patterns of Discontinuous Medication Treatment Among Medicaid-Insured Youths With ADHD. Psychiatr Serv. 2018 Mar 1;69(3):322-331. doi: 10.1176/appi.ps.201600469.	Clinical sample
Yallop, L. P. Attention-deficit/hyperactivity disorder in Manitoba young adults: a population-based study. Thesis. University of Manitoba. 2013.	Clinical sample
Yallop, L. P. Rates of diagnosis and treatment of Attention Deficit/Hyperactivity Disorder in Manitoba children: considering the socioeconomic gradient. Thesis. University of Manitoba. 2008, jan.	Clinical sample
Yallop, L.; Brownell, M.; Chateau, D. et al. Lifetime Prevalence of Attention-Deficit Hyperactivity Disorder in Young Adults: Examining Variations in the Socioeconomic Gradient. Can J Psychiatry. 2015 Oct;60(10):432-40. DOI: 10.1177/070674371506001004	Clinical sample
Zetterqvist, J.; Asherson, P.; Halldner, L.; Långström, N.; Larsson, H. Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009. Acta Psychiatr Scand. 2013 Jul;128(1):70-7. doi: 10.1111/acps.12004.	No proper ADHD diagnosis
Zhou, Z.; Betts, K. A.; Bocharova, I.; Kinrich, D.; Spalding, W. M. Concomitant Use of Psychotropic Medication With Stimulants for the Treatment of ADHD in Children and Adolescents: A Retrospective Insurance Claims Study in the United States. J Atten Disord. 2018 Jul 1:1087054718784668. doi:10.1177/1087054718784668	Clinical sample
Zhu, Y.; Liu, W.; Li, Y.; Wang, X.; Winterstein, A. G. Prevalence of ADHD in Publicly Insured Adult. J Atten Disord. 2018 Jan;22(2):182-190. doi: 10.1177/1087054717698815	Prevalence based on medical visits
Zima, B. T.; Bussing, R.; Crecelius, G. M.; Kaufman, A.; Belin, T. R. Psychotropic medication treatment patterns among school-aged children in foster care. J Child Adolesc Psychopharmacol. 1999;9(3):135-47. DOI: 10.1089/cap.1999.9.135	Clinical sample
Zito, J. M.; Safer, D. J.; DosReis, S.; Gardner, J. F.; Boles, M.; Lynch, F. Trends in the prescribing of psychotropic medications to preschoolers. JAMA. 2000 Feb 23;283(8):1025-30. DOI: 10.1001/jama.283.8.1025	No proper ADHD diagnosis
Zito, J. M.; Safer, D. J.; DosReis, S.; Magder, L. S.; Gardner, J. F.; Zarin, D. A. Psychotherapeutic medication patterns for youths with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 1999 Dec;153(12):1257-63. PMID: 10591302	Prevalence based on prescriptions
Zito, J. M.; Safer, D. J.; Riddle, M. A.; Johnson, R. E.; Speedie, S. M.; Fox, M. Prevalence variations in psychotropic treatment of children. J Child Adolesc Psychopharmacol. 1998;8(2):99-105. DOI: 10.1089/cap.1998.8.99	No proper ADHD diagnosis
Zito, J. M.; Safer, D. J.; Sai, D. et al. Psychotropic medication patterns among youth in foster care. Pediatrics. 2008 Jan;121(1):e157-63. doi: 10.1542/peds.2007-0212.	Prevalence based on medical visits

Zoëga, H.; Baldursson, G.; Halldórsson, M. Use of methylphenidate among children in Iceland 1989-2006. Laeknabladid. 2007 Dec;93(12):825-32. PMID: 18057472	No proper ADHD diagnosis
Zoëga, H.; Furu, K.; Halldórsson, M.; Thomsen, P. H.; Sourander, A.; Martikainen, J. E. Use of ADHD drugs in the Nordic countries: a population-based comparison study. Acta Psychiatr Scand. 2011 May;123(5):360-7. doi: 10.1111/j.1600-0447.2010.01607.x.	No proper ADHD diagnosis
Zoëga, H.; Rothman, K. J.; Huybrechts, K. F. Et al. A population-based study of stimulant drug treatment of ADHD and academic progress in children. Pediatrics. 2012 Jul;130(1):e53-62. doi: 10.1542/peds.2011-3493.	No proper ADHD diagnosis
Zoëga, H.; Valdimarsdóttir, U. A.; Hernández-Díaz, S. Age, academic performance, and stimulant prescribing for ADHD: A nationwide cohort study. Pediatrics. 2012 Dec;130(6):1012-8. doi: 10.1542/peds.2012-0689	No proper ADHD diagnosis
Zur, M.; Magnezi, R.; Portuguese, S.; Reuveni, I.; Kedem, R.; Fruchter, E. The Impact of Adherence to Treatment for ADHD on the Quality of Military Service - The Israeli Military Experience. Mil Med. 2018 Jul 11. doi: 10.1093/milmed/usy161.	No proper ADHD diagnosis
Zuvekas, S. H.; Vitiello, B. Stimulant medication use in children: a 12-year perspective. Am J Psychiatry. 2012 Feb;169(2):160-6. DOI: 10.1176/appi.ajp.2011.11030387	No proper ADHD diagnosis
Zuvekas, S. H.; Vitiello, B.; Norquist, G. S. Recent trends in stimulant medication use among U.S. children. Am J Psychiatry. 2006 Apr;163(4):579-85. DOI: 10.1176/appi.ajp.163.4.579	No proper ADHD diagnosis

Table S5: Characteristics of included adult studies

Study	Sample description	Country	Design	Diagnosis	Age	Controls		ADHD		NOS		
						Treatment Negative	Treatment Positive	Treatment Negative	Treatment Positive	selection (up to 4)	comparability (up to 2)	total
Cohen et al., 2015	Joyce and Irving Goldman Medical School, 2013	Israel	Cross Sectional	Question	26	188	19	2	20	2	1	3
Graff et al., 2008	WHO World Mental Health (WMH) Survey Initiative	worldwide	Cross Sectional	DSM	18-44	-	-	317	19	3	0	3
Gudmundsdottir et al., 2016	Undergraduates from 4 Icelandic Universities	Iceland	Cross Sectional	DSM	28	468	6	19	28	1	1	2
Fairman et al., 2020	Project DECOY, 2014-2015	USA	Cross Sectional	Question	18-25	2599	23	109	96	2	0	2
Mortier et al., 2015	University of Leuven, 2012-2014	Belgium	Cross Sectional	DSM	>18	2434	53	183	37	3	1	4

Table S6: Characteristics of included preschooler studies

Study	Sample description	Country	Design	Diagnosis	Age	Controls		ADHD		NOS		
						Treatment Negative	Treatment Positive	Treatment Negative	Treatment Positive	selection (up to 4)	comparability (up to 2)	total
Danielson et al., 2017	National Survey of Children's Health (NSCH) 2011-2012	USA	Cross Sectional	Question	2-5	-	-	11202	8695	1	0	1
Luby et al., 2007	St. Louis metropolitan area, USA	USA	Cross Sectional	DSM	3-5	228	5	40	4	4	1	5

Figure S1: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed adults and preschoolers

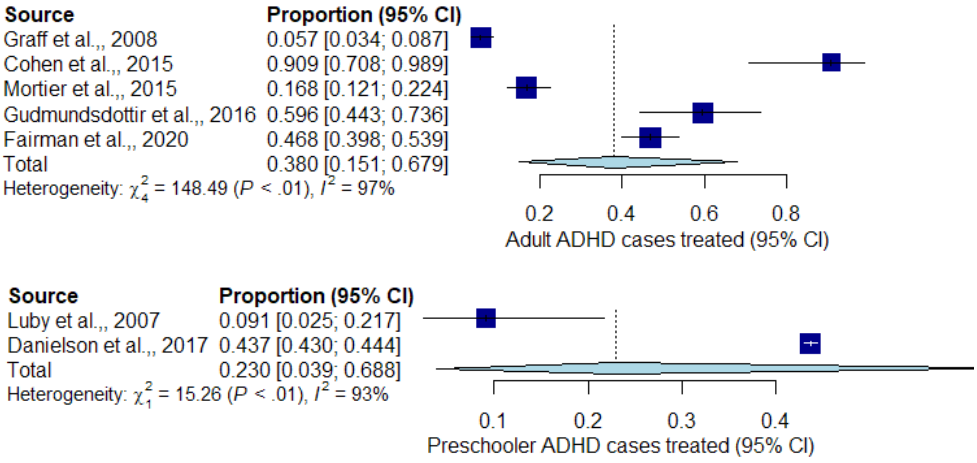


Figure S2: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed adults and preschoolers

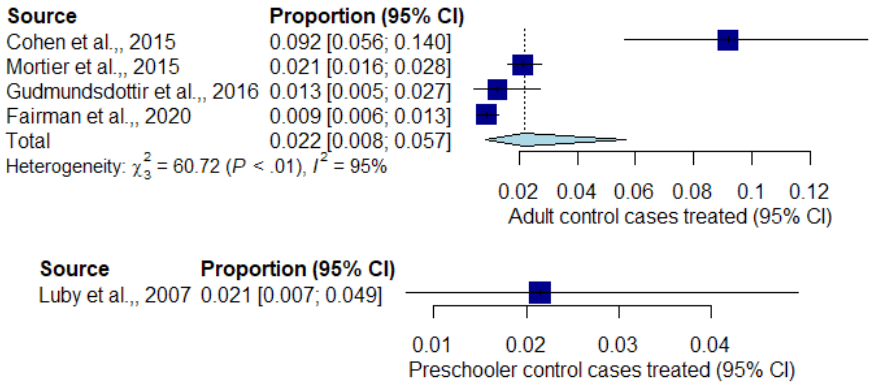


Figure S3: Funnel plot relative to the analysis in children and adolescents diagnosed with ADHD using DSM/ICD criteria

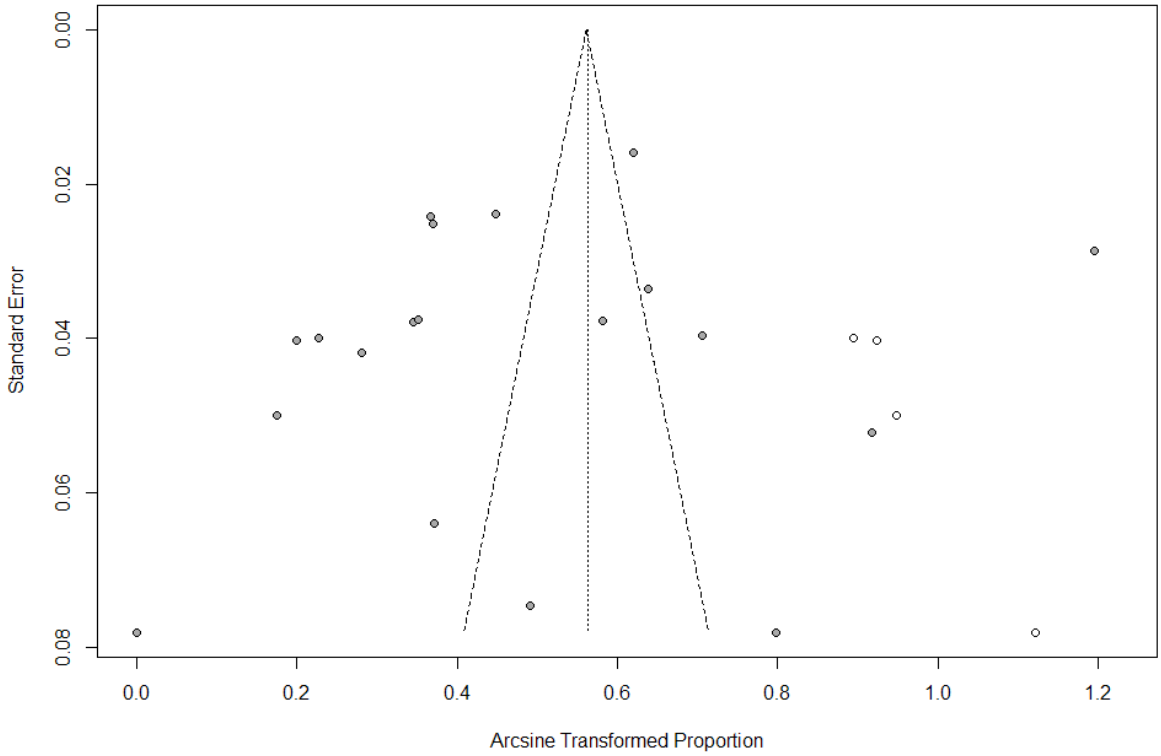


Figure S4: Funnel plot relative to the analysis in non-diagnosed children and adolescents, using DSM/ICD criteria

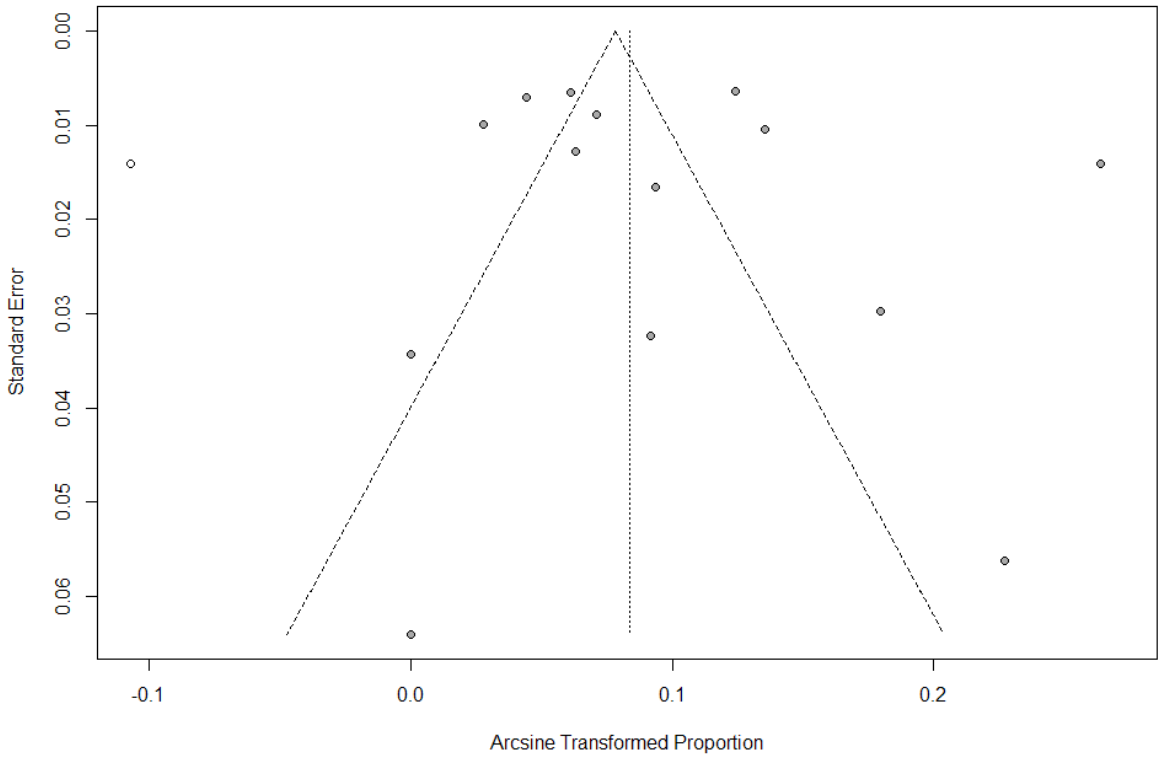


Figure S5: Jackknife sensitivity analyses results for the ADHD diagnosed children and adolescents using DSM/ICD criteria

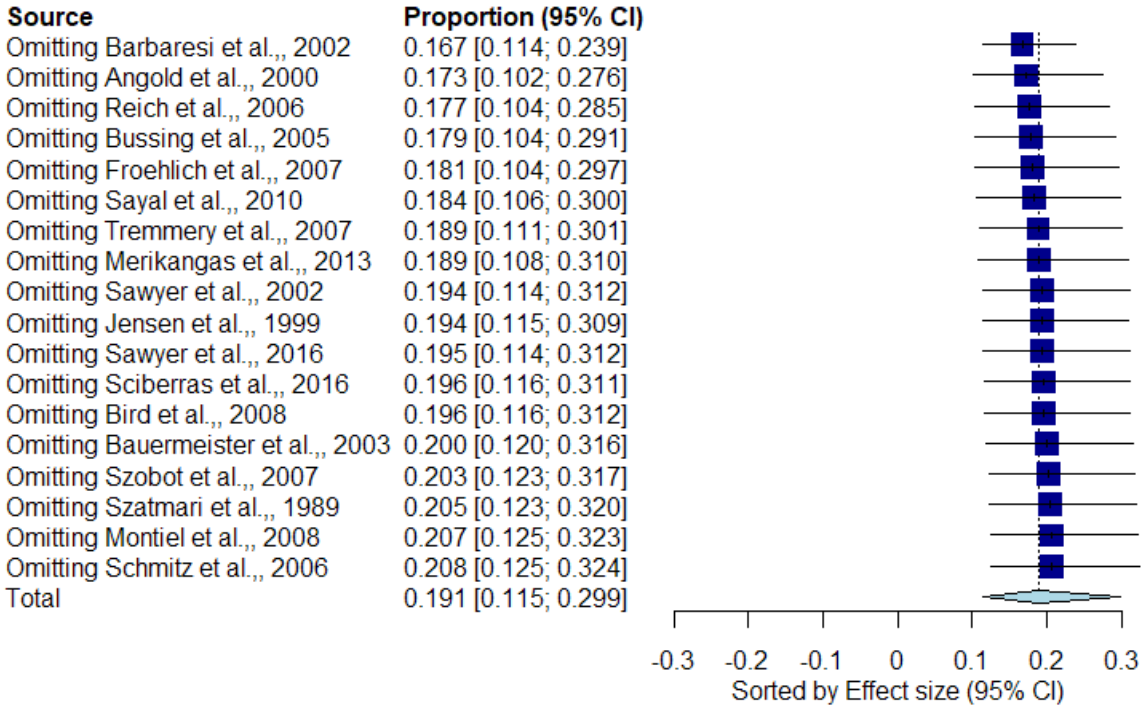


Figure S6: Jackknife sensitivity analyses results for the non-diagnosed children and adolescents using DSM/ICD criteria

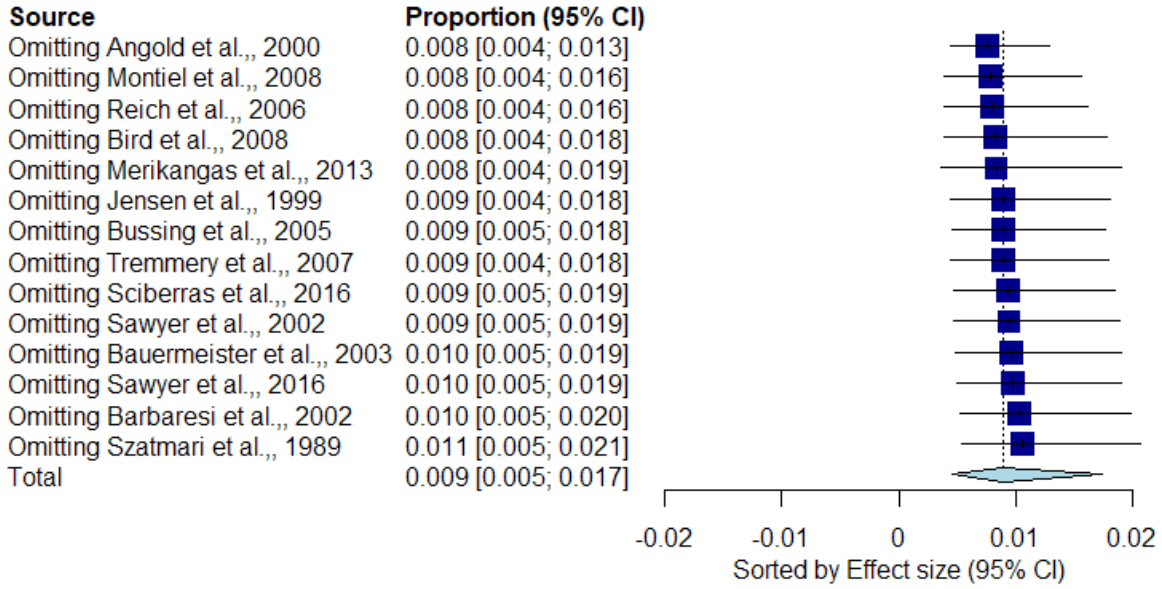


Figure S7: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed children and adolescents using DSM/ICD criteria, subgrouped by continent

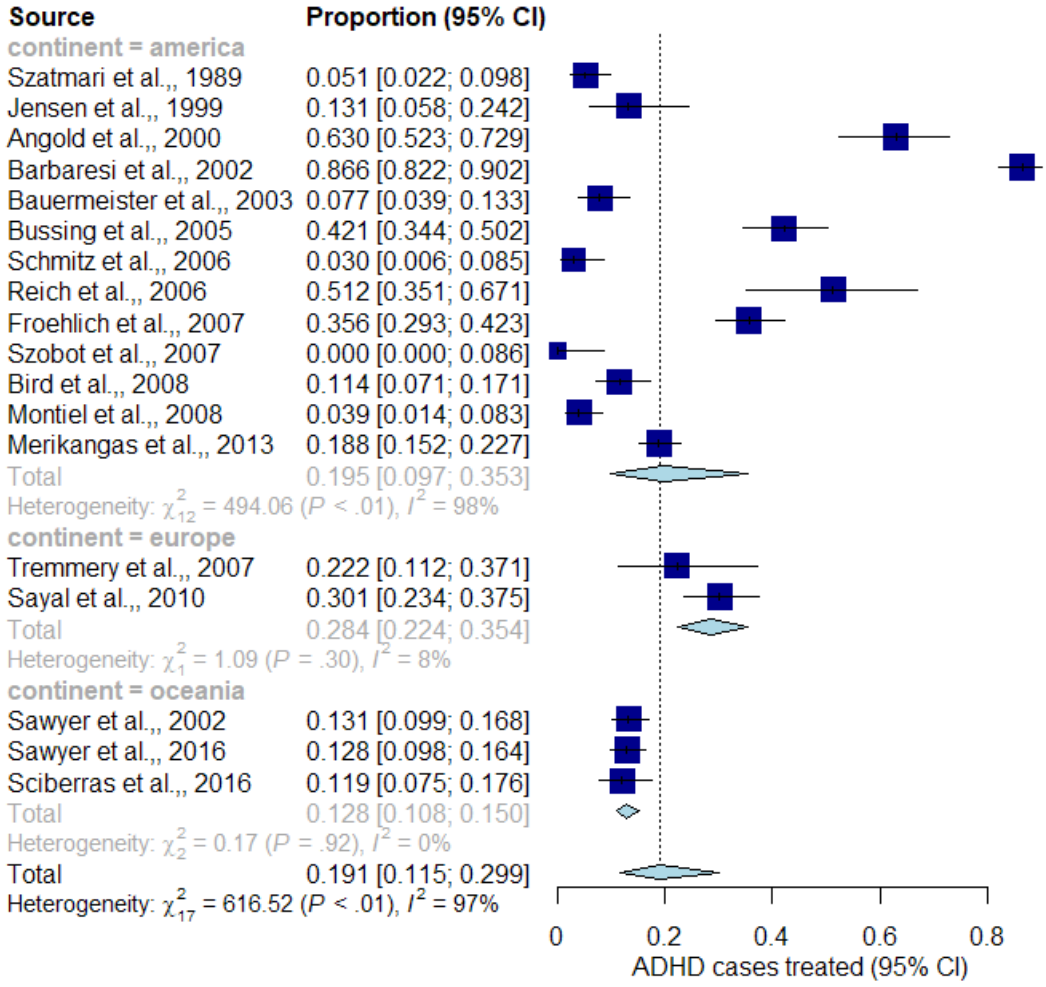
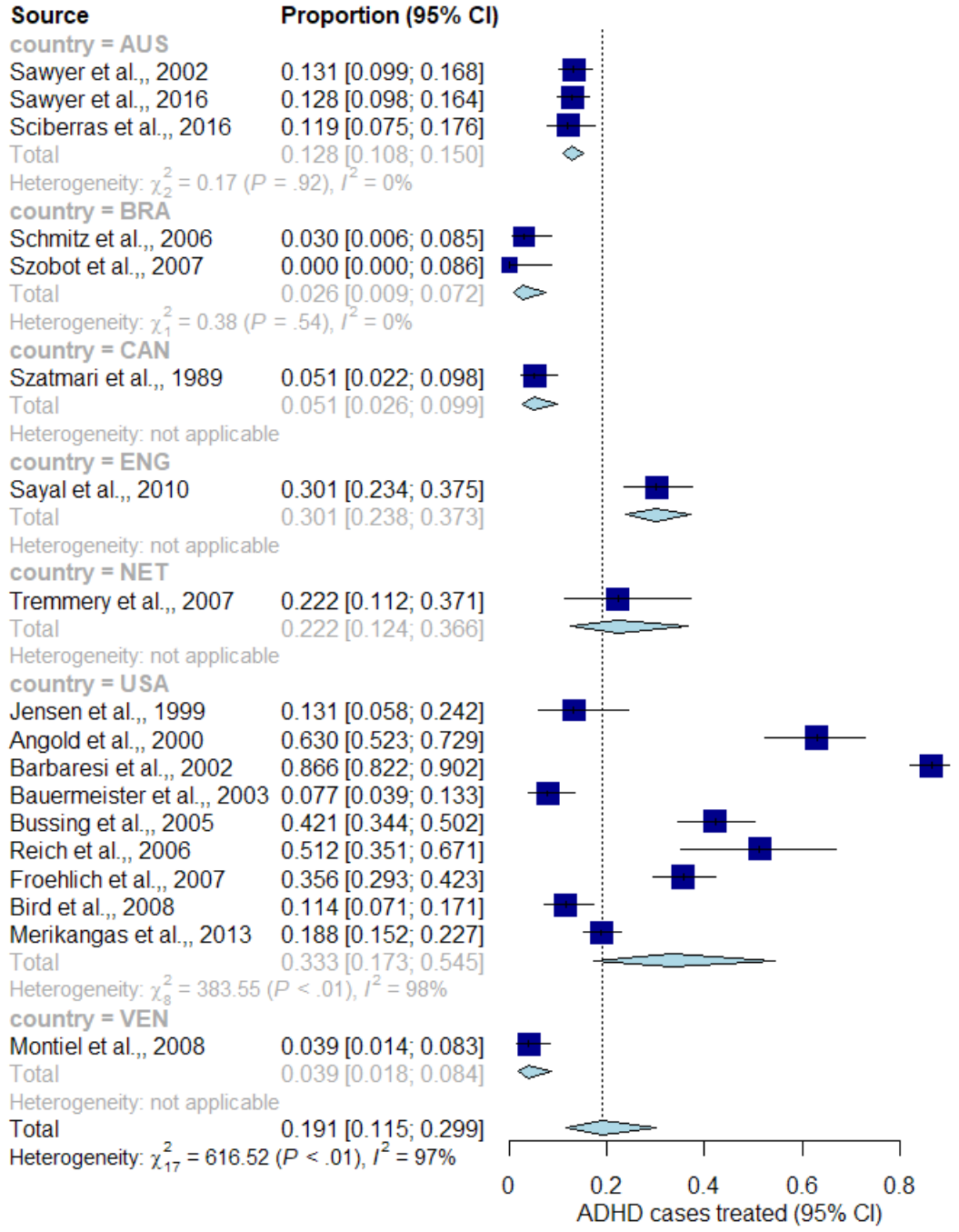
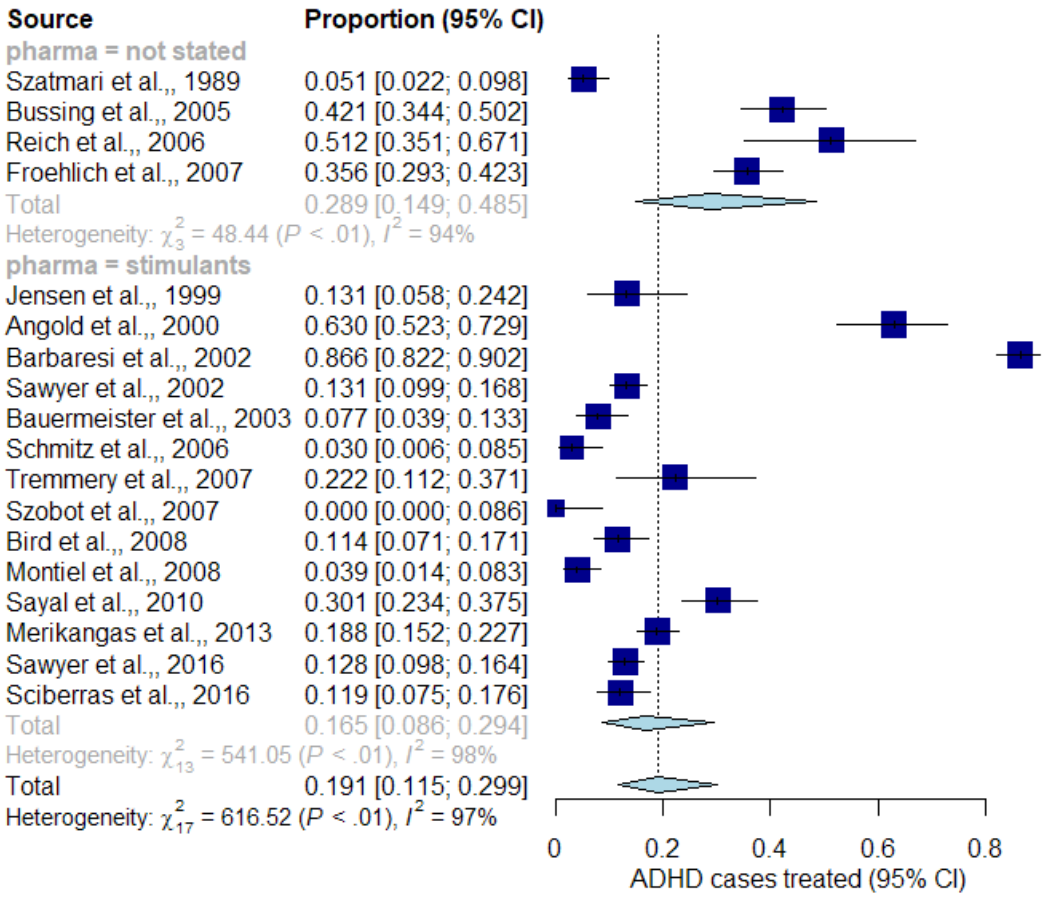


Figure S8: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed children and adolescents using DSM/ICD criteria, subgrouped by country



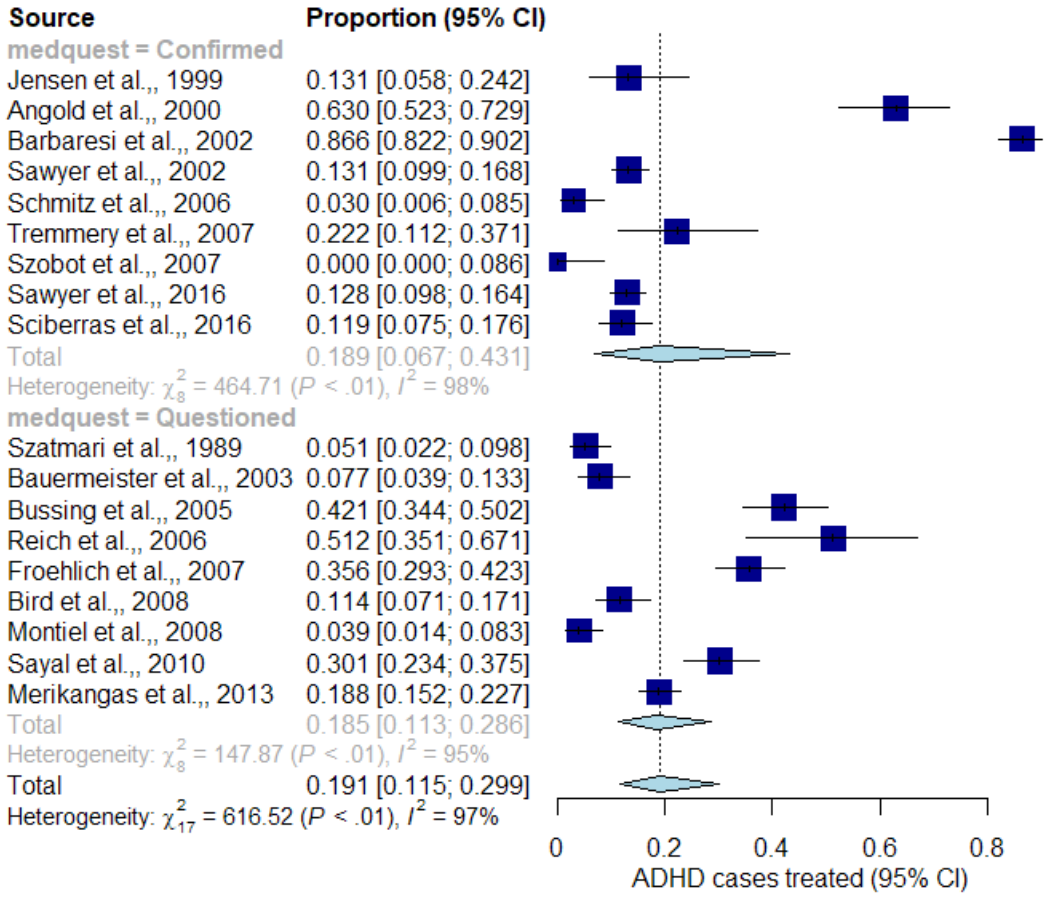
"AUS" = Australia; "BRA" = Brazil; "CAN" = Canada; "ENG" = England; "NET" = Netherlands; "USA" = United States of America; "VEN" = Venezuela.

Figure S9: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed children and adolescents using DSM/ICD criteria, subgrouped by treatment description



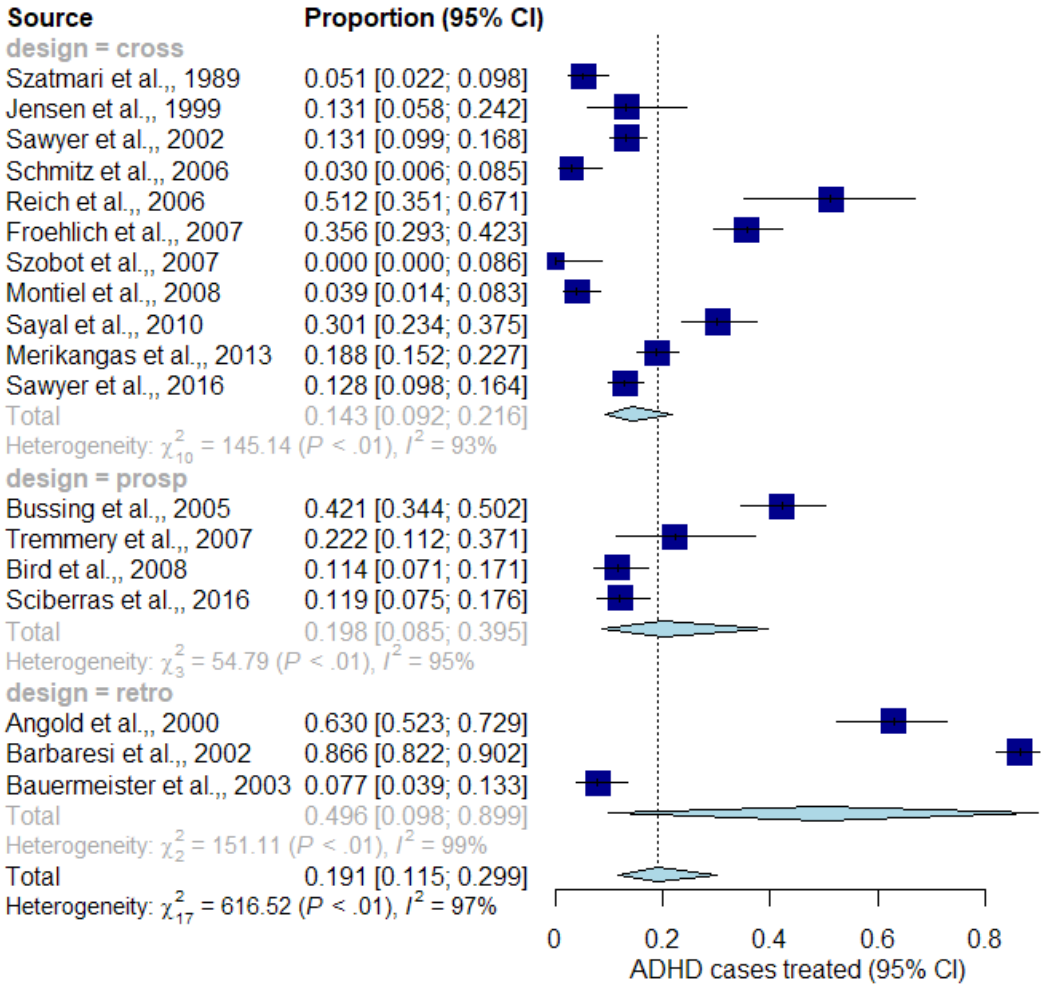
"pharma = not stated" = description of "medication for ADHD", without further details
"pharma = stimulants" = description of medications, and all included medication are stimulants and/or atomoxetine

Figure S10: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed children and adolescents using DSM/ICD criteria, subgrouped by medication assessment method



"Confirmed" = the study used a method to confirm the medication prescription/use; "Questioned" = the study questioned the patient/caregiver regarding ADHD medication use.

Figure S11: Forest plot showing the meta-analysis results of the rates of medication use among ADHD diagnosed children and adolescents using DSM/ICD criteria, subgrouped by study design



"cross" = cross-sectional; "prosp" = prospective; "retro" = retrospective.

Figure S12: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed children and adolescents using DSM/ICD criteria, subgrouped by continent

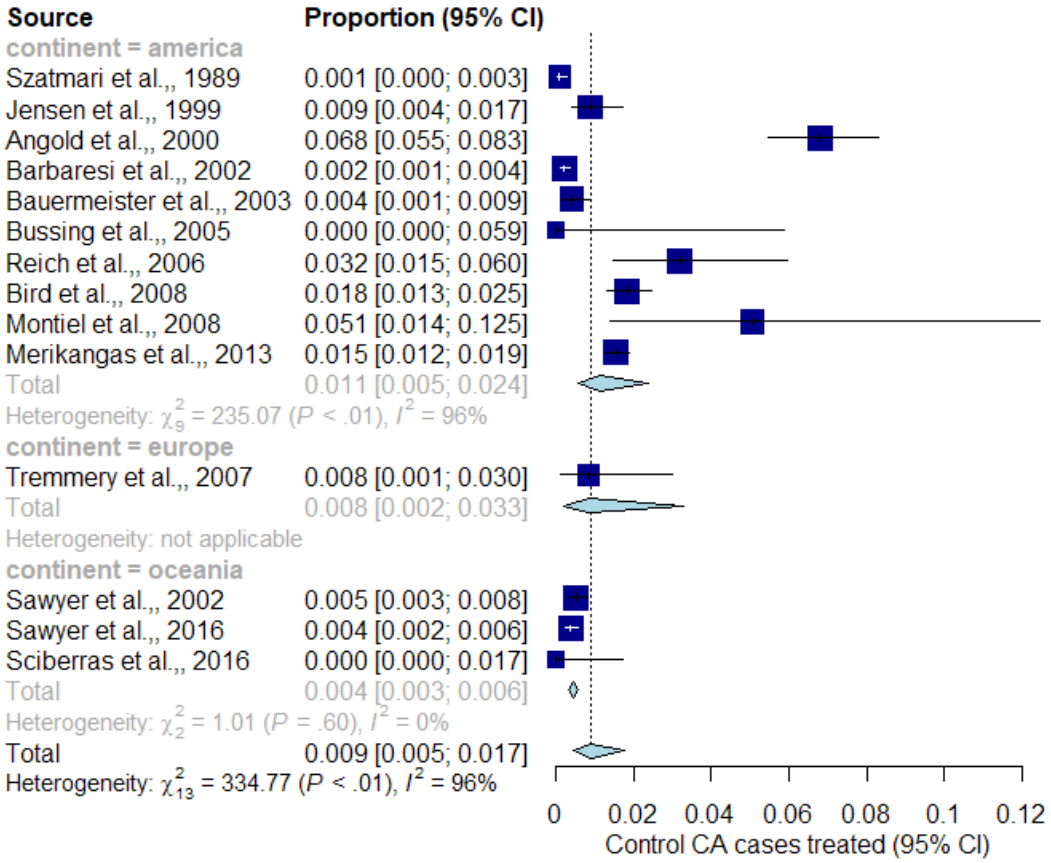
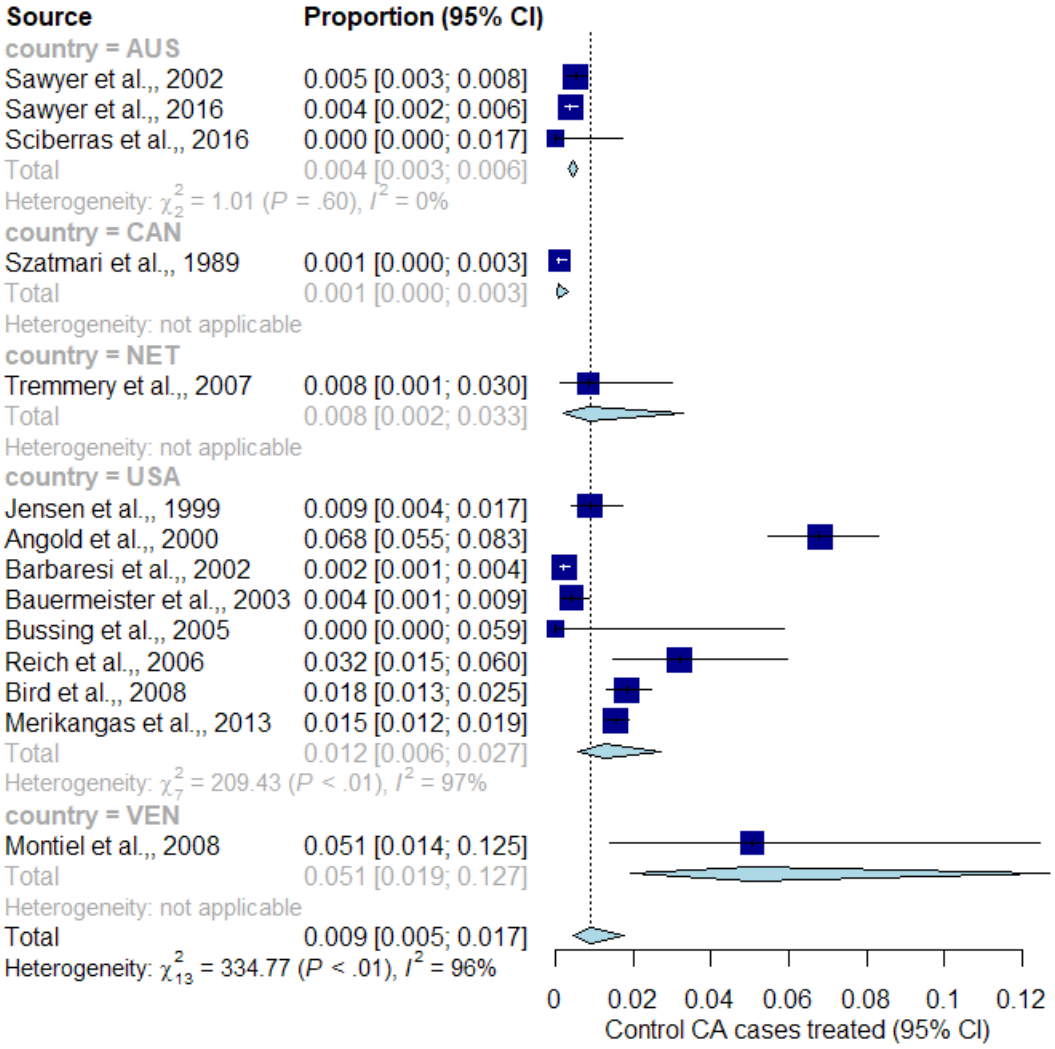
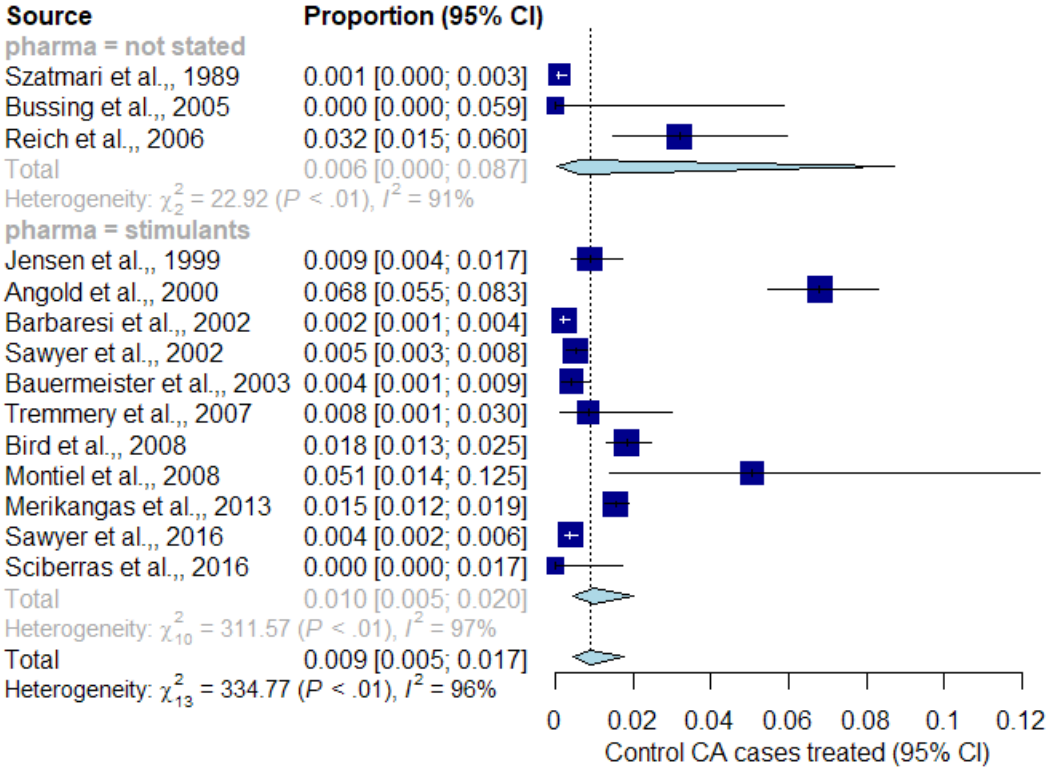


Figure S13: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed children and adolescents using DSM/ICD criteria, subgrouped by country



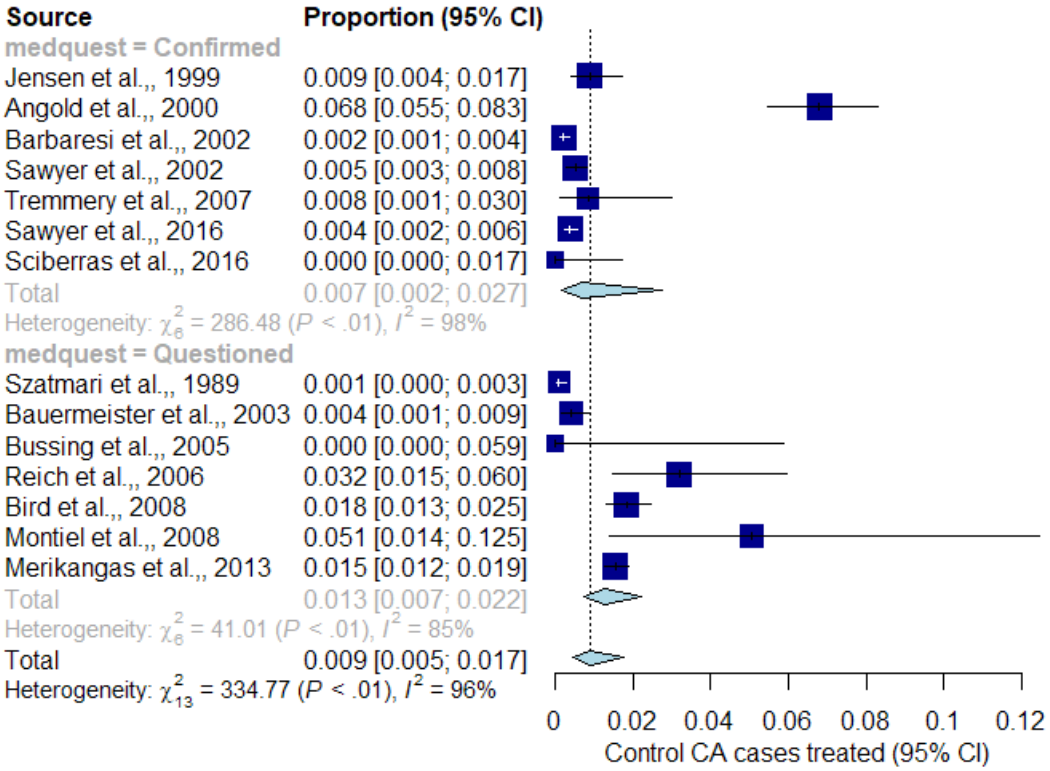
"AUS" = Australia; "CAN" = Canada; "NET" = Netherlands; "PUE" = Puerto Rico; "USA" = United States of America; "USA+PUE" = United States od America and Puerto Rico; "VEN" = Venezuela.

Figure S14: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed children and adolescents using DSM/ICD criteria, subgrouped by treatment description



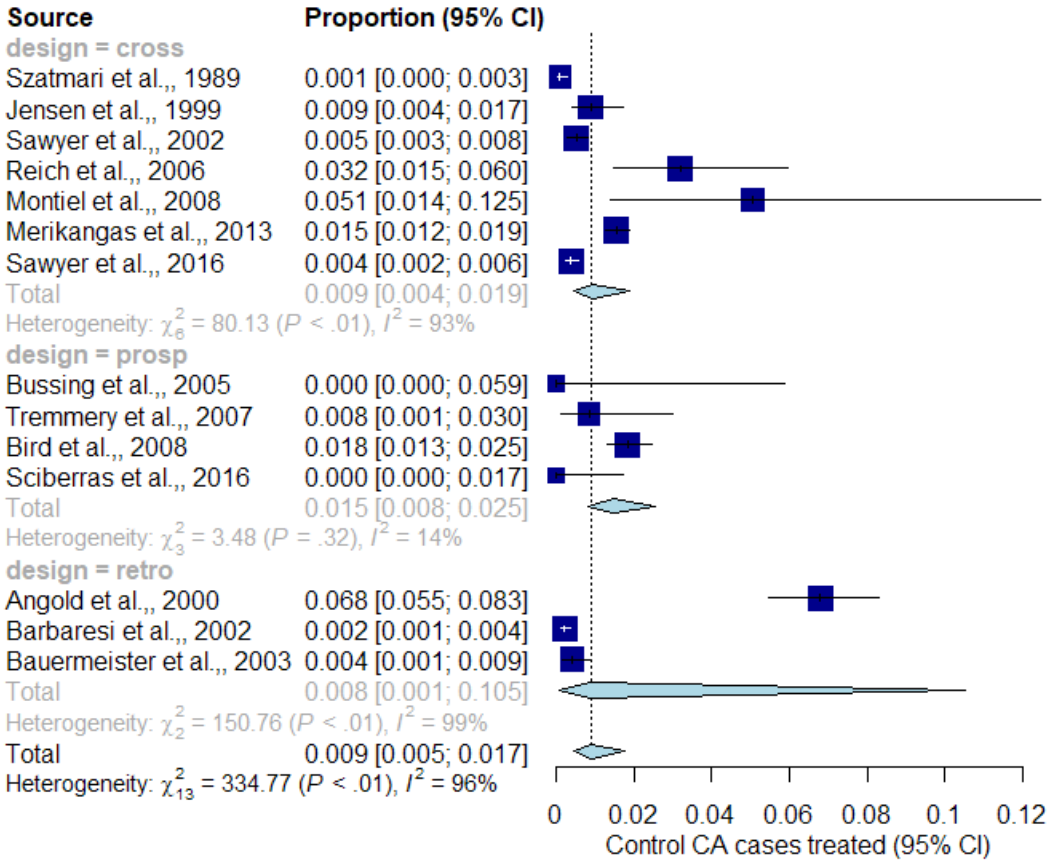
"pharma = not stated" = description of "medication for ADHD", without further details;
"pharma = stimulants" = description of medications, and all included medication are stimulants and/or atomoxetine

Figure S15: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed children and adolescents using DSM/ICD criteria, subgrouped by medication assessement method



"Confirmed" = the study used a method to confirm the medication prescription/use; "Questioned" = the study questioned the patient/caregiver regarding ADHD medication use.

Figure S16: Forest plot showing the meta-analysis results of the rates of medication use among non-diagnosed children and adolescents using DSM/ICD criteria, subgrouped by study design



"cross" = cross-sectional; "prosp" = prospective; "retro" = retrospective.

Table S7: Meta-regression in relation to ADHD diagnosed children and adolescents using DSM/ICD criteria

Metaregression in relation to ADHD diagnosed children and adolescents using DSM/ICD criteria

Study characteristics	Univariate meta-regression models						
	Estimate	*SE*	*95% CI*		*p-valor*	Moderator analysis	
						p-valor	*HAF*
Quality of the study						**0.0349**	**23.54%**
Newcastle Ottawa Scale	0.7624	0.3615	0.0539	1.4708	**0.0349**		
Year of the study						0.8141	2.36%
Year	-0.0112	0.0478	-0.1048	0.0824	0.8141		
Continent of the study							
America (reference)	-	-	-	-	-	0.7036	1.20%
Europe	0.3472	0.9605	-1.5353	2.2297	0.7177		
Oceania	-0.5498	0.8020	-2.1217	1.0222	0.4931		
Country of the study							
Australia (reference)	-	-	-	-	-	**0.0391**	**14.97%**
Brazil	-1.8504	1.2427	-4.2860	0.5852	0.1365		
Canada	-0.9869	1.3698	-3.6716	1.6979	0.4713		
England	1.0958	1.3310	-1.5130	3.7045	0.4104		
Netherlands	0.6849	1.3686	-1.9976	3.3674	0.6168		
United States of America	1.2489	0.7714	-0.2631	2.7608	0.1055		
Venezuela	-1.2678	1.3849	-3.9822	1.4466	0.3600		
Type of medication						0.3582	0.00%
Not described (reference)	-	-	-	-	-		
Stimulants	-0.6819	0.7421	-2.1364	0.7726	0.3582		
Medication assessment						0.1258	0.00%
Questioned (reference)	-	-	-	-	-		
Confirmed	0.1258	0.6365	-1.1218	1.3734	0.8433		
Study Design						**0.0230**	**33.69%**
Retrospective (reference)	-	-	-	-	-		
Cross sectional	-1.8700	0.6810	-3.2047	0.5354	**0.0060**		
Prospective	-1.4207	0.7917	-2.9724	0.1310	0.0727		

HAF = heterogeneity accounted for

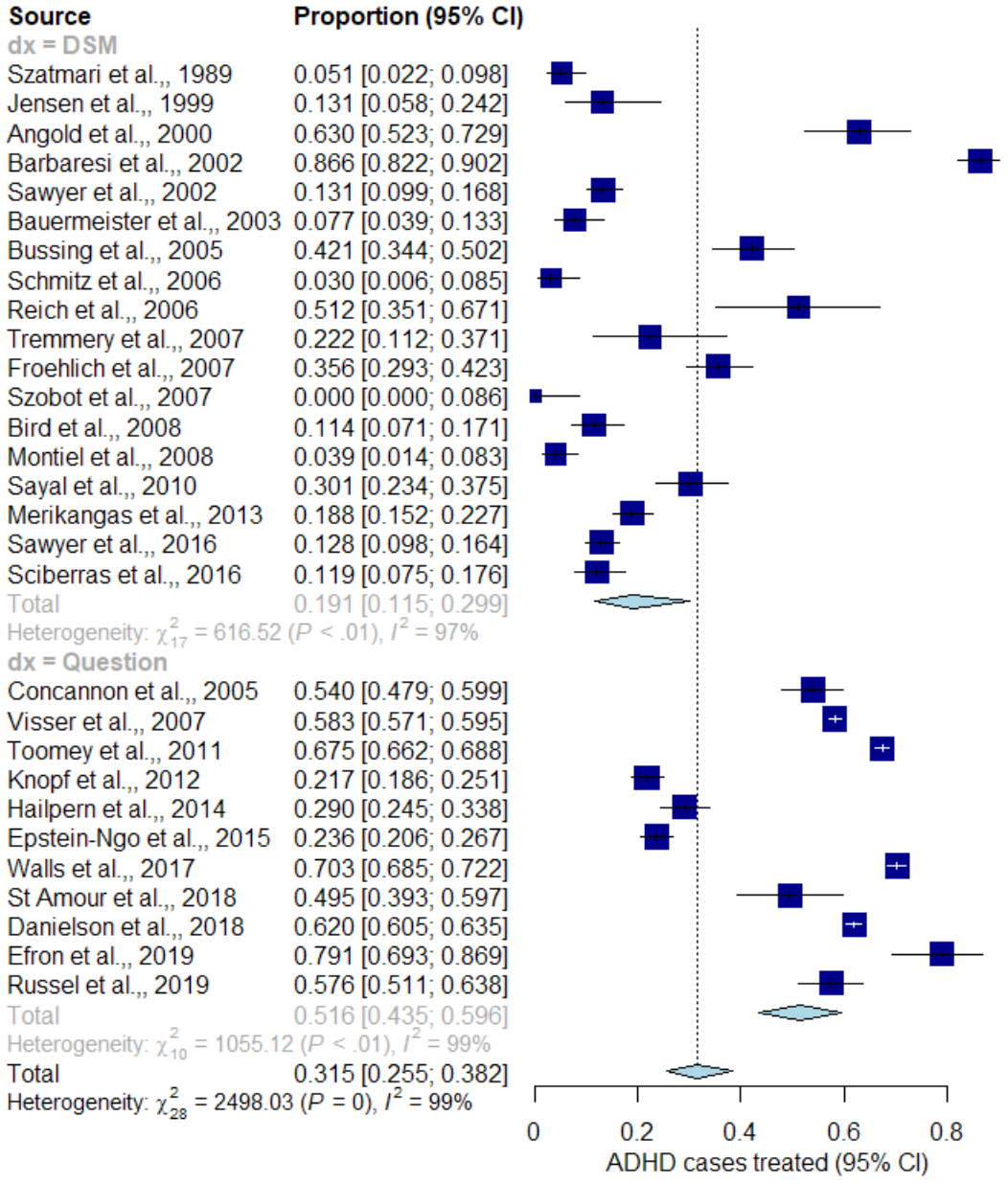
Table S8: Meta-regression in relation to non-diagnosed children and adolescents using DSM/ICD criteria

Meta-regression in relation to non-diagnosed children and adolescents using DSM/ICD criteria

Study characteristics	Univariate meta-regression models						
	Estimate	*SE*	*95% CI*		*p-valor*	Moderator analysis	
						p-valor	*HAF*
Quality of the study						0.9649	8.10%
Newcastle Ottawa Scale	0.0205	0.4650	-0.8908	0.9318	0.9649		
Year of the study						0.4227	0.00%
Year	0.0437	0.0545	-0.0632	0.1506	0.4227		
Continent of the study						0.3942	20.52%
America (reference)	-	-	-	-	-		
Europe	-0.3115	1.3180	-2.8948	2.2717	0.8131		
Oceania	-1.0719	0.7865	-2.6134	0.4695	0.1729		
Country of the study						0.0716	26.24%
Australia (reference)	-	-	-	-	-		
Canada	-1.6200	1.4071	-4.3778	1.1377	0.2496		
Netherlands	0.7568	1.4084	-2.0036	3.5173	0.5910		
United States of America	1.1609	0.7786	-0.3652	2.6870	0.1360		
Venezuela	2.5963	1.3201	0.0089	5.1837	**0.0492**		
Type of medication						0.6780	0.00%
Not described (reference)	-	-	-	-	-		
Stimulants	0.3812	0.9182	-1.4184	2.1809	0.6780		
Medication assessment						0.5521	0.00%
Questioned (reference)	-	-	-	-	-		
Confirmed	-0.4629	0.7785	-1.9887	1.0629	0.5521		
Study Design						0.9993	0.00%
Retrospective (reference)	-	-	-	-	-		
Cross sectional	0.0359	0.7935	-1.8314	1.9031	0.9700		
Prospective	0.0312	1.1369	-2.1970	2.2594	0.9781		

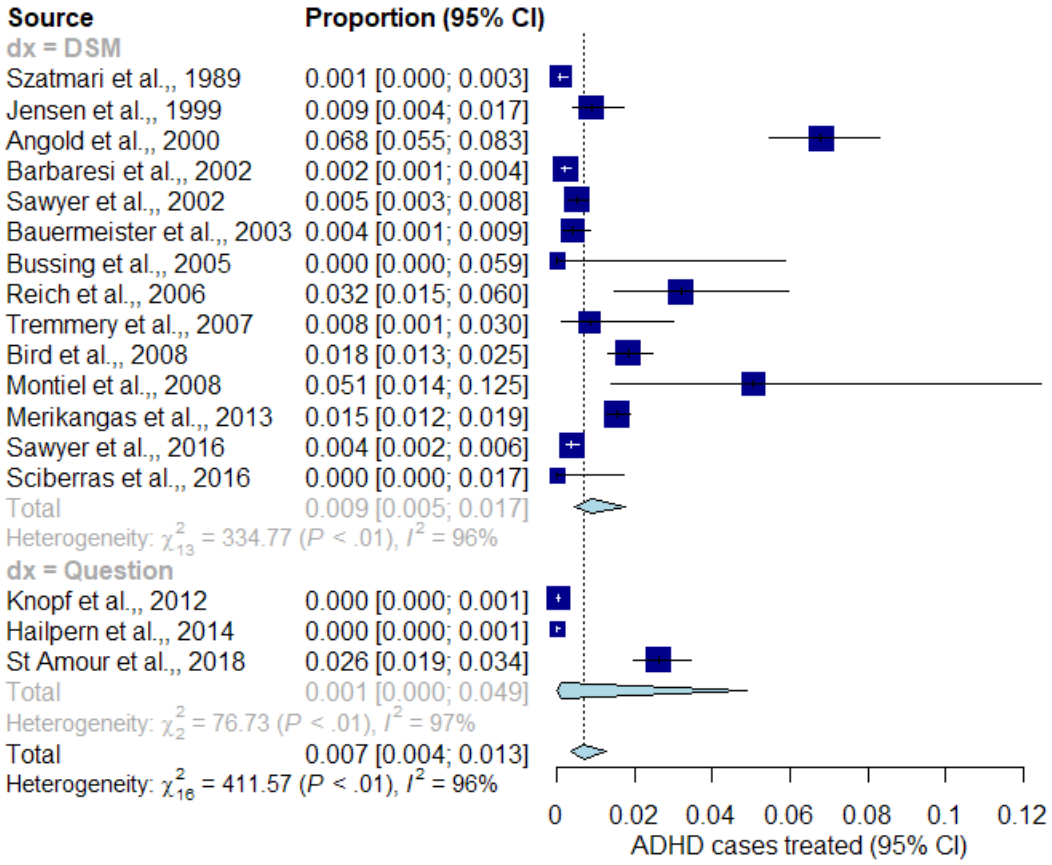
HAF = heterogeneity accounted for

Figure S17: Forest plot showing the meta-analysis results of the rates of medication use among all ADHD diagnosed children and adolescents, subgrouped by diagnostic method



"dx = DSM" = diagnosis by DSM criteria;
"dx = Question" = diagnosis by answering the question "does any doctor has diagnosed you [or your familiar] with ADHD?".

Figure S18: Forest plot showing the meta-analysis results of the rates of medication use among all non-diagnosed children and adolescents, subgrouped by diagnostic method



"dx = DSM" = diagnosis by DSM or ICD criteria;
"dx = Question" = diagnosis by answering the question "does any doctor has diagnosed you [or your familiar] with ADHD?".

Figure S19: Forest plot showing the meta-analysis results of the rates of medication use among all ADHD diagnosed children and adolescents.

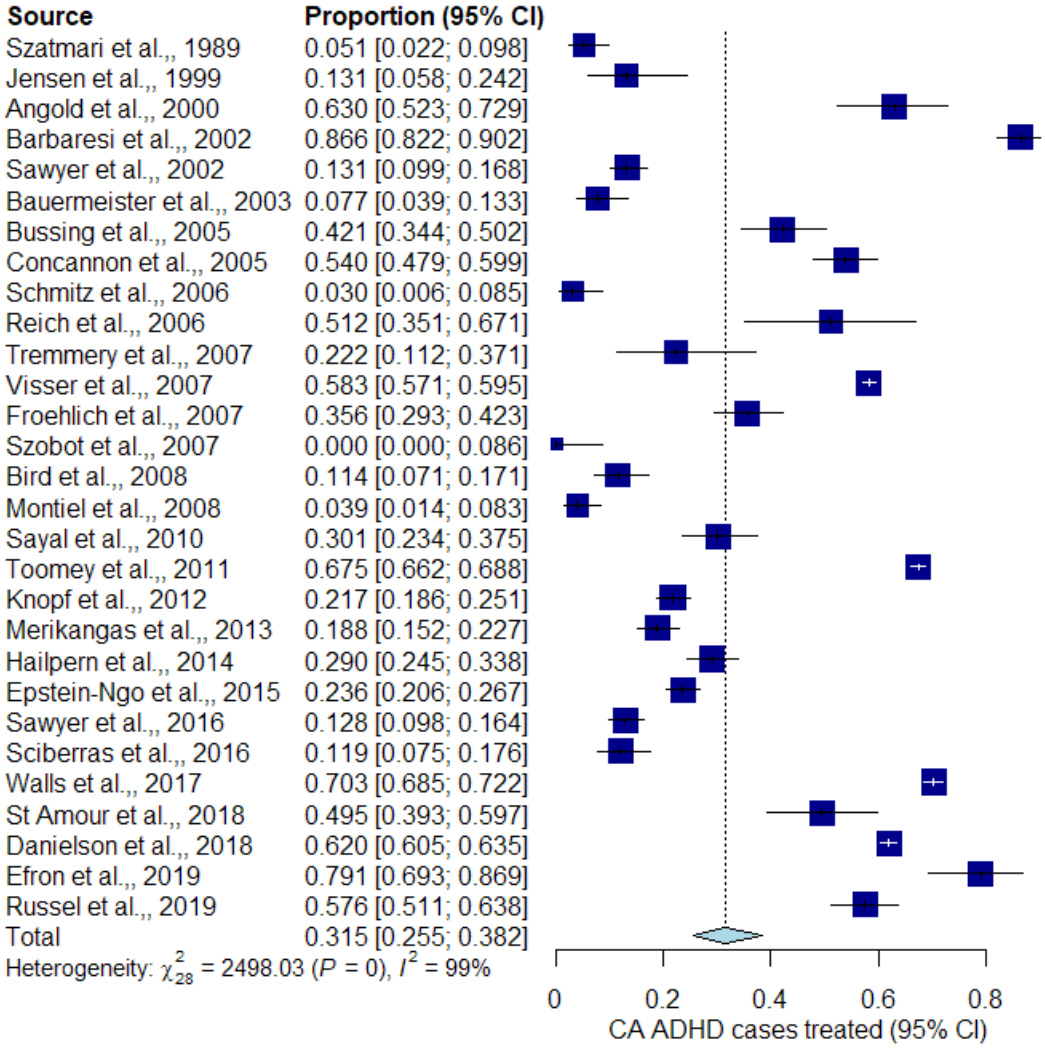


Figure S20: Forest plot showing the meta-analysis results of the rates of medication use among all non-diagnosed children and adolescents.