Forståelse og forklaringer af årsagen til øget risiko for depression hos ADHD-populationen, samt mulige forebyggelses og interventions strategier

Katrine Biltoft Noe: 20175239
Aalborg Universitet
Børnesprogklinikken
KAPSY202010: Kandidatspeciale, 4. semester
Vejleder: Patrick K. Bender
Afleveringsdato: 6. januar 2023
Samlet tegn og sideantal for rammesættende del: 59.988 (24,9 sider)
Samlet antal tegn og sideantal for artikel: 59.996 (24,9 sider)

Abstract

Background. Research has established that people with ADHD have an increased risk of developing depression. Furthermore, this comorbidity is followed by increasing consequences on both the individual life quality and the societal burden and economics. Multiple explanations models and research on this relation exist. **The objective** of this project was to explain and understand the etiology of comorbid ADHD and depression. Furthermore, the aim was to understand how this comorbidity could be treated and prevented **Method**. To answer this, the project was split in 3 sections, each contributing with some explanation. The first section presented different explanation models as well as their rationale and complexity. Furthermore, different research designs applicability in investigating causality were presented. The second part of the project investigated the evidence of direct and indirect causational factors as explanations of a relation from ADHD to depression, in a systematic review. The third section aimed to understand the best prevention and interventions strategies for depression in an ADHD population, based on the finding of the systematic review and the national clinical guidelines of Denmark as well as other research. **Results** In the first section it was established that both common etiology and direct and indirect causal factors of ADHD most likely contribute to the explanation of the association between ADHD and depression. Furthermore, the complexity of these processes was presented, demonstrating that these can be difficult to disentangle from each other in research. The second part found suggestions of a negative effect of having; the ADHD-IN subtype, decreasing self-perception, sleep problems, maternal psychopathology, traumatic experiences, and social difficulties, as well as no positive or negative effect from ADHD medication and performance EF. Lastly, mixed findings existed regarding the influence of ADHD symptoms, academic difficulties, and the family environment. The third section established that research is lacking on intervention and prevention strategies targeting specifically comorbid ADHD and depression. However, multiple treatments already suggested for ADHD or depression, combined well with the findings of the SR, suggesting a possible effect on depression. Examples of such includes, parent training programs, sleep interventions, cognitive behavioral therapy, and social skills training. In **Conclusion** the association between ADHD and depression seems to include a complex etiology. However, indirect, and direct factors of the ADHD diagnosis could explain part of this, and multiple factors is

suggested in the research. Furthermore, these add well up with many intervention strategies already recommended in clinical guidelines.

Indholdsfortegnelse

Bilag

Bilag 1/Appendix 1: Search protocol

Bilag 2/Appendix 2: Modified/elaborated Newcastle-Ottawa Scale for cohort studies

Indledning

Diagnosen Attention Deficit/ Hyperactivity Disorder (ADHD) angives at være den hyppigst forekommende neuropsykiatriske udviklingsforstyrrelse i Danmark med en prævalens på 4,5% hos danske børn fra 10-24 år i 2016 (Jeppesen et al., 2020, p. 185). Det angives ydermere, at "det er mere reglen end undtagelsen, at unge med ADHD i løbet af opvæksten udvikler symptomer svarende til en eller flere andre psykiske sygdomme (…) Hvor drengene typisk reagerer med adfærdsforstyrrelser og misbrug, er det hos pigerne mere almindeligt at udvikle angstlidelser og depression" (Jeppesen et al., 2020, p. 192). Denne statistik understøttes af en overbevisende mængde forskning, der fastslår, at ADHD er associeret med depression og heriblandt også selvmordstanker (Hinshaw et al., 2012, p.1041; Angold et al., 1999, p. 57; Libutzki et al., 2019, p. 38; Meinzer et al., 2014, p. 600f; Erskine et al., 2016, p. 844). I et review fandt Angold et al. (1999, p. 66) at hyppigheden for at udvikle Major depressive disorder (MDD) er 5,5 gange så høj hos unge med ADHD i forhold til typisk udviklede unge. Dette må vurderes i lyset af, at MDD samtidigt er en diagnose med en livstidsprævalens estimeret til omkring 20% i den neurotypiske population, hvilket betyder, at denne komorbide gruppe er yderst prævalent (Kendall et al., 2021, p. 5).

ADHD- og depression er begge kendt for at medføre en række negative psykosociale og funktionelle vanskeligheder. Hvor personer med ADHD udover førnævnte komorbide lidelser ofte oplever problemer inden for afhængighed/misbrug (Di Lorenzo et al. 2021, pp. 287-291; Shaw et al., 2012, p. 4ff), akademisk formåen (Arnold et al. 2015, p. 73; Shaw et al., 2012, p. 4ff), social formåen, antisocial adfærd og selvværd (Harpin et al. 2013, p. 295; Shaw et al., 2012, p. 4ff). De har ligeledes en højere dødelighed inden for unaturlige dødsårsager såsom uheld og selvmord (Catalá-López et al., 2022, p. 10).

Personer med depression oplever, udover de depressive symptomer, også ofte en række andre effekter såsom lavt selvværd, skyldfølelse, søvnproblemer, selvmordstanker, træthed og ændringer i appetit, eller funktionelle problematikker såsom problemer på arbejdet, i skolen eller i familielivet (WHO, 2012). Slutligt giver depression også en øget risiko for selvmord (Laursen et al. 2016, p. 204f). Udover disse negative konsekvenser, der følger hver diagnose, er der indikationer for, at kombinationen af begge medfører større konsekvenser end hver diagnose for sig.

Dette omhandler b.la. forringet social og akademisk formåen (Blackman et al., 2005, p. 195) samt begyndelse, varighed og sværhedsgraden af de depressive symptomer (Biederman et al., 2008, p. 426). Ydermere er de overordnede sundhedsmæssige omkostninger højere end ved hver diagnose alene (Fishman et. al., 2007; Daviss, 2008, p. 566).

Problemfelt

Opsummerende er det etableret, at der i ADHD-populationen ses en større hyppighed af depression end hos normalbefolkningen. Denne komorbiditet er fundet at forværre en række både personlige konsekvenser såvel som samfundsøkonomiske konsekvenser. Der er derfor relevant at overveje forebyggende strategier, som kan være effektive for ADHD-populationen. For at forstå hvilke initiativer, der effektivt kan forebygge, er det dog essentielt at have en forståelse af årsagen til associationen mellem AHD og depression. På baggrund af dette vil dette projekt have til formål at danne et overblik over og fremme forståelse af forskellige forklaringsmodeller for årsagen til associationen mellem ADHD og depression. Derudover ønskes at etablere, hvilke risikofaktorer relateret til ADHD-diagnosen der er evidens for, samt at sætte dette i relation til interventions og forbyggende strategier.

Problemformulering

Hvordan kan årsagen til en øget risiko for depression hos ADHD-populationen forklares og forstås, samt hvordan kan denne risiko forebygges og interveneres på?

Metateoretiske Overvejelser

I dette afsnit vil de metateoretiske overvejelser udfoldes. Ifølge Jacobsen et al. (2015, p. 14ff) defineres en metadisciplin som noget, der ligger bag en given disciplin, hvor der f.eks. reflekteres over den type spørgsmål og svar, der gives indenfor disciplinen. Dette projekt vil tage udgangspunkt i deskriptiv-empirisk videnskabsteori grundet et ønske om at klarlægge et fænomen, som det optræder ud fra den empiriske virkelighed (Jacobsen et al., 2015, p. 14ff).

Formålet med dette projekt er, som beskrevet i ovenstående problemformulering, både at forklare og forstå en årsag samt ud fra denne forståelse at kunne muliggøre forebyggelse af problemet. I denne sammenhæng ønskes først og fremmest en forståelse af de mulige forklaringsmodeller for tidligere nævnte association mellem ADHD og depression. Dernæst ønskes at afgøre hvilke faktorer, der bedst kan forklare at ADHD-diagnosen leder til øget risiko for depression. Dette

ønske kan forstås i led med Habermas erkendelsesinteresser. En interesse for at forklare/forudsige relaterer sig til en positivistisk tilgang med eksperimental forskning (Brinkmann, p. 71). Denne positivistiske tilgang er også netop udgangspunktet, til at forklare associationen fra ADHD til depression. Her vil empirisk forskning anvendes til at afgøre evidensen for faktorerne igennem et systematisk review (SR). Som omtalt i Brinkmann (2015, p. 71) vil der dog være elementer af en forstående og fortolkende tilgang i alle tilgangene. I det SR vil også efterstræbes at forstå den interne konsistens i de fundne resultater og deres relation til hinanden.

Disposition

Dette projekts problemformulering vil besvares igennem tre dele. Den første del vil introducere mulige forklaringsmodeller samt berøre kausalitet og arv/miljø interaktioner i relation til psykopatologi. Anden del vil centrere sig om et SR af direkte og indirekte faktorer relateret til ADHD-diagnosen, som kan påvirke risikoen for depression. Først vil metodiske overvejelser angående valg og udførsel af det SR fremgå. Herefter præsenteres det SR i artikelform. I projektets tredje del vil præventive tiltag samt behandling af depression hos ADHD- populationen diskuteres i lyset af det SR's implikationer, kliniske retningslinjer og anden forskning.

Del 1 – Ætiologi

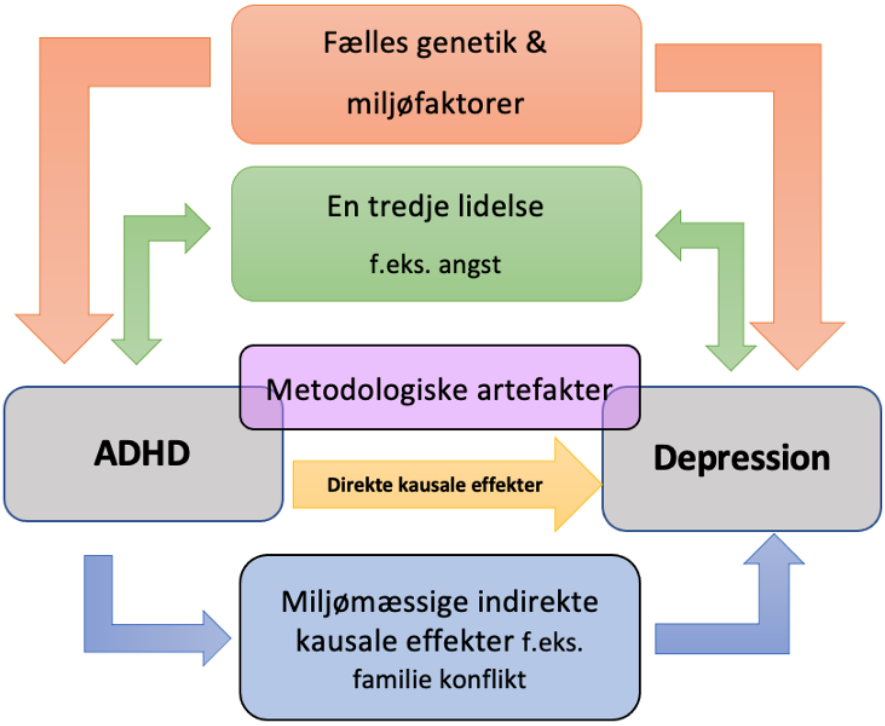
I det indledende afsnit blev det klarlagt, at flere studier har fundet en korrelation imellem ADHD og depression (Angold et al., 1999, p. 57; Libutzki et al., 2019, p. 38; Meinzer et al., 2014, p. 600f; Erskine et al., 2016, p. 844). En korrelation mellem to variable betyder dog ikke nødvendigvis, at den ene leder til den anden, altså at der er kausalitet imellem dem. I dette afsnit vil de forskellige forklaringsmodeller for associationen mellem ADHD og depression, samt deres bagvedliggende forudsætninger, blive udfoldet. Dernæst vil kompleksitet i disse forsimplede forklaringsmodeller blive belyst ud fra gen-miljø interaktioner. Slutteligt berøres det, hvilke implikationer forskellige metoder bidrager med i henhold til at opnå evidens angående ætiologi.

Forklaringsmodeller

Der eksisterer forskellige forklaringsmodeller for årsagen til korrelationen mellem ADHD og depression. Disse er illustreret i figur 1, og vil udfoldes i dette afsnit.

Figur 1

Forklaringsmodeller for associationen mellem ADHD og depression



Note. (1) Fælles genetiske og miljømæssige risikoer for ADHD og depression; (2) En tredje lidelse associeret med både ADHD og depression; (3) Et artefakt af den benyttede metodologi og overlappende symptomer imellem ADHD og depression; (4) Direkte kausale effekter fra ADHD til depression; (5) indirekte kausale effekter fra ADHD til depression igennem miljømæssige komponenter. Denne model er tilpasset ud fra: "Practitioner Review: Attention-deficit hyperactivity disorder and autism spectrum disorder–the importance of depression" by A. Thapar, Livingston, L. A., Eyre, O., & Riglin, L.,2022, *Journal of Child Psychology and Psychiatry*, 64(1), 4–15, https://doi.org/10.1111/jcpp.13678. Copyright under the terms of the Creative Commons Attribu-

Fælles Risikofaktorer

En foreslået forklaring er fælles risikofaktorer, hvor ADHD og depression optræder samtidigt som følge af en tredje faktor uafhængig af ADHD (Wichstrøm, 2017, p. 1239; Thapar et al., 2023, p. 6f). Her kan være tale om en genetisk sårbarhed, hvor genetiske elementer giver øget risiko for både ADHD og depression. Ligeledes kan der være tale om miljømæssige faktorer, som er uafhængige af de enkelte diagnoser.

ADHD er estimeret til en arvelighed på ~80% (Faraone & Larsson, 2019; Chen et al. 2016), hvilket er højere end den estimerede arvelighed for depression på ~30-

50% (Kendall et al., 2021; Chen et al., 2015). Arveligheden for komorbid ADHD og depression er også undersøgt i tvillingestudier (Cole et al., 2009; Chen et al., 2015; Rydell et al., 2017). Disse studier finder overordnet, at arvelighed forklarer mellem 64% og 84% af årsagen til komorbid ADHD og depression. Særlige forhold angående fortolkning af denne arvelighedsprocent vil blive præsenteret i kommende afsnit, hvor tvillingestudiers metode vil blive fremlagt.

En række fælles miljømæssige faktorer er også blevet undersøgt i relation til udviklingen af både ADHD og depression. Eksempler herpå inkluderer prænatale og perinatale faktorer såsom lav fødselsvægt (Litt et al., 2020; Orri et al., 2021) og stress hos mødre under graviditeten (Park et al., 2014). Derudover kan nævnes faktorer associeret med det overordnede helbred såsom kost og fysisk aktivitet (Wu et al., 2018). Nogle af disse ovennævnte miljøfaktorer vil pr. definition være uafhængige af ADHD og vil derfor agere som bagvedliggende fælles faktor for både ADHD og depression. Dette inkluderer f.eks. de peri- og prænatale faktorer, da disse sker på et så tidligt stadie i personens liv at adfærden fra ADHD højest sandsynligt ikke kan være årsagen til at faktorerne opstår. Faktorerne kost og motion er sværere at afgøre, da disse kunne være initieret eller forværret af en adfærd der udspringer fra ADHD-diagnosen, hvorved de ville betegnes som indirekte kausale effekter fra ADHD. Samme tvivl eksisterer ved en lang række miljøfaktorer, som kan være af interesse i henhold til udviklingen af både ADHD og depression, såsom traumatiske begivenheder, konflikter med forældre eller skole samt mobning. Det vil således ofte være nødvendigt at undersøge om en miljøfaktor agerer afhængigt af ADHD, i interaktion med ADHD eller uafhængigt af ADHD, for at forstå årsagssammenhængene.

En Tredje Lidelse

I tillæg til disse miljømæssige faktorer, kan også nævnes somatiske sygdomme såsom astma (Litt et al., 2020), eller mentale lidelser såsom angst, hvilket i modellen går under kategorien *en tredje lidelse*. Disse må anses særskilte, da det er svært at afgøre kausaliteten i deres relation med både ADHD og depression.

Metodologiske Artefakter

Metodologiske artefakter som årsagsforklaring fremsætter at der ikke er tale om, at de to diagnoser fremtræder komorbidt, men at artefakter får det til at se ud som om der er to diagnoser. Det, at de to diagnoser fremkommer, foreslås at være

enten på baggrund af overlappende symptomer (Milberger et al., 1995; Biederman et al., 1995) eller metodiske bias såsom informationskildens forventninger (Angold et al., 1999). Disse forklaringer er er dog blevet modbevist i flere studier (Milberger et al., 1995; Biederman et al., 1995; Angold et al., 1999), som finder, at der er tale om to separate diagnoser til stede på samme tid.

Direkte og Indirekte Kausale Effekter

De sidste forklaringsmodeller fremsætter, at der eksisterer en kausalitet mellem ADHD og depression, som kan forklares ved enten direkte påvirkning eller gennem en eller flere medierende faktorer, som påvirkes af ADHD symptomerne og giver øget risiko for depression (Se figur 1) (Wichstrøm, 2017, p.1239; Thapar et al, 2023, p. 6f). Eksempler på dette præsenteret i litteraturen indebærer 1) *Akademisk fiasko* – hvor krav fra skolen er særligt udfordrende for børn med ADHD, hvilket kan lede til konflikt med lærere såvel som utilfredshed med at gå I skole eller et negativt selvværd (Carrick & Tunick, 2020, p. 128). 2) *Social fiasko* – sociale vanskeligheder hos børn med ADHD er et kendt fænomen, som ofte leder til afvisninger fra jævnaldrende (Carrick & Tunick, 2020, p. 129; Bagwell et al., 2001), og ydermere er fundet associeret med depression. 3) *Familie konflikt* – der er indikationer for, at negative og inkonsistente opdragelsesmetoder kan trigges af at have et barn med ADHD (Ostrander et al., 2006). Disse opdragelsesmetoder er ligeledes fundet associeret med depression (Rudolph & Kurlakowsky, 2001). Ydermere kan sådanne konflikter formodes at lede til øget risiko for, at forældre udvikler depression eller udvikler ægteskabelige problemer. I den sammenhæng er det også foreslået, at mødre med depression har et mere negativt syn på deres barn, hvilket kan adapters af barnet og lede til en kognitiv stil karakteriseret ved en følelse af hjælpeløshed og negative selvevaluering (Gelfand & Teti, 1990). 4) *Indre faktorer* – såsom forringet emotionsregulering (Carrick & Tunick, 2020, p. 129). Dette er associeret med ADHD-diagnosen og relationen til at øge risikoen for depression kan være flerartet. Det kan virke ved at påvirke ovennævnte sociale relationer negativt, hvilket der er fundet indikationer for at forringet emotionsregulering hos personer med ADHD gør (McKay et al., 2022, p. 8f). Emotionsregulering kan også formodes at øge risikoen for depression ved at input fortolkes og processeres anderledes, hvor det er forslået en manglende effektiv strategi til bearbejdningen af negative emotioner (Steinberg & Drabick, 2015, pp. 955;959) 5) *Medicin* – særlig medicin anvendes ofte i forbindelse med behandlingen af ADHD, og det er foreslået, at denne medicin potentielt kan øge

risikoen for depression som en uønsket bivirkning (Carrick & Tunick, 2020, p. 129; Daviss, 2008, p. 567).

Forklaringsniveauer indenfor Ætiologi

Den høje arvelighedsprocent, som er fundet for komorbid ADHD og depression angivet i forrige afsnit, kan give anledning til at se genetik som den primære forklaring samt de to diagnosers sammenfald som forudbestemt og fastlåst. En sådan fortolkning vil betyde, at de resterende faktorer vurderes af mindre betydning. Inden for menneskelig udvikling er årsagsmodeller dog mere komplekse og involverer ofte en række af sammenfaldne hændelser (Lervåg, 2019, p. 603). I forståelsen af kausale mekanismer i udviklingen af psykopatologi indgår tre forskellige forklaringsniveauer. Disse består i 1) det biologiske, som indbefatter strukturer i hjernen - neurologiske systemer som er bestemt af genetikken 2) det kognitive, som udgør de kognitive processer, der ligger bag handlinger, men som eksisterer på baggrund af førnævnte biologiske strukturer 3) det adfærdsmæssige niveau, som netop udgør de handlinger, som er manifestationen af de kognitive processer, som er bestemt af de biologiske komponenter (Lervåg, 2019, p. 603). For at opnå en fuld forståelse af en patologi, må disse tre niveauer inddrages såvel som deres interne interaktioner med hinanden samt deres interaktioner med det omgivende miljø (Lervåg, 2019, p. 603). Således kan nogle af de forskellige forklaringsmodeller fremsat i figur 1 altså være svære at adskille fra hinanden og kan måske i højere grad ses som forskellige forklaringsniveauer. I det kommende afsnit vil kompleksitet angående genetikkens sammenspil med miljøet udfoldes med eksempler fra ADHD-diagnosen.

Samspil mellem Genetik, Adfærd og Miljø

Interaktion mellem genetik og det omgivende miljø kan omtales som både gen-miljø interaktion (GxE) og gen-miljø korrelation (rGE). Hvor GxE referer til, hvordan individets genetik kan medføre en øget sensitivitet over for bestemte miljømæssige faktorer (Jaffe & Price, 2012, p. 1253f) og derfor i interaktion med miljøet øger risikoen. Her er der f.eks. indikationer for, at genetisk sårbarhed kan øge sensitiviteten overfor stressfulde begivenheder, således at disse begivenheder giver større risiko for udvikling af depression hos individet end hos individer uden den pågældende genetiske sårbarhed (Kendler et al., 2010). I dette tilfælde vil individet

altså udsættes for samme miljømæssige påvirkning som andre, men det vil reagere anderledes på grund af den genetiske disposition.

Gen-miljø korrelationen (rGE) henviser til en række forskellige måder, hvorpå den genetiske disposition påvirker miljøet (Jaffe & Price, 2012, p.253f). Flere typer af rGE eksister, som i det følgende vil blive beskrevet i relation til eksempler fra ADHD-diagnosen. 1) De passive – som referer til, at den genetiske disposition indirekte påvirker miljøet, idet forældrene også vil være i besiddelse af et psykopatologisk gen, hvis barnet har det (Jaffe & Price, 2012, p. 253f). Derved påvirkes barnet både igennem den direkte genetiske indvirkning og igennem den adfærd, som forælderen har, fordi de selv har genet. Eksempelvis kan et barn med ADHD opvokse med et højt niveau af konflikt i hjemmet, fordi en eller begge forældre har ADHD eller træk derfra. 2) De evokative – som referer til bestemte miljømæssige reaktioner baseret på individets adfærd, som er genetisk bestemt (Jaffe & Price, 2012, p. 253f). Dette kunne f.eks. indebære et barn med en hyperaktiv adfærd i skolen, som kunne lede til, at lærere opføre sig mere stringent eller med mere frustration overfor dette barn. 3) De aktive - som referer til, hvordan individets genetisk bestemte handlinger og kognition påvirker, hvilket miljø de placerer sig selv i. Dette kunne f.eks. være personer med ADHD, som har en tendens til forøget risikovillighed, hvilket drager dem imod farlige situationer såsom biluheld (Pollak et al., 2019, p. 2) eller imod bestemte sociale grupper, som også har en øget risikovillighed og en risikofyldt adfærd. Igennem disse rGE bliver det belyst, hvordan en genetisk bestemt ADHD-diagnose som første led kan have indflydelse på en række andre miljømæssige faktorer, som dermed ikke kan ses som uafhængige af barnets genetik. Disse processer viser altså, hvordan genetisk bestemt adfærd og kognition kan påvirke miljøet. Det miljø, der ændres, kan derefter vise sig at bidrage til en øget risiko for depression, ved f.eks. at dårlige oplevelser i skolen eller mange traumatiske oplevelser giver en øget risiko for depression. Dette implicerer samtidig at, hvis rGE udgør hele eller dele af årsagen til, at arvelighed forklarer den øgede risiko, så har vi mulighed for at intervenere på den, ved at forsøge at ændre kognitionen og/eller adfærden, eller ved at forsøge at tilpasse miljøernes reaktion på adfærden.

Forskningsmetoder indenfor *Ætiologi*

For at opnå større viden om hvilke af de foreslåede årsagsmodeller (Figur 1), der gør sig gældende, er det essentielt at forske på området. Design af studier kan

dog være mangeartede. I det nedstående vil forskellige undersøgelsesdesigns blive belyst i relation til undersøgelse af ætiologi.

Tvillingestudier

I afgørelsen af ætiologien for sygdomme og diagnoser er tvillingestudier et populært valg. Disse er særligt effektive til at afgøre, om lidelsen er genetisk bestemt, eller miljøbestemt. Studierne beror på en 'ens-miljø præmis' (Felson, 2014). Disse studier virker ved at undersøge en gruppe monozygotiske (MZ) tvillinger, som pr. definition vil dele en identisk genetiske disposition samt opvokse i det samme familiemiljø, og en gruppe dizygotiske (DZ) tvillinger, som deler halvdelen af deres gener og samme miljø. Således kan korrelationen for en bestemt lidelse beregnes mellem MZ-tvillinger og sammenlignes med korrelationen for lidelsen mellem de DZ-tvillinger (Felson, 2014, p. 185f). Dette betyder, at miljømæssige forskelle kan kontrolleres for, hvilket er nærmest umuligt i andre metodiske design. I Dalmaijer (2020, pp. 1-4) blev det dog undersøgt, igennem en simulationsanalyse, hvordan resultater fra sådanne tvillingestudier blev påvirket, hvis nogle af ovennævnte rGE eksisterer, og præmissen for ens miljø i tvillingestudier derved er brudt. Denne analyse viste, at der vil opstå en overvurdering af arveligheden, hvis evokative og aktive rGE er til stede (Dalmaijer, 2020, pp. 1-4). Dette viser, at det er væsentligt at undersøge, hvorvidt rGE er aktuelle i udviklingen af en psykopatologi, og det er væsentligt at tage højde for dette i fortolkningen af tvillingestudier på området, som kan vise sig at overvurdere det arvelige komponent.

Kontrollerede Randomiserede Studier

I forrige afsnit bliver det tydeligt at det er relevant at se nærmere på, hvordan indirekte effekter af ADHD kan påvirke depression. I henhold til sådanne undersøgelser er det afgørende at etablere kausalitet for at opnå større sikkerhed for, at det ikke er en fælles uafhængig faktor, som er årsag til begge diagnoser, eller at det er depression, som påvirker ADHD. Den forskningsmetode, som giver mest sikkerhed omkring kausalitets processer, er de kontrollerede randomiserede studier og eksperimenter, hvor det er muligt at manipulere en variabel og følge udfaldet i et bias-frit miljø. I realiteten er dette dog sjældent muligt inden for undersøgelser af psykopatologi af både praktiske og etiske grunde (Lervåg, 2019, p.603f). Dette relaterer sig f.eks. til problemer i henhold til at kontrollere for alle relevante variable på området, samtidig med at f.eks. genetiske faktorer er svære og anset uetiske at

ændre på. Derudover kan det naturligvis ikke, selv hvis det var muligt, forsvares at indføre elementer, der bidrager til øget risiko for ADHD eller depression. En mulig eksperimentel tilstand, der indirekte bidrager med information om mediatorer mellem ADHD og depression, er interventionsstudier.

Observationsstudier

På baggrund af førnævnte begrænsninger vil observationsstudier ofte være første led i etableringen af kausalitet, inden der kan udvikles interventionsstudier (Lervåg, 2019, p. 604; Boyko, 2013, p. 642). Fordelen ved longitudinelle eller retrospektive studier frem for tværsnitsstudier er, at disse giver mulighed for at sige noget om retningen for sammenhængen, grundet tidselementet (Lervåg, 2019, p. 604; Garber & Hollon, 1991, p. 130). Her findes overordnet tre forudsætninger, som må mødes i et longitudinelt studie, for at der kan drages konklusioner om kausalitet (1) Kovariation - den undersøgte faktor må være eller have været til stede, hvis diagnosen er til stede; (2) tidsmæssig forudgående – den undersøgte faktor må have været til stede inden udviklingen af diagnosen; og (3) ikke falsk – som indbefatter at andre mulige forklaringer udelukkes (Garber & Hollon, 1991, p. 129f).

En anden metode ofte anvendt til at undersøge ætiologi er case-control-studier. Disse er fordelagtige, når en bestemt lidelse undersøges, og den/de udløsende faktorer er bredt udbredt. Metoden virker ved at sammenligne en gruppe med den specifikke lidelse med en anden grupper uden lidelsen. Målene for disse faktorer kan enten være af retrospektiv karakter eller måles i den pågældende tid (Boyko, 2013, p. 643). Hvilke af disse, der gør sig gældende, er naturligvis afgørende for, om der kan drages konklusioner om kausalitet

Delkonklusion

Igennem denne del fremgår, at associationen mellem ADHD og depression ikke nødvendigvis betyder, at der er en kausal sammenhæng mellem de to. Der er fremsat evidens for både fælles genetik og miljøfaktorer som en årsag til komorbid ADHD og depression såvel som indikationer for direkte og indirekte kausale effekter fra ADHD-diagnosen til depression (Meinzer et al., 2014; Thapar et al., 2023). Ydermere er der indikationer for, at arveligheden kan være overvurderet, når disse indirekte effekter gør sig gældende. På baggrund af dette er det altså relevant at undersøge sådanne indirekte effekter nærmere. For at afgøre, om der eksisterer en kausal sammenhæng, kan longitudinelle, retrospektive og eksperimentelle studier

med fordel anvendes. Derudover er case-control studier fordelagtige til at forstå forskelle mellem grupper med og uden den specifikke lidelse.

I relation til præventive tiltag og interventioner er adfærd, kognition og miljøfaktorer nemmere at forebygge og intervenere imod, end en genetisk disposition er. Ydermere vil faktorer relateret til netop ADHD-diagnosen kunne give implikationer for en effektiv strategi til netop den population. På baggrund af dette vil fokuseres på faktorer defineret som direkte eller indirekte kausale mekanismer fra ADHD til depression. Når der udvikles interventionsmetoder, er der altid et ønske om at udvikle den intervention, der har størst mulig effekt for færrest mulige omkostninger. For at opnå en mere effektiv intervention, vurderer jeg det fordelagtigt at forsøge at opnå et tydeligere billede af hvilke risikofaktorer, der er mest evidens for. Dette vil være fokus i det SR, som fremkommer i næste del.

Del 2 - Systematisk Review

I dette kapitel vil der fremgå en kort beskrivelse af formålet med det SR, dets kendetegn og overvejelser i forbindelse med valget af et SR. Dernæst fremgår en uddybning af refleksioner i forbindelse med inklusions- og eksklusionskriterierne. Slutligt præsenteret det SR som en særskilt artikel.

Formål

Ideen om at udarbejde et SR fremkom på baggrund af ønsket om et bedre overblik over de mange forskellige forskningsartikler og foreslåede forklaringer vedrørende årsagen til komorbid ADHD og depression, som fremgår i forrige del. Dette med henblik på at få en forståelse af, hvordan denne gruppe bedst kan afhjælpes. Igennem den indledende undersøgelse af feltets teorier, blev det tydeligt, at nogle af de mulige årsager, omend gyldige nok, ikke var mulige at forebygge eller intervenere på. Dette indebærer f.eks. en fælles genetisk disposition og tidlige miljørisikofaktorer såsom stress under graviditeten, som er svære at sætte ind imod uden at skulle forebygge inden en ADHD-diagnose er stillet. På den baggrund blev det besluttet, at formålet med det SR skulle være at undersøge faktorer ved ADHD-diagnosen, som giver forøget risiko for at udvikle depression.

Det Systematiske Review

Et SR adskiller sig fra bogkapitler og andre reviews ved dets systematiske og gennemsigtige måde at sammenfatte informationer på. Et litteratur review eller et bogkapitel kan formidle det samme forskningsområde vidt forskelligt alt efter

perspektiv og pointe (Petticrew & Roberts, 2006, p. 5). Formålet med dette SR er netop at få et mere systematisk overblik over de risikofaktorer, som omtales i litteraturen. Derudover er et SR også fordelagtigt ved større mængder forskning, som kan være svære at overskue. I et SR bliver alle studier udvalgt ud fra samme forudbestemte selektionskriterier og sammenfattet til en mere overskuelig informationsmængde. Det er ligeledes vigtigt at et SR undersøger og bidrager med noget nyt (Petticrew & Roberts, 2006, p. 36). På baggrund af dette blev databaser og PROSPERO indledende søgt for mulige eksisterende eller igangværende projekter med samme formål. Her forelagde et igangværende projekt med en lignende interesse, som blev kontaktet, og det blev bekræftet, at forskellene var store nok til at fortsætte dette projekt. Slutligt må der eksistere et klart formål med det SR i henhold til et ønske om at påvirke politik, et praksisområde eller et forskningsfelt (Petticrew & Roberts, 2006, pp. 12ff). Dette SR har til formål både at informere forskningsområdet og i forbindelse med dette også at påvirke og informere praksis i form af viden om hvilke interventioner, som kan være relevante i forbindelse med behandling og forebyggelse af komorbid ADHD og depression.

Dataindsamling

I det følgende vil strategien og kriterierne for dataudvælgelsen først beskrives, hvorefter udvalgte aspekter af processen og valg deri vil blive uddybet.

Søgestrenge og Strategi

Der blev søgt efter relevante studier på databaserne WOS (Web of Science), PubMed og PsycInfo fra databasens start til 9. september 2022. For yderlige beskrivelse af søgestrategien se SR eller bilag 1.

Inklusions- og Eksklusionskriterier

I det følgende beskrives de inklusions og eksklusions kriterier, som blev anvendt. For at blive inkluderet må studierne (1) være på engelsk; (2) være peer-reviewed; (3) undersøge en risikofaktor(Z), der bidrager til forklaringen af forholdet mellem ADHD(X) og depression(Y); (4) have et enten longitudinelt, retrospektivt, case-control eller eksperimentelt design;)5) kun inkludere deltagere med en ADHD-diagnose, defineret ved enten en klinisk diagnose eller symptomer over cut-off score på en valideret ADHD-rating skala; og (6) Måle symptomer på depression(Y) på en særskilt skala, eller indeholde en klinisk depressions diagnose.

Studierne blev ekskluderet hvis (1) Y-målet indeholdt angst eller maniske elementer; (2) de undersøgte beskyttende faktorer defineret ved tiltag initieret af samfundet og ikke naturligt forekommende såsom interventioner og støtte i skolen. Medicinsk behandling undersøgt som risikofaktor udgør en undtagelse; (3) Z-målet udgør en somatisk eller psykisk sygdom såsom astma, stofmisbrug eller angst; og (4) Z-målet er ikke tilstedet som en konsekvens af ADHD-diagnosen, hvilket kunne være faktorer som køn, genetik, prænatale og perinatale faktorer.

Proces og Overvejelser

Søgningen resulterede i 3470 artikler, hvoraf 812 var duplikater. Disse blev først screenet for inklusionskriterie 1, 2 og 3 samt eksklusionskriterie 1 og 2, hvilket resulterede i at 326 artikler opfyldte kriterierne. Af ressourcemæssige og overbliksmæssige årsager var det ikke hensigtsmæssigt at inddrage 326 artikler i det SR. På denne baggrund blev der efterfølgende implementeret en række yderligere kriterier. Overvejelser bag disse vil blive præsenteret i det følgende. Efter implementering af disse yderligere kriterier, endte det SR med at inddrage 28 artikler.

Metodisk Design Da dette SR har til formål at give overblik på området, var det ikke ønskværdigt kun at fokusere på én type risikofaktorer og derigennem udelukke en del. I stedet blev det besluttet at prioritere studier af højere metodiske kvalitet for at give overblik over de risikofaktorer, hvor der er mest sikkerhed omkring evidensen. I den forbindelse blev det besluttet kun at inkludere longitudinelle, case-control, retrospektive og eksperimentelle studier, i henhold til viden fra forrige del.

Definering af Diagnoser I den første sorteringsfase blev det tydeligt, at vidt forskellige mål for ADHD og depression blev anvendt. Det blev besluttet, at deltagerne i studierne skulle have en klinisk ADHD-diagnose eller testresultater, der indikerer, at de krydser den kliniske grænse og ikke blot har symptomer (Inklusionskriterie 5) Dette valg blev taget for at holde fokus på personer med ADHD i den kliniske betydning og deres risiko for komorbid depression eller depressive symptomer og ikke blot risikoen ved variationer i ADHD-symptomer som fremkommer i normalbefolkningen. Det behøver dog ikke nødvendigvis at være klinisk refererede. Beslutningen om ikke kun at inkludere klinisk refererede blev støttet af fund fra Meinzer at al. (2014, p. 600f), som fandt, at både klinisk refereret og ikke refereret ADHD (over cut-off) viste en korrelation med depression.

Det blev også tydeligt, at flere diagnostiske grupper eller symptomer blev samlet i klynger som en samlet deltagergruppe, f.eks. ’mood disorders’ som helhed. På baggrund af dette blev inklusionskriteriet omkring en særskilt skala indført (Inklusionskriterie 6) samt en eksklusion af skaler, som inddrager angst og mani (eksklusionskriterie 1). Dette valg blev taget på baggrund af, et ønske om at simplificere, hvorfor fokus er den unipolare depression, som også er mest udbredt.

Det Systematiske Review

På de følgende sider er det SR indsat.

How can features of an ADHD diagnosis increase the risk of developing depression. A Systematic Review

Katrine B. Noe

Department of Communication and Psychology, Aalborg University

KAPSY202010: Master's thesis

Patrick K. Bender Ph.D.

January 6., 2023

Abstract

Background. Research has established that people with ADHD have an increased risk of developing depression. Furthermore, this comorbidity is followed by increasing consequences on both the individual life quality and the societal burden and economics. Multiple explanations models and research on this relation exist. **The objective** of this study is to investigate and synthesize research investigating factors related to ADHD explaining the relation from ADHD to depression. **Method**. Relevant articles on the topic were searched in WOS, PsycInfo and Pubmed and sorted by the inclusion and exclusion criteriums. The studies must be in English and peer reviewed. Their method should be a longitudinal, retrospective, or a case-control study, and should investigate a risk factor explaining the relationship from ADHD to depression. Only participants with either a clinical ADHD diagnosis or threshold symptoms were included. The exclusion criterium included the exclusion of other psychological or somatic comorbidities as risk factors, and depression measures mixed with manic and anxiety elements. **Findings.** The search resulted in 28 articles that were systematically reviewed, quality assessed and narratively presented. **Interpretation** These results suggested a negative effect of having; the ADHD-IN subtype, decreasing self-perception, sleep problems, maternal psychopathology, traumatic experiences, and social difficulties, as well as no positive or negative effect exists from ADHD medication and performance EF. Mixed findings exist regarding the influence of ADHD symptoms, academic difficulties, and the family environment. **Discussion** Uncertainty exists on the relation between investigated factors and the ADHD diagnosis, as well as the influence of gender. In **Conclusion,** preliminary evidence was established that some factors of the ADHD-diagnosis influence later depression.

Key words: Attention-deficit hyperactivity disorder, depression, etiology, co-morbidity

Introduction

The neuropsychiatric diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) is estimated to affect 3–5% of children and adolescents worldwide (Polanczyk et al., 2007; Polanczyk et al., 2015) and 4% of adults (Kessler et al., 2006). It is considered the most common psychiatric disorder among children in Europe and the United States (Meyer, 2005). Both adults and children with ADHD are at high risk of experiencing a comorbid psychiatric disorder, with estimates ranging from 50–100% (Jensen & Steinhausen, 2015; Gillberg et al., 2004; Sobanski, 2006; Sobanski et al., 2007). The most frequently appearing comorbidities in children and adolescents with ADHD are considered to be conduct disorder (CD)/oppositional defiant disorder (ODD) and thereafter anxiety and mood disorders (Jensen & Steinhausen, 2015), whereas mood disorders and thereafter anxiety are reported as the most prevalent comorbidities in adults with ADHD (Mayer et al., 2021).

Regarding Major Depressive Disorder (MDD), one meta-analysis found a strong effect size of a correlation between ADHD and MDD in a clinic-referred sample and medium effect sizes in the non-referred sample with ADHD. The longitudinal studies did not show significant findings (Meinzer et al., 2014). However, another metanalysis accessing longitudinal studies found ADHD to predict depression (OR 2.31; Erskine et al., 2016). Considering this increased risk, and the fact that mood disorders such as depression already occur with a high lifetime prevalence of appx. 20% in the neurotypical population (Kendall et al., 2021), it can be concluded that comorbid ADHD and depression is a highly prevalent group.

Consequences

ADHD and depression are both disorders with a range of negative long-term consequences, concerning both psychological (Hodgkins et al., 2012; WHO,2012; Renouf & Harter., 1990),

psychosocial (Hodgkins et al., 2012; WHO,2012; Coryell et al., 1993) and functional areas (Hodgkins et al., 2012; WHO,2012; Goethe & Fischer, 1995), as well as increased mortality (Catalá-López et al., 2022; Laursen et al., 2016).

Additionally, it must be added, that the combination of the disorders seems to be leading to even worse consequences than each disorder alone. Examples of these worsened consequences are centered around increased impairments in social and academic ability (Blackman et al., 2005), as well as a worse depression course, concerning factors such as onset, duration, severity (Biederman et al., 2008), and recurrence (Rohde et al., 2001). Furthermore, cooccurrence leads to a three times higher risk of completing suicide, than each disorder alone (James et al., 2004). In addition, the overall health-care costs are higher than for each individual disorder (Fishman et. al., 2007; Daviss, 2008). Considering these consequences for individuals, as well as the economic consequences for society, mixed with the high prevalence of this group, it becomes clear that there is a need to understand this co-morbidity. More knowledge of which mechanisms are evoking this comorbidity, will help to develop more effective intervention and prevention strategies.

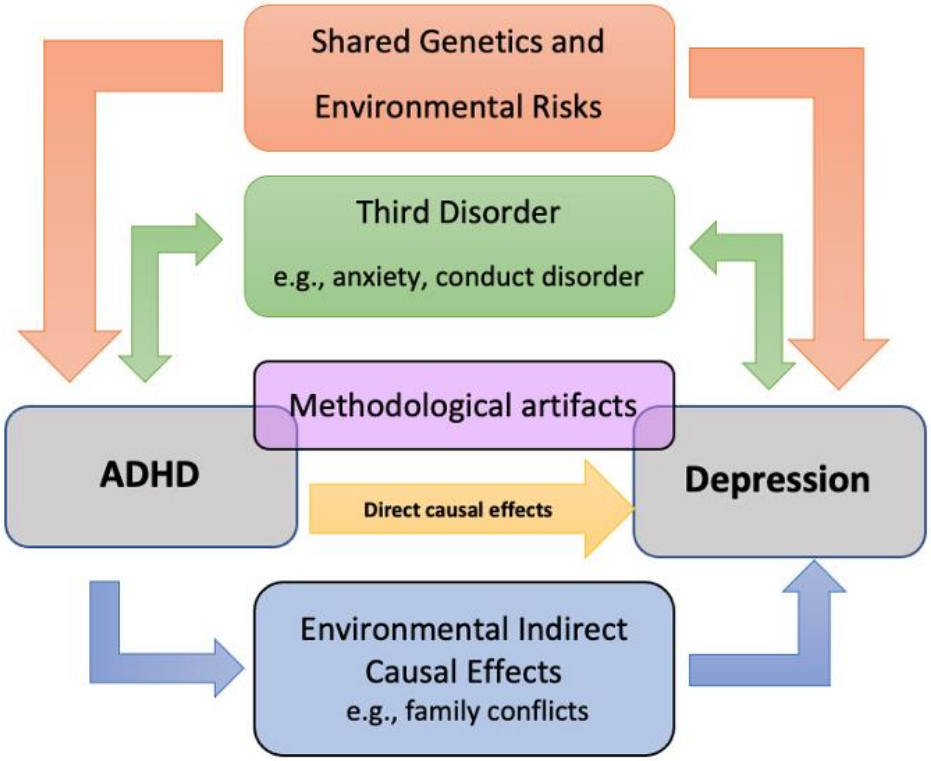
Suggested Mechanisms

The etiologies of both attention ADHD and depression are considered a mix of heritability, environmental determinants, and their interaction (Kendall et al., 2021; Faraone & Larsson, 2019; Chen et al., 2016; Dunn et al., 2015). Furthermore, several different mechanisms have been

suggested as explanations for their co-occurrence (Figure 1; Meinzer et al, 2014; Thapar et al., 2023).

Figure 1

Possible mechanisms linking ADHD and depression.



Note. ADHD may be correlated with depression due to: (1) shared genetic and environmental risks between ADHD and depression; (2) ADHD and depression both being associated with a third disorder; (3) An artefact of the used methodology and overlapping symptoms; (4) Direct causal effects from ADHD to depression; (5) indirect causal effects from ADHD to depression via environmental components. This model was adapted from "Practitioner Review: Attention-deficit hyperactivity disorder and autism spectrum disorder–the importance of depression" by A. Thapar, Livingston, L. A., Eyre, O., & Riglin, L.,2022, *Journal of Child Psychology and Psychiatry*, 64(1), 4–15, https://doi.org/10.1111/jcpp.13678. Copyright under the terms of the Creative Commons Attribution License.

These mechanisms differ in their overall logic. Some assume that the presence of ADHD and its symptoms causes the other diagnosis, which include the direct and indirect causal mechanisms (4 and 5) presented in Figure 1. The indirect causal mechanisms model assumes that environmental factors that affect the development of depression are likely to be generated – or aggravated – by the initial presence of ADHD (Wichstrøm et al., 2017; Meinzer at al., 2014). Whereas direct causal mechanisms include that the symptoms affect increased risk of depression directly. An example of this model could be an internal cognitive process related to ADHD diagnosed, which could affect how the environment is processed and interpreted and thereby infer depression. Others assume that ADHD and depression do not cause each other (Mechanism 1 & 3 in Figure 1), but rather that they are present simultaneously due to other explanations, such as methodological artifacts or a common etiology, with an emphasis on genetics and independent environmental factors (Meinzer et al., 2014; Wichstrøm et al., 2017). Examples of these methodological artifacts include common methods, reporting biases, and symptom overlap (Wichstrøm et al., 2017). Nevertheless, studies have established that the comorbidity between ADHD and depression is not due to overlapping symptoms (Milberger et al., 1995; Biederman et al., 1995), referral bias, rater expectancies, or multiple informants (Angold et al., 1999). This leaves methodological artifacts as an unlikely explanation for the co-occurrence. In opposition to this, evidence of both *common etiologies* as explanations as well as a third disorder, and *direct and indirect causal models* is present in research (Meinzer et al., 2014; Daviss, 2008). It is rather complex to determine directionality of a third disorder associated with both ADHD and depression, since the many possible explanations suggested between ADHD and depression, likewise exists regarding this third disorder's relation to ADHD and depression respectively (Garey et al., 2020).

Previous Reviews

To date, no systematic review (SR) has investigated all these mechanisms that might affect the relationship between ADHD and depression. However, reviews have investigated this topic, and SRs exist regarding specific factors associated with ADHD and depression. One SR investigated the influence of bullying and found that it could serve as both a moderator and mediator between ADHD and depression (Simmons & Antshel, 2021). Another SR investigated cognitive factors as an underlying explanation for depression in people with ADHD. It compared studies of cognitive mechanisms in MDD and ADHD populations to identify common mechanisms between them. This SR suggested executive functions (EFs) and long-term memory problems as candidates for pre-existing risk factors for depression (Mayer et al., 2021). A third SR investigated parenting practices in relation to functional impairments, including depression (Deault, 2010). This SR inferred that the ability to draw conclusions was limited and called for more longitudinal research that follows the theoretical assumptions of a complex gene and environment interaction (Deault, 2010). All the aforementioned SRs did mostly include cross-sectional studies, and therefore, they have been unable to infer the direction of associations.

Lastly, three reviews (Daviss, 2008; Meinzer at al., 2014; Thapar et al., 2023) have assessed the overall research into possible mechanisms explaining the link between ADHD and depression. As possible etiologies, they mentioned both common genetics and environmental effects, as well as factors of direct and indirect causal mechanisms from ADHD. However, these reviews are not systematic and include both cross-sectional and longitudinal studies.

Objective and Research Question

Although a correlation between ADHD and depression has been established, uncertainties and disagreements exist regarding its explanation. Evidence indicates that the direct and indirect

effects of ADHD symptomatology can explain part of this association, and common genetic and environmental etiologies can explain another part (Meinzer et al., 2014; Thapar et al., 2023). However, intervening in genetic factors is difficult, and it would not contribute well to interventions or prevention. Similarly, environmental factors independent of ADHD diagnosis would require intervention before the onset of ADHD; this would influence a much larger population group for the intervention, and not specifically the ADHD population. Thus, I focused this SR on the factors possibly affected by an ADHD diagnosis. Except for factors relating to a third disorder, which was assumed to have a complexity demanding a separate review. No former SR has examined multiple direct and indirect causal effects models together. Furthermore, previous reviews have been based on mostly cross-sectional studies, that lacked the ability to determine directionality (Daviss, 2008; Meinzer et al., 2014; Thapar et al., 2022). Therefore, the aim of the present SR was to review longitudinal, retrospective, and case-control studies to examine the indirect and direct effects of ADHD on the risk of developing depression. Accordingly, the following research question guided this SR:

RQ: Which direct and indirect factors of an ADHD diagnosis predict the risk of depression in people with ADHD?

Method

The present SR followed the PRISMA guidelines (Page et al., 2020). The search strategy, keywords, and inclusion and exclusion criteria were defined a priori (see Appendix 1), which are described in the following subsections.

Search Procedure

Relevant studies were searched in the Web of Science (WOS), PubMed, and PsycInfo databases from their inception date through September 9, 2022. The search string combined

identifiers for “ADHD”, “Risk factors”, and “Depression” using free-text keywords inspired by relevant literature as well as keywords from *Medical Subject Heading (MeSH)* and *APAThesaurus*. The search was restricted to terms appearing in the titles or MeSH of publications regarding the “ADHD” and “Depression” identifiers. The “Risk factors” identifier was searched in titles and abstracts in PsycInfo and PubMed, whereas all identifiers were searched in titles and abstracts in WOS; for details, see the search protocol in Appendix 1. The included studies were searched for “similar articles” and “citations” in PubMed (See full description of this additional search in appendix 1).

Inclusion Criteria

The searched publications were systematically sorted in accordance with the following inclusion and exclusion criteria. For inclusion in this review, the studies had to (1) be in English; (2) be peer-reviewed; (3) investigate a risk factor (Z) explaining the relationship from ADHD (X) to depression (Y); (4) have either a longitudinal, retrospective, case-control, or experimental design; (5) include only participants with an ADHD diagnosis defined as either a clinical diagnosis or threshold symptoms measured, except for control groups; and (6) have a Y-measure as a depression scale or a clinical depression diagnosis.

Exclusion Criteria

Studies were excluded if (1) the Y-measure included anxiety or manic elements, and thus, not a measure alone of unipolar depression; (2) they investigated protective factors, defined as measures initiated by society and not naturally occurring, such as school support and interventions; medical treatment investigated as a risk factor was excepted; (3) the Z-measure was a psychiatric or somatic disease/disorder, such as asthma, substance use disorders, or anxiety; and (4) the Z-measure could not be present due to a consequence of the ADHD

diagnosis, which could be factors such as genetics, demographics, and prenatal and perinatal factors.

Data Extraction and Quality Assessment

Structured forms were developed for the data extraction process. The studies were organized and presented in overall categories as well as subcategories based on the themes investigated – namely psychological, biological, and psychosocial. In the case of multiple relevant factors in the same study, they were presented separately in their corresponding category.

The following data were extracted from the articles: (1) number of participants, mean age at the beginning and end of the study, and gender distribution; (2) the direct and indirect effect of ADHD and its measurement type; (3) the type of measure and measurement of depression; (4) the number of assessment points and the time between the baseline measure and last measure; (5) the type of design; (6) the global score of the quality assessment (see the full quality assessment in appendix 3); and (7) the overall result of the investigated factors influence on depression. Only significant results are reported as an effect.

The quality of the studies is assessed in Supplementary Table 1 with a modified version of the Newcastle–Ottawa quality assessment scale (NOS; Wells, 2022). The original themes and questions were kept intact; however, weak definitions were elaborated on and adapted to the topic of this SR (see the modified quality assessment manual in Appendix 2). Two studies are not quality-assessed in this table due to them employing a meta-analysis design (Bryant et al., 2022) and an experiment design (Becker et al., 2020).

Effect Size Calculations

The effect sizes reported in the studies were extracted in their original form and presented in Table 1; however, they were interpreted in the narrative synthesis according to conversions. The odds ratio (OR) and hazard ratio (HZ) were interpretated based on calculations from Chen et al. (2010), which were based on the boundaries from Cohen's d (0.2 = low; 0.5 = medium; 0.8 = high). These conversions were dependent on the percentage of the investigated disease in the nonexposed group, and calculations were made for 1% disease and 5% disease. Calculation forms for the 5% disease-rate where chosen, since a recent meta-analysis established a point prevalence of 8% for MDD and 4% of dysthymic disorder in adolescents (Shorey & Wong, 2022). Furthermore, r^2 values were interpreted according to Foster et al. (2008), who compared them with Pearson's r boundaries.

Results

This section will present the systematic search and unfold the descriptive and methodological characteristics of the included studies, as well as the overall findings from the included articles. Full data extraction of the included studies will appear in a table.

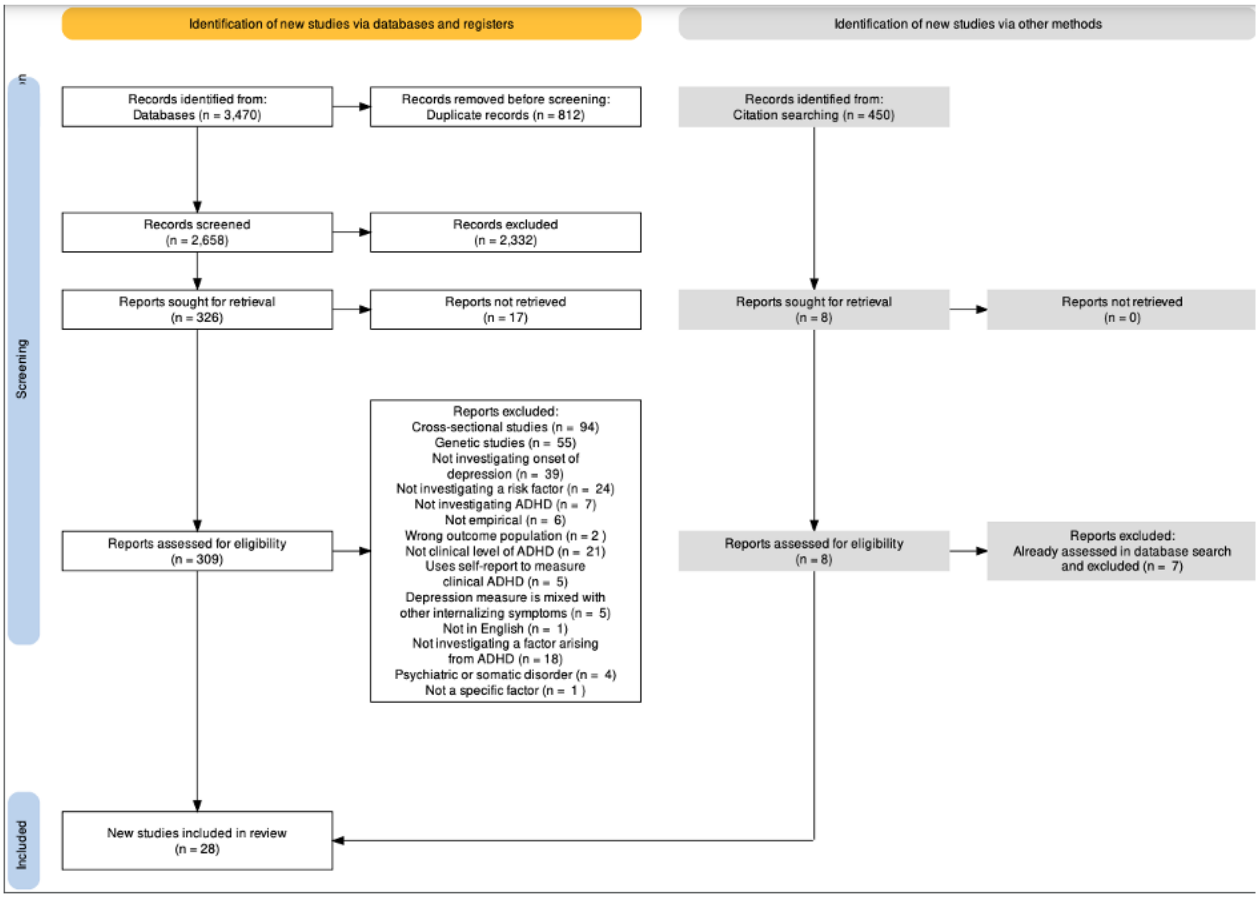
Study Selection

The search resulted in 3,470 records. These were first exported to RefWorks to remove duplicates (812), and the remaining 2,658 records were exported to Rayyan (Ouzanni et al., 2016) for eligibility screening. Initially, the records were screened according to inclusion criteria 1, 2, and 3 and exclusion criteria 1 and 2. Based on the number of remaining studies (326), the remaining inclusion and exclusion criteria were implemented. The 326 studies were again screened in abstracts and titles considering these new inclusion and exclusion criteria. If information from the abstract was not sufficient for determining eligibility, the article was sought for retrieval and assessed for eligibility in full text. The reasons for exclusion are reported for this last phase.

Finally, 28 articles met the inclusion and exclusion criteria; see the PRISMA Flow Diagram in Figure 2.

Figure 2

Flow Diagram of the search process.



Note. Produced using: Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230.

Descriptive Information

The number of participants in the studies ranged from 23 to 71,080. After excluding the three database studies (*N* = 71,080, Lee et al., 2015; *N* = 38,752, Chang et al., 2016; N = 22,452, Jerrell et al., 2013) and one meta-analysis study (*N* = 22,316. Bryant et al., 2022), the remaining studies had an average of 157 participants. The gender distribution of the participants ranges from 0% to 100% female, with an average of 31.3% female participants.

The mean age of participants at baseline ranged from 5.2 years to 15,2 years, with an average of 10.3 years. However, baseline age was only reported or applicable in 18 of the 28 studies. Besides a study of an older population (avg. 68 years), the mean age at follow-up or start of retrospective/case-control studies ranged from 12 years to 34.4 years, with an average of appx. 16,6 years. However, only nine studies out of the 28 included, reported on this measure. Overall, participants in this SR were mainly children and adolescents.

Methodological Characteristics

All studies performed statistical analyses. Among the 28 included studies, 16 were longitudinal cohort studies, five were retrospective cohort studies, five were case-control studies, one was an experimental study, and one was a meta-analysis. The meta-analysis included only randomized controlled intervention trials, wherefore none of the studies was included in the present SR. ADHD symptoms, indirect factors of ADHD and depression (symptoms and diagnosis) were assessed with; database data, clinical interviews with the subjects or parents, as well as self-, parent-, and teacher-reported questionnaires; furthermore, some studies used multiple assessment tools. Some assessments of indirect factors of ADHD also included performance tests or to ask subjects directly without a known structured questionnaire.

Moreover, eight of the 28 studies were judged to have a good quality rating (Biederman et al., 2008; Chang et al., 2016; Eyre et al. 2016; Feldman et al., 2017; Guendelman, 2016; Jerrell, 2015; Lee et al., 2015; Øie et al., 2018); seven were evaluated to have a fair quality rating (Becker et al., 2015; Chronis-Tuscano et al., 2010; Dvorsky et al., 2019; Mrug et al., 2012; Staikova et al., 2010; Daviss et al., 2008; Tallberg et al., 2022); and 11 were evaluated to have a poor quality rating (Bagwell, 2006; Chang et al., 2021; Eadeh et al., 2017; McQuade et al., 2010; McQuade et al., 2014; Semeijn et al., 2014; Blackman et al., 2005; Fischer et al. 2006; Harris et al., 2006; Mitchell et al., 2013; Drabick et al.,2006). It should be noted that one component of the assessment scale was only applicable to two of the longitudinal studies, since the studies did not contain a nonexposed group of the exposure variable of interest. Making such a group with continuous variables would be difficult, since this is a matter of grades and not either/or. This could have led the overall evaluation to be lower. Likewise, the case-control studies were all evaluated low for the *ascertainment of exposure* since this is required to be blinded and it is difficult to blind parents and subjects from the fact that the individual has depression or depressive symptoms. Full assessment manual and quality assessment is provided in Supplementary Table 1 and Appendix 3.

Direct and Indirect Causal Effects Models or Common Environmental Factors?

In this SR the investigated factors must be a direct or indirect effect of ADHD, which means that the investigated factors cannot be as frequent in the neurotypical population. The investigated factors were assumed to be unique for the ADHD population based on different evidence and logics. Some investigated factors were self-explanatory, such as ADHD type, persistence and symptoms, ADHD medication, and affiliate stigma (Chang et al., 2021), which can only be present due to the subjects' ADHD diagnosis. Other studies established the relation using a mediation analysis (Eadeh et al., 2017, Semeijn et al., 2014; Feldman et al., 2016).

However, the remaining studies exhibited weaknesses in establishing this association and the results need to be interpreted with greater caution in relation to a direct or indirect causal model. Some studies performed statistical analyses that established that the ADHD population had higher values of maltreatment (Guendelman et al., 2016) as well as social and academic difficulties (Blackman et al., 2005) than controls while controlling for depression. However, this method does not exclude the possibility that high values on these factors are due to common etiologies; therefore, support for these factors as a symptom of ADHD is discussed in each section of the discussion. Furthermore, many of the studies established the relationship between the investigated factor and ADHD through their initial statement of other research (Tallberg et al., 2022; Øie et al., 2018; McQuade et al., 2010; Dvorsky et al., 2019; Becker et al., 2020; Becker et al., 2015; Fischer et al., 2006, Mrug et al., 2012). Lastly, some studies did not state the factor's association to ADHD directly; however, based on other literature, the present author evaluated the factors as possibly dependent on the ADHD diagnosis. These factors were family conflict (Biederman et al., 2008) and maternal depression (Chronis-Tuscano et al., 2010; Harris et al., 2006), and their associations with ADHD are assessed in the discussion section.

Thematized Outcomes

In this section, the outcomes of the studies are presented narratively according to the investigated factors' overall theme – psychological, biological, or psychosocial – and further divided by the subthemes found in each category. Since all the studies were performed on an ADHD population, it is only clearly stated if the results do not apply to an ADHD population.

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
Psychological								
ADHD symptoms/persistence/type								
Bagwell 2006 NR	Externalization symptoms	N=142 M[1]=NR M[2]= 15,2 ♀ 6,3%	*ADHD-persistence:* Parent-Q, Teacher-Q, Parent-I *ADHD-desisters:* Only ADHD in childhood *Externalization symptoms:* Teacher-Q, Parent-Q	*MDD/DD*: Interview, Parent-I	N=2 T= 5.6	LNG	Poor	Being in the ADHD-persistence group compared to CG or ADHD- desisters were not associated with MDD/DD. Higher externalizing-symptoms predicted DD (OR=3,75, *) in the ADHD-population
Eyre 2019 UK	Irritability	N=124 M[1]=10.9 M[2]= 14.7 ♀ 20%*	*Irritability*: Parent-I *Persistent irritability*: Parent-I	*DEP-s*: Self-report, Parent-Q *MDD:* Parent-I	LNG	LNG	Good	Irritability predicted DEP-s (β=0.14, *) in the ADHD-population. This association attenuated when either anxiety symptoms(B) or ADHD-s(B) were included as covariates. Persistent irritability's association with DEP-s, did not attenuate, including all covariates (β=0.35, ***).
Blackman 2005 USA	ADHD symptoms Aggression	N=309 M[1]=N/A M[2]= NR R=6,6-17,5 ♀ 21%	*ADHD-s and aggression:* Self-report, Parent-Q, Teacher-Q	*Groups:* Parent-I - ADHD-only - ADHD+MDD/DD	N=1 T= N/A	CC	Poor	No difference on ADHD-s and aggression were found between groups of ADHD-only and ADHD+MDD/DD:
Daviss 2008 Texas	ADHD-s ADHD type	N=75 M[1]=N/A M[2]= 13,9 ♀40%*	*Current ADHD-s:* Parent-Q, Teacher-Q *ADHD-s at onset:* Parent-I *ADHD-age onset* *ADHD-t:* Interview, Parent-I - ADHD-IN - Other NR	*Groups:* Interview, Parent-I, Database - ADHD-only - *ADHD+ MDD*	N=1 T= N/A	CC	Fair	No difference on ADHD type, ADHD age onset, or ADHD-s (current/ at onset) were found between ADHD-only and ADHD-+MDD group
Fischer 2006 Brazil	ADHD-s ADHD type	N=320 M[1]= N/A M[2]= 34,4 ♀ 46,2%	*ADHD-s*: Self-report *ADHD-t*: Parent-I - NR	*Groups:* Parent-I - ADHD only - ADHD+MDD/DD:	N=1 T= N/A	CC	Poor	No association between ADHD type and ADHD-s and belonging to ADHD+MDD/DD group.
Tallberg 2022 Sweden	ADHD-s ADHD type	*N=111* M[1]=12,4 M[2]= 15 ♀ 30%	*ADHD-t:* Parent-Q - ADHD CT - ADHD- IN - ADHD- HI	*DEP-s:* Self report	N=2 T= 3	LNG	Fair	The ADHD-CT symptoms were associated w DEP-s. (B=0.16, **) However, in the separated models only ADHD-IN were associated w DEP-s (B=0.48, ***).

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
Chronis-Tuscano 2010 USA	ADHD type	N=125 M[1]=5,2 M[2]= NR ♀ 14,4%*	*Groups ADHD-t*: Parent-I, Teacher-Q - ADHD-HI - ADHD-CT - ADHD-IN	*MDD/DD*: Parent-I	N=11 T= 13	LNG	Fair	Children with the combined ADHD-CT (χ^2=19.73, ***; HZ= 5.59) and ADHD-IN (χ^2=6.49, *; HZ, 4.23) were at greater risk for MDD/DD than a non-ADHD CG, but ADHD-HI were not associated w. increased risk.
Lee 2015 Taiwan	ADHD type	N=71.080 M[1]= 9.3 M[2]= NR ♀19,6%*	*Groups ADHD-t:* Database - ADHD-IN - ADHD HI or CT	*MDD/DD/NOS:* Database	N=1 T= 11	Retro	Good	In comparison w ADHD-IN patients, patients w. ADHD-HI /CT were at greater risk of developing either MDD/DD/NOS (HR=1.48; **)
Øie 2018 Norway	ADHD type	N=75 M[1]=11,6 M[2]= NR ♀ 48%*	*Groups ADHD-t*: Parent-Q - ADHD-IN - ADHD-HI	*DEP-s*: Parent-Q, Self- reported	N=2 T= 2	LNG	Good	For girls a reduction in ADHD-IN was associated w. a decline in parent rated DEP-s.For both boys and girls a reduction in ADHD-IN was associated with an increase in self-reported DEP-s. Lastly, a reduction in ADHD-HI was associated w a decrease in self-reported DEP-s in boys, but an increase in girls.
				Cognition				
Tallberg 2022 Sweden	EF	*N=111* M[1]=12,4 M[2]= 15 ♀ 30%	*EF:* Parent-Q, Test - Metacognitive index - Behavioral regulation index	*DEP-s:* Self report	N=2 T=3	LNG	Fair	More problems on the metacognitive index (Parent-Q of EF) predicted DEP-s (B=0.23, ***). No test measures, or the behavioral index of EF showed effects
Øie 2018 Norway	EF	N=75 M[1]=11,6 M[2]= NR ♀ 48%*	*EF:* Test - Working memory - Inhibition - Cognitive flexibility	*DEP-s*: Parent-Q, Self- reported	N=2 T=2	LNG	Good	Inclusion of EF in models, did not result in any improvement in model fit
Mitchell 2013	Negative automatic thoughts	N=81 M[1]= N/A M[2]= 9,89 ♀ 57%	*Negative automatic thoughts*: Self-report- Q	*Groups*: Interview - ADHD only, - ADHD + depressive disorders - CG		CC	Poor	The ADHD + depression group scored higher than ADHD-only (d=0.8, ***) and CG (d=1.48, ***) on negative automatic thoughts, and the ADHD-only group higher than CG (d=0.6, **).

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
McQuade 2010 USA	Self-Perception	N= 88 M[1]=9,6 M[2]= 12 ♀ 0%	*Self-perception*: Interview - Scholastic - Behavioral - Social *Teacher perception of competence:* Teacher-I	*DEP-s:* Self-report-Q	N=2 T=2-3	LNG	Poor	No negative change in the scholastic (R^2=0.24, ***), behavioral (R^2=0.24, ***) and social (R^2=0.31, ***) self-perception protected against DEP-s. Social competency was the only domain which remained associated with DEP-s (= −.29, t (83) = −2.97, **), when entering all domains simultaneously. Teacher rated competence did not predict DEP-s.
Dvorsky 2019	Self-Worth	N=324 M[1]=12,32 M[2]= NR ♀ 29%*	*Self-worth:* Self-reported - High - increasing - Moderate - decreasing - Low - decreasing	*DEP-s:* Self-reported	N=3 T=1,5	LNG	Fair	Higher self-worth protected against DEP-s. High vs. moderate self-worth (χ^2=38.53, ***). High vs. low self-worth (χ^2=75.26, ***). Moderate vs low self-worth (χ^2=11.20, ***)
				Biological				
				Sleep				
Becker 2020 USA	Sleep restriction	N=48 M[1]=15.21 M[2]= NR ♀ 25%	*Sleep restriction*: 6.5 hours in bed allowed *Sleep extension:* 9-5 hours in bed allowed	*DEP-s*: Self-Report, Parent-Q	N= T=3 weeks	EXP		Greater DEP-s (% one questionnaire) in restricted sleep compared to extended sleep. Parent-Q (d=0.84, ***), Self-reported (d=0.31, *).
Becker 2015 USA	Sleep problems	N= 81 M[1]=12,2 M[2]= NR ♀ 24,7%	*Sleep problems*: Parent-Q	*DEP-s*: Self-report-Q	N=2 T=1	LNG	Fair	Sleep problems were positively associated w DEP-s (β = .23, *; ΔR^2 =.04)
				Medication				
Bryant 2022 UK	Medication	N=22.316 M[1]=10.8 M[2]= NR ♀ 23%	*Medication* (MPH, ATX): Used in intervention studies	*DEP-s*: Parent-Q, Self-Report, Teacher-Q, Interview	N=N/A T=N/A	MA		No evidence of neither a negative nor a positive effects of ADHD medication on risk of DEP-s
Chang 2016 Sweden	Medication	N=38752 M[1]= N/A M[2]= NR R= 8-46 ♀32%*	*Medication* (MPH, AMP, D-AMF, ATX): Database	*MDD:* Database	N=2 T=4	Retro	Good	ADHD medication reduced the risk of MDD (HR=0.58*).

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
Staikova 2010 USA	Stimulant medication	**N=97** M[1]=9,09 M[2]= NR ♀10,7%	*Groups*: Parent-I - ADHD + medicated - ADHD not medicated	*DEP-s*: Self-report *MDD/DD/NOS:* Interview, Parent-I	N=1 T=9	Retro	Fair	No difference was found between the ADHD-medicated and ADHD-not medicated group in DEP-s nor MDD/DD/NOS.
Jerrell 2013 USA	Medication	N=22.452 M[1]= <17 M[2]= NR ♀30,9%*	*Medication (*Pemoline, ATX, AMP, D-AMP, MPH): Database	*MDD:* Database	N=1 T=11	Retro	Good	All ADHD medications, except MPH were associated w increased risk of MDD. Pemoline (OR = 1.69**), ATX (OR=1.31**), D-AMP (OR=1.28**)
Lee 2015 Taiwan	Medication	N=71.080 M[1]= NR M[2]= 9.3 ♀19,6%*	*Medication* (*MPH, ATX):* database	*MDD/DD/NOS:* Database	N=1 T=11	Retro	Good	In people w ADHD-d longer duration of MPH was associated with a reduced risk of the development of MDD/DD/NOS (aOR=0.91, **). No effects were found for ATX.
Daviss 2008 Texas	Medication	N=75 M[1]=N/A M[2]= 13,9 ♀40%	*Medication* (stimulants, alpha agonists, ATX, bupropion and tricyclic antidepressants): Interview, Parent-I, Database	*Groups:* Interview, Parent-I, Database - ADHD only - ADHD+ MDD	N=1 T=N/A	CC	Fair	The ADHD- only group showed higher rates of receiving any ADHD pharmacotherapy. The time delay between first ADHD-s and first ADHD-pharmacy were greater in ADHD+MDD group. Time of first ADHD medication was predictive of MDD in a protective manner, however not when controlling for sex.
Fischer 2007 Brazil	Treatment	N=320 M[1]=N/A M[2]= 34,4 ♀ 46,2%	*Psychotherapy, medication*: Asking subjects	*Groups:* Parent-I - ADHD only - ADHD+MDD/DD	N=1 T=N/A	CC	Poor	The ADHD + MDD/DD group were more likely to have a history of psychotherapy (Wald X^2= 14.52, **; OR=3.1) and medication (Wald X^2= 4.18, *, OR=1.7)
				Psychosocial				
				Academic				
Eadeh 2017 USA	Academic impairment	N= 326 M[1]=12,26 M[2]= NR ♀ 30%*	*ADHD-s*: Parent-Q *Academic impairment*: Teacher-Q, Parent-Q *Parent-adolescent conflict*: Self-report, Parent-Q	*DEP-s*: Self- report	N=3 T=2-3	LNG	Poor	Academic impairment predicted DEP-s (F= 32.80, ***) and improved prediction of DEP-s (ΔR^2=.01, ΔF=5.05, *). The association was not mediated by parent-adolescent conflict.
Drabick 2006 USA	Academic/ functioning,	N=91 M[1]=7,9 M[2]= NR	*ADHD-d*: Differentiates between evaluation of mother and teacher	*DEP-s:* Parent-Q	N=2 T=5	LNG	Poor	Academic and cognitive performance did not predict DEP-s in ADHD- population, controlling for family and peer relations.

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
		♀ 0%	*Academic/cognitive performance*: Test, Teacher-Q					
Blackman 2005 USA	Academic achievement	N=309 M[1]=N/A M[2]= NR R=6,6-17,5 ♀ 21%	*Academic achievement*: Test, Self-report	*Groups:* Parent-I - ADHD only - ADHD + MDD/DD	N=1 T=N/A	CC	Poor	No difference in academic achievement between groups.
Fischer 2007 Brazil	School and employment	N=320 M[1]=N/A M[2]= 34,4 ♀ 46,2%	*School suspension and expulsion, grade repetition, unemployment*: Asking subjects	*Groups*: Interview - ADHD only - ADHD +MDD	N=1 T=N/A	CC	Poor	No findings on school expulsion and unemployment. The ADHD + MDD group were less likely to experience school suspension (OR=0.4) or grade repetition (0.6). This group were also more likely to be female.
				Social				
Feldman 2016 USA	Social skills	*N=124* M[1]=7,4 M[2]= NR ♀26,6%*	*ADHD-s:* Parent-Q *Social skills*: Parent-Q, Teacher-Q	*DEP-s*: Parent-Q	N=2 T=2	LNG	Good	The parent rated social skills; assertion (B= −.91, **), responsibility (B=−.33, *), and self-control (B=.56, **) and teacher rated social skills; cooperation (B=−.38, *) and assertion (B=−.40, *) negatively mediated the association between ADHD-s and later DEP-s.
Blackman 2005 USA	Social competence	N=309 M[1]=N/A M[2]= NR R=6,6-17,5 ♀ 21%	*Social competence:* Parent-Q, Teacher-Q, Self-report	*Groups:* Parent-I - ADHD only - ADHD+MDD/DD	N=1 T=N/A	CC	Poor	The ADHD + MDD/DD group showed higher impairment in social competence, than the only ADHD- group (***).
Eadeh 2017 USA	Social impairment	N= 326 M[1]=12,26 M[2]= NR ♀ 30%*	*Social impairment*: Self-report, Parent-Q *Parent-adolescent conflict*: Self-report, Parent-Q	*DEP-s*: Self- report	N=3 T=2	LNG	Poor	Impairment in social functioning predicted DEP-s (F= 36.07, ***) and improved prediction of DEP-s (ΔR^2=.03, ΔF=14.41, ***). The association was partially mediated by parent-adolescent conflict (R^2 = 15% *)
Drabick 2006 USA	Social problems	N=91 M[1]=7,9 M[2]= NR ♀ 0%	*ADHD-d:* Differentiates between evaluation of mother and teacher *Social problems*: Teacher-Q	*DEP-s*: Parent-Q	N=2 T= 5	LNG	Poor	Social problems predicted dep-s in in both mother and teacher rated ADHD (b=.19 and .18, *, respectively)
McQuade 2014 USA	Self-perceived SA	N=226 M[1]=9,7 M[2]= NR	*Peer-rated social preference:* Peer-reported *Self-perceived SA*: Self-report-Q	*DEP-s:* Self-report-Q	N=2 T=1	LNG	Poor	In children with lower peer preference, self- perceived social acceptance protected against increase in DEP-s (β=–

Table 1

Summary of reviewed studies

Author	Variable	N, M[1,2], ♀	ADHD exposure variable	Depression measure	Follow-up[3]	Design	Quality[4]	Outcome[5]
Chang 2021 Taiwan	Affiliate Stigma	N= 382 M[1]=10,9 M[2]= NR ♀19.9%*	*Affiliate Stigma*: Parent-Q	*DEP-s*: Parent-Q	N=2 T=1	LNG	Poor	Caregivers affiliate stigma predicted DEP-s (B= .260, ***), however the magnitude declined (B=.119, **) when controlling for baseline behavior problems and caregivers DEP-s(B).
				Trauma				
Semeijn 2014 Nether-lands	Adverse life events	N=23 M[1]=N/A M[2]= 68 ♀ 52%*	*Serious conflicts:* Self-report	*DEP-s*: Self-Report	N=3 T=1,6	Retro	Poor	The association between ADHD diagnosis and DEP-s was partially mediated by serious conflict (B=0.57, **)
Guendel-man 2016 USA	Maltreat-ment	N= 140 M[1]=9,6 M[2]= 19,7 ♀ 100%	*Groups:* Parent-Q, Database, Ob-servations - Maltreatment - No maltreatment	*Depression/DD*: Interview *DEP-s:* Self-report	N=3 T=10	LNG	Good	No difference between ADHD-group or control in the as-sociation between maltreatment and Depression/DD. Maltreated participants (in the ADHD-population) had higher Dep-s than did non-maltreated participant (F = 7.02, *, d = 0.54.)
Daviss 2008 Texas	Trauma	N=75 M[1]=N/A M[2]= 13,9 ♀40%	*Trauma exposure:* Self-report	*MDD:* Interview	N=1 T=N/A	Retro	Fair	The number of different traumatic event types predicted MDD (Wald X^2 = 12.01, Df=1, ***)

Note [1], Mean age at baseline time; [2], mean age at last follow-up; [3], N=Number of measurement points; T= time from baseline to last follow up in years, if not otherwise specified; [4], Global quality assessment ratings based on Newcastle-Ottawa rating scale (see appendix 2. & 3);5 *, p<0.05; **, p<0.01; ***, p<0.001

Abbreviations: ADHD-s; ADHD symptoms; ADHD-d, ADHD diagnosis; ADHD-CT, ADHD combined type; ADHD-IN; ADHD predominant inattentive type; ADHD-HI, ADHD predominant hyperactivity; DEP-s; depressive symptoms; Self-report-Q, self-reported questionnaires; Interview, Clinical interview with participant as informant; Parent-Q, Parent questionnaire; Teacher-Q, teacher questionnaire; Parent-I, Clinical interview with parent as informant; Database, database/medical record/patient register; School-E; School evaluations including, grades and exams;; MDD, Major depressive disorder; DD, dysthymic disorder; NOS, Depressive disorder not otherwise specified; w, with; B, baseline; ATX, atomoxetine; MPH, methylphenidate; LDX, lisdexamfetamine; AMP, Amphetamine; D-AMP, Dexamfetamine; L-AMF, Lis; SA, Social Acceptance;; AD, Anxiety disorder; EF, Executive function; EXP, Experiment; LNG, Longitudinal; Retro, Retrospective; CC, Case-Control; R, Range; ♀, Percentage female participants

Psychological Category

In the psychological category, the following subthemes were derived: ADHD symptoms and persistence, ADHD subtype, and cognition.

ADHD Symptoms and Persistence. Three case-control studies did not find any difference in the severity of ADHD symptoms between an ADHD group and a comorbid depression group (Fischer et al., 2006; Daviss et al., 2008; Blackman et al., 2005). Likewise, one longitudinal study found that the persistence of ADHD symptoms did not increase the risk of belonging to a comorbid depression group, compared with children who only had ADHD symptoms in childhood or children who did not have ADHD (Bagwell et al., 2006).

However, two longitudinal studies investigated more behavioral symptoms and found that the severity of externalized symptoms (Bagwell et al., 2006) and persistent irritability (Eyre et al., 2019) predicted a depression diagnosis and symptoms (Eyre et al., 2019). The effect of externalized symptoms yielded a medium effect size (OR = 3.75; Bagwell et al., 2006).

ADHD Subtype. Five studies investigated the ADHD subtype (Daviss et al., 2008; Fischer et al., 2006; Chronis-Tuscano et al., 2010; Lee et al., 2015; Øie et al., 2018), most of which found an influence of ADHD type on the risk of depression. However, two case-control studies found no influence of the type of ADHD and having comorbid depression (Daviss et al., 2008; Fischer et al., 2006). Nevertheless, these did not clearly state which type was being tested; furthermore, Fischer et al. (2006) yielded a low-quality rating.

By contrast, two longitudinal studies found that the ADHD combined type (ADHD-CT) predicts depressive symptoms (Tallberg et al., 2022) or depression (Chronis-Tuscano et al., 2010). Two studies found that only ADHD- predominantly inattentive (ADHD-IN) predicted depressive symptoms (Tallberg et al., 2022) or depression (Chronis-Tuscano et al., 2010;

Tallberg et al., 2022) compared with controls. The results of Chronis-Tuscano et al. (2010) yielded high effect sizes (HZ = 5.59 and 4.23). In opposition, one retrospective database study found that ADHD-IN did not predict a greater risk of depression compared with a combined ADHD-CT and ADHD – predominantly hyperactivity (ADHD-HI) group, which were found to increase the risk (Lee et al., 2015).

In addition, one study examined these subtypes in combination with the gender of the participants and the type of assessor of depression symptoms, revealing various patterns, which will be unfolded in discussion (Øie et al., 2018).

Executive Function. Two longitudinal studies investigated the predictive value of EFs on depressive symptoms (Tallberg et al., 2022; Øie et al., 2018), and neither found any effect of EFs assessed by performance tests on depressive symptoms. However, one of the studies also assessed EF using a parent questionnaire and found the metacognitive index to be a predictor of depressive symptoms (Tallberg et al., 2022).

Self-Perception. Three studies found that aspects related to self-perception influence depressive symptoms (McQuade et al., 2010; Mitchell et al., 2013; Dvorsky et al., 2019). One case-control study found higher values of negative automatic thoughts in the comorbid group than in the ADHD-only group, yielding a high effect size (d = 0.8; Mitchell et al., 2013). Another study found a decrease in self-perception of social competencies to predict an increase in depressive symptoms, with a medium effect size (McQuade et al., 2010). Furthermore, teachers' perception of competence did not predict depressive symptoms or affect the results. The last of the three studies found that lower self-worth increased the risk of depressive symptoms (Dvorsky et al., 2019).

Biological Category

In the biological category, the two subthemes of sleep and medication were derived.

Sleep. Two studies found that sleep problems in children with ADHD predicted depressive symptoms (Becker et al., 2020; Becker et al., 2015). One of the studies was experimental and revealed a high effect size (d = .84) for parent-rated depressive symptoms and a small effect size for self-reported depressive symptoms (d = .31; Becker et al., 2020).

Medication. Seven studies examined whether the use of different ADHD medications predicted later depression and most found that ADHD medications had no effect (Bryant et al., 2022; Staikova et al., 2010; Lee et al., 2015) or even a protective role against depression (Chang et al., 2016; Lee et al., 2015; Daviss et al., 2008). However, low effect sizes were found for this protective role (HZ = .58, Chang et al., 2016; OR = .91, Lee et al., 2015).

By contrast, two studies found that medications or psychotherapy increased the risk of depression or belonging to a comorbid depression group (Jerrell et al., 2013; Fischer et al., 2006). Jerrell et al. (2013) found low effect sizes (OR = 1.69, 1.31, 1.28), whereas Fischer et al. (2006) found a medium effect size (OR = 3.1) for psychotherapy and a low effect size (OR = 1.7) for medications.

Psychosocial Category

In the psychosocial category, the following subthemes were derived: academic domain, social skills and relations domain, family domain, and trauma.

Academic Domain. Four studies investigated the impact of academic performance on the development of depression or depressive symptoms and reported mixed findings (Blackman et al., 2005; Eadeh et al., 2017; Drabick et al., 2006; Fisher et al., 2006). One study found a low effect size ($R^2 = .01$) for academic functioning as a mediator between ADHD symptoms and later depressive symptoms (Eadeh et al., 2017). By contrast, two studies found that academic factors did not predict depressive symptoms (Drabick et al., 2006) or belonging to a comorbid depression group (Blackman et al., 2005). The last study investigated school suspension and grade repetition, finding the group with comorbid depression to be less likely to get suspended or repeat a grade (Fischer et al., 2006). However, these findings yielded low effect sizes (OR = .4, .6).

Social Skills and Relations Domain. Seven studies investigated a social component, and five of these found social elements to influence later depressive symptoms (Feldman et al., 2017; Eadeh et al., 2017; Drabick et al., 2006; McQuade et al., 2014) or depression (Blackman et al., 2005). Eadeh et al. (2017) found a low effect size ($R^2 = .03$) of the mediating role of social functioning between ADHD symptoms and depressive symptoms. Two studies found no effect of social elements on depressive symptoms (Mrug et al., 2012) or depression (Bagwell et al., 2006).

Family Domain. Five studies investigated factors related to family (Drabick et al., 2006; Biederman et al., 2008; Harris et al., 2006; Chronis-Tuscano et al., 2010; Chang et al. 2021). Notably, mixed findings were reported on the role of family conflict. One study found parenting behaviors and family environment to predict depressive symptoms (Drabick et al., 2006), whereas one other study found that familial conflict did not predict depression (Biederman et al., 2008) and another found that familial functioning or marital adjustment did not differ across the ADHD-only and comorbid depression groups (Harris et al., 2006).

Regarding the role of maternal psychopathology, a consensus was found to exist. Two studies found maternal psychopathology to predict depression in children with ADHD (Harris et al., 2006; Chronis-Tuscano et al., 2010). Harris et al. (2006) found medium effect sizes for maternal anxiety (d = .57) and depression (d = .78), and Chronis-Tuscano et al. (2010) found a low effect size for maternal depression (HZ = 2.08). In addition, a third study found another effect related to caregivers (Chang et al. 2021). Specifically, it found an increase in caregiver affiliate stigma to predict depressive symptoms in children, even when it controlled for caregivers' depressive symptoms and child problem behavior at baseline.

Trauma. Three studies investigated traumas and adverse life events, and all of them found some predictive effects for depressive symptoms/depression. One study found that the group of maltreated participants with ADHD had higher values of depressive symptoms, with a medium effect size (D = .54; Guendelman et al., 2016). However, in the same study, maltreatment was not found to influence the risk of a depression diagnosis (Guendelman et al., 2016). One study found effects of the number of different traumatic life events to predict MDD (Daviss et al., 2008), while another found serious conflict to mediate the prediction between ADHD diagnosis and depressive symptoms (Semeijn et al., 2014).

Discussion

This SR investigated which direct and indirect factors of an ADHD diagnosis that predicts the risk of depression in people with ADHD. In this section, the results for each identified aspect are interpreted in relation to other findings, and suggestions for future research directions are provided. Lastly, overall methodological issues and their implications for further investigations are presented.

ADHD Symptoms

The included studies did not identify a link between the severity of ADHD symptoms and belonging to a comorbid depression group. This finding conflicts with those of other non-included studies (Powell et al., 2020; Michielsen et al., 2012; Roy et al. 2014; Seymour et al., 2014), which have found that ADHD symptoms predict later depression. Two main differences between the included studies and these other studies, is (1) a longitudinal versus a case-control design; and (2) the inclusion of clinical versus subclinical levels of ADHD.

Most of the included studies (3 of 4) that found no effects involved case-control designs in which the ADHD symptoms were measured at the same time as depression and not years before depression onset, in opposition to the longitudinal research of the non-included studies (Powell et al., 2020; Michielsen et al., 2012, Roy et al. 2014; Seymour et al., 2014). Suggesting that ADHD symptoms existing years before depression onset could be of greater importance, than at the time of onset of depression. However, this suggestion was contradicted by the case-control study of Daviss et al. (2008), which also measured ADHD symptoms at ADHD onset and found no difference in symptoms between the ADHD only group and comorbid depression group. Likewise, Bagwell et al. (2006) found no effect of either childhood ADHD or persistent ADHD on depression.

The second proposed explanation for the nonfindings involves the populations investigated. This SR only included participants with clinical levels of ADHD, whereas Roy et al. (2014), Seymour et al. (2014), and Powell et al. (2020) and Michielsen et al. (2012) investigated subclinical ADHD levels in community populations. This discrepancy suggests that ADHD symptom severity is more important when assessing the risk of depression in populations with subclinical ADHD levels, such as community samples, rather than in clinical populations. It is possible that children with ADHD have exceeded a critical level of ADHD symptoms, where

more symptoms do not influence a higher risk of depression. This idea implies that areas other than symptom severity should be assessed to understand why some people with ADHD develop depression and others do not.

One possible explanation for why people with the same level of ADHD symptoms exhibit varied risks could be that the symptoms yield different responses in different environments. Investigating this suggestion could result in research on the moderating role of environmental factors in the association between ADHD symptoms and depression, such as the psychological robustness of caregivers.

Another suggestion is that specific types or aspects of ADHD symptoms—rather than severity—determine whether individuals experience difficulties. This SR found agreement among the studies that groups with more behavioral or irritability problems had an increased risk of later depression. Authors of a recent study have argued for an irritability ADHD subtype, which seems to predict the onset of psychiatric comorbidities (Karalunas et al., 2019). However, they found no effect between irritability type and (overall) mood disorders. However, another cross-sectional study found an association between irritability and depression in ADHD diagnosed (Eyre et al., 2017). In addition, investigating the new DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD) would be interesting, considering it is correlated with both irritability and depression (Eyre et al., 2017). It also correlates with current maternal depression, which was another aspect detected in this SR (Eyre et al., 2019), suggesting that irritability might affect depression by initiating maternal depression. However, it cannot be ruled out that these associations occur because of a genetic liability between the irritability subtype and depression.

Overall, it appears that more specific characteristics than just ADHD symptoms are required to understand the processes related to depression in clinical groups. The irritability subtype is a promising direction that should be investigated further. In addition, future

researchers should consider their research aim when deciding whether to include subclinical or clinical levels of ADHD.

ADHD Subtype

Regarding ADHD subtypes, this SR revealed mixed findings, and the varied methodologies in the studies could explain the disparate results. For example, the only study that combined ADHD-CT and ADHD-HI into one group found ADHD-HI to predict depression (Lee, 2015). Furthermore, the two case-control studies both found no effect of subtype and belonging to a comorbid depression group. However, these studies measured subtype and depression at the same time-point, and therefore lack the ability to disprove a potential causal mechanism if another subtype was dominant earlier.

Nevertheless, an overweight of the studies found elements of inattention, either predominant inattention or combined, to increase the risk of depression. In addition, the meta-analytic review of Meinzer et al. (2014) found that the correlations between ADHD and depression had higher effect sizes when later DSM editions, which emphasize inattention, were used. Other studies have similarly found an association between ADHD-IN and internalizing symptoms but not an association of ADHD-HI (Humphreys et al., 2013; Meinzer et al., 2014, p. 603). One explanation for the influence of inattention might be its relationship with self-worth (Kita & Inoue, 2017), which also correlates with later depression and is discussed in a later section on self-perception. However, additional explanation models should be investigated in the future.

The most complex results to interpret regarding the ADHD subtype were those of Øie et al. (2018), in which a decrease in ADHD-IN led to decrease in parent-reported symptoms and increase in self-reported symptoms. Øie et al. (2018) suggested that the differences in self- and parent-rated depression symptoms, could have been caused by parents mixing depression and

ADHD symptoms or participants exaggerating their symptoms. However, two studies from the SR both found belonging to or having more symptoms of ADHD-IN and ADHD-CT predicted depression, when using self-reported depressive symptom (Tallberg, 2022) and parent interview (Chronis-Tuscano et al., 2010), respectively. This leaves the question of why an increase in self-reported symptoms exists when ADHD-IN increase in Øie et al. (2018). Hence more studies should investigate if a difference appear between self-report and parent-report in the future.

Another complex finding from Øie et al. (2018) includes different findings between gender. The boys differed from the girls in that a reduction in severity of ADHD-HI decreased self-reported depression symptoms in boys but increased them in girls (Øie et al., 2018). These results cannot be compared to other findings from this SR, since it was the only study to present results for each gender. Several suggestions and discussion of the reason for these results are made in Øie et al. (2018). However, these will not be presented and discussed here, due to space limitations.

Executive Function

Mayer et al. (2021) suggested that executive dysfunction, especially selective attention, verbal fluency, and working memory, could explain the comorbidity of ADHD and depression, and the author called for longitudinal studies on this matter. However, a longitudinal study from this SR that investigated EF performance and working memory did not reveal an effect (Øie et al., 2018). However, the analyses controlled for ADHD symptoms, which could have overlapped with executive dysfunction and hid any effect.

In another study, a metacognitive element of EF was found to be of importance (Tallberg et al., 2022). This element measures the ability to self-manage and monitor one's own behavior and performance (Tallberg et al., 2022). An association between metacognitive EF and social

functioning was found in an autism spectrum disorder population (Torske et al., 2018), and this relationship might also be present in ADHD populations, suggesting that metacognitive abilities influence depression through its effects on social functioning.

Overall, EF should be investigated further because only one longitudinal study has investigated the effects of performance tests and only one has examined everyday EF through a parent questionnaire. This metacognitive element in particular should be investigated further, along with its potential relationship with social functioning.

Family Functioning

Meinzer at al. (2014) proposed that family dysfunction explains a covariation between ADHD and depression. The study referred to the negative-reactive response pattern theory (Johnston, 1996), which suggests that the higher rates of disruptive behavior that children with ADHD exhibit lead to more negative parenting styles. However, it cannot be ruled out that this pattern occurs from parenting practices affecting ADHD symptoms. This relationship needs to be examined in longitudinal studies to establish directionality.

Regarding parent management, one cross-sectional study of children with ADHD supported the idea that parent management and child locus of control (Ostrander & Herman, 2006) mediate the association between ADHD symptoms and depressive symptoms. Another longitudinal study in a community population found that parent–child dysfunction predicted depressive symptoms (Humphreys et al., 2013), although the longitudinal studies included in this SR reported inconsistent findings. Two included studies that used the exact same measures of family functioning (Moos & Moos, 1987) reported opposite findings (Biederman et al., 2008; Drabick et al., 2006). However, the study that found effects of family functioning investigated only male participants (Drabick et al., 2006), whereas the study that found no effects investigated only

female participants (Biederman et al., 2008). The final longitudinal study included in this review, which did not find effects, did not report on gender distribution (Harris et al., 2006).

Another important difference was that Drabick et al.'s study (2006) was the only one to investigate depressive symptoms and not depression diagnoses. Thus, it is likely that family functioning affects depressive symptoms, but the effect is not strong enough to yield a prediction of a depression diagnosis. Likewise, another study in this SR reporting that social impairment predicted depressive symptoms found that parent–adolescent conflict mediated this prediction (Eadeh et al., 2017).

Overall, it seems that family functioning might affect depressive symptoms but not depression diagnosis; however, more studies are needed to confirm this. It should also be considered whether gender differences exist in how family functioning affects individuals. In addition, it could be questioned whether family function and parenting practices represent the same variable or two different factors, in which case parenting practices should be investigated in longitudinal studies with clinical samples.

Caregiver Depression

The abovementioned negative-reactive response pattern theory (Johntson, 1996) also suggests that higher rates of disruptive behavior lead to low self-esteem in parents (Meinzer et al., 2014), which could be related to caregiver depression. It could be that low self-esteem, as well as stress, parental disagreements, and stigmatization related to having a child with ADHD, contributes to increased depression in caregivers; however, this hypothetical relationship has not been established in the literature, and one should be aware that a genetic liability could also explain the correlation between maternal and child depression. Although a consensus existed in this SR that maternal or caregiver depression predicts the risk of depression in children, one study had a case-control design measuring both variables at the same time-point and was therefore note

capable to infer causality (Harris et al., 2006). Furthermore, the longitudinal study did not perform mediation analyses to establish the relationship with initial ADHD symptoms/diagnosis (Chronis-Tuscano et al., 2010). However, Chang et al. (2021) found that the affiliate stigma of the mother influenced not only maternal depression but also child depression independent of the mother's depression, indicating that the affiliate stigma of having a child with ADHD could explain maternal depression and likewise influence depression in other ways, perhaps through the aforementioned parenting practices.

To summarize, caregiver depression appears to be a critical aspect in relation to depression in the ADHD population. However, uncertainties exist regarding the cause of caregiver depression and its relation to the child's ADHD diagnosis, but affiliate stigma is one suggestion.

Academic Difficulties

The studies on whether academic difficulties explain future depression yielded mixed findings. Different interpretation of this findings will be presented in this section.

Fisher found that people with comorbid ADHD and depression were less likely to be suspended or repeat a grade, but this group was also more likely to be female, possibly affecting the results, as girls might function better overall in school (Spinath et al., 2014). Future studies should be aware of gender bias when investigating the scholastic domain

Blackman et al. (2005) that found no effects of academic difficulties had a case-control design not including retrospective measures. This type of method could potentially exclude causational effects of earlier academical struggles. It could be assumed that former academic struggles could lead to a negative self-perception style or perception of others attitude toward one, that would continue to affect depression, even if academic struggles attenuate. Furthermore, a range of cognitive model suggests that impaired self-perception or negative attributional style

as generated by negative life experience, can form a path of cognitive vulnerability that increase the risk of developing depression (Jacobs et al., 2008).

Different assessment tools could also explain the variations in findings. Blackman et al. (2005) established academic competency, based on tested reading skills, teacher-rated study skills, and self-rated intellectual or academic competencies (Blackman et al., 2005). Drabick et al. (2006) that likewise found no effects measured academic competencies, as reading skills, IQ, and teacher perception of performance. By contrast, Eadeh et al. (2017), who did find effects, used behavioral measures in addition to specific academic competence and skills also. These behavioral measures included the Impairment Rating Scale (IRS) and subscales of the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P). The IRS measures how children's problems interact with their academic progress, and the subscales of the WFIRS-P investigate how the children's emotional or behavioral problems affect learning and behavior in school. The learning area targets whether the children require further help, have trouble with homework, or receive grades lower than their abilities. The behavioral component includes questions regarding having problems in the school yard, getting "time-outs," and missing classes or being late.

These varied measurements indicate that these studies defined academic functioning differently, and it can be argued that measuring difficulties in learning situations rather than perceptions of competencies is more likely to result in a prediction of depression. One explanation is that the relationship to depression is dependent on feelings of not fitting in or belonging in school, which have been found to account for 33.6% of depressive symptoms in a normal population (Parr et al., 2020). In addition, one retrospective study found that high school victimization, exclusionary discipline, and a sense of school belonging predicted the internalization of symptoms in a population with ADHD and learning disabilities (Zapata, 2022).

Therefore, it could be interesting to investigate the perception of failure, school dissatisfaction, and conflicts at school rather than or supplemental to actual performance or perceived performance of the teacher and parents.

Based on these suggestions, future researchers should be aware of how they assess academic difficulties. It would be beneficial to focus on the learning milieu and possibly children's perceptions of difficulties.

Social domain

According to most of the studies included in this SR, social difficulties seem to predict depression in people with ADHD. This explanation model has some level of internal consistency, as it is well established that children with ADHD have social difficulties (Ros & Graziano, 2018) and that social difficulties are associated with depression; however, the causality of this relationship has not been determined (Segrin, 1990).

Regarding social functioning or skills, four of the five studies found that overall social functioning or social skills predicted depression. No obvious reason exists for the contradictory findings of Bagwell et al. (2006). This suggests that social functioning is most likely an influential factor, but a better understanding is needed of which factors lead some studies not to find effects.

Regarding peer relations a previous SR found bullying to be a possible mediator or moderator of the relationship between ADHD and depression (Simmons & Antshel, 2021). However, another study in this SR did not find effects of friendship or peer rejection (Mrug et al., 2012). In contrast to most of the studies in the SR of Simmons and Antshel (2021), this study measured social elements through the reports of peers rather than parents, which is not a

validated method. It can be assumed that children answer differently if told it is wrong to dislike others instead of answering what they think the right answer is.

Another critical factor to consider is gender. Simmons and Antshel (2021) mentioned that the results of their review were mostly representative of males with ADHD. The study in this SR that investigated peer relations was also overweighted with male participants, with only 20% of the participants being female (Mrug et al., 2012). In addition, Roy et al. (2015) found that victimization and peer-dislike mediated the relationship between ADHD symptoms and depression only in female participants. This could explain why Mrug et al. (2012), found no effects. Thus, future researchers should be more aware of gender differences and attempt to recruit a sufficient number of female participants to perform a robust gender analysis.

Self-Perception

In this SR, a consensus existed among the studies regarding the protective roles of high self-worth and positive self-perception against the development of depression as well a negative role of negative automatic thoughts. The protective effects of self-perception were also found in one of the included studies on social components. This study found that the perception of social acceptance protected against depression in children with low peer preference (McQuade et al., 2014). The same findings were obtained in two cross-sectional studies in the SR of Simmons and Antshel (2021), in which the perception of social acceptance protected against the effects of bullying. These results are similar to those of another study in this SR, which found the perception of social competency to be predictive of depression (McQuade et al., 2010). This result suggests that a child's perception can act as a protector and is necessary to access in addition to observable social functioning, which was mentioned previously.

The studies did not agree regarding whether ADHD diagnoses increased or decreased this self-perception. One of the studies assumed self-perception to be a resilience factor, based on indications of a positive illusory bias in children with ADHD compared with controls in earlier research (McQuade et al., 2010). However, researchers in another study had a basic understanding that self-worth was generally lower in people with ADHD (Dvorsky et al., 2019). It is possible that both concepts are true. Studies found that even though children with ADHD underestimated their performance compared with teacher or parent reports, they still reported higher levels of difficulties (Colomer et al., 2020) or lower self-perception than their peers (Barber et al., 2005). These results suggest that although children with ADHD might have lower self-worth due to poor performance, they are protected from an even lower sense of self-worth through positive illusory bias.

In addition, inattentive symptoms might affect such self-perceptions. One study found that inattention was associated with global self-worth, but hyperactivity was not found to be associated with it. Furthermore, global self-worth was correlated with depression (Kita & Inoue, 2017). Likewise, Mitchell et al. (2013) found that inattention symptoms, but not hyperactivity symptoms, predicted negative automatic thoughts. This result indicates that self-worth and negative automatic thoughts are more pronounced in the ADHD-IN subtype than in the ADHD-HI subtype, and these pathways should be considered in future studies. This suggestion is in line with the present SR's indication that ADHD-IN predicts depression better than ADHD-HI.

Trauma

Overall, the results suggest that elements of trauma are predictive factors for depression. However, uncertainties exist regarding the explanations of the relationship between ADHD and maltreatment or trauma. One theory is that ADHD increases the risk of later trauma through poor

self-regulation, which could place children in harmful position. It was proposed that distractibility and hyperactivity can lead to conflicts or attachment issues. Furthermore, it was suggested that ADHD behaviors in more impulsive individuals may increase the risk of accidental trauma (Ford et al.,2000). However, trauma and maltreatment were also proposed to exacerbate ADHD, making it difficult to interpret a relationship between trauma and ADHD (Ford et al. ,2000). Likewise, Guendelman et al. (2016) reported that they were unable to determine whether the effects were unique to the ADHD population.

In addition, one of the studies found that the number of different traumatic events was important (Daviss et al., 2008). The article did not state any association between having ADHD and a greater number of different traumatic events. However, one study of people with alcohol dependence found the subgroup with ADHD to have had more experiences of potentially traumatic events (Luderer et al., 2020). This tendency could be theorized to be related to the many different theories for how ADHD can affect conflict or unwanted situations, as briefly mentioned above. Other potential aspects include (1) exhibiting higher risk-taking behavior, leading to dangerous situations (Pollak, 2019); (2) having more conflicts with others due to social skill difficulties or temperamental difficulties; (3) seeking the company of other at risk-groups, increasing the risk of experiencing death; and (4) facing the genetic risk of having family members with psychopathology, which would also increase the risk of experiencing adverse sickness or death.

To summarize, the various studies have found that different aspects of traumatic experiences, or the number of events experienced, could predict depression or depressive symptoms in an ADHD population. Indications exist that this could be related to indirect causal processes, but uncertainties remain, and the relationship could be a matter of a common etiology. Therefore, the logic behind this relationship should be investigated further.

Medication

Daviss et al. (2008) included concerns regarding a negative effect of ADHD medication on later depression in their review due to results from animal studies. However, most studies included in this SR found that medications do not have an influence on later depression, and some even found positive effects of medication. Furthermore, it should be noted that one of the two studies that found medication to be a risk exhibited a poor quality rating and used unvalidated or reliable methods to access medication (Fisher, 2007). By contrast, all other studies had a fair or good evaluation and most used database data (Lee et al., 2015; Jerrell et al., 2013; Chang et al., 2016) or a meta-analysis (Bryant et al., 2022), and they had very high (<20,000) numbers of participants (Lee et al., 2015; Jerrell, et al., 2013; Chang et al., 2016, Bryant et al., 2022). The other study to find medication to be a risk inferred that susceptible individuals may be affected by certain ADHD medication, but the overall risk was assessed as low (Jerrell et al., 2013). In addition, the study did not control for ADHD severity, which could mean that persons with more symptoms were more likely to receive medication but were also more likely to develop depression.

Overall, these studies have established that ADHD medications most likely do not increase the risk of depression.

Sleep Problems

A consensus existed in this SR that sleep problems have negative effects on depressive symptoms in people with ADHD. However, since only two studies investigated this area and both only investigated the symptoms and not the diagnosis, more studies should be conducted to confirm this effect on clinical depression. ADHD is considered to be associated with a range of sleep disorders, which could explain the sleep problems measured in the studies (Alfano &

Gamble, 2009). One of the studies in this SR was experimental and demonstrated that being put in an extended sleep condition affects fewer depressive symptoms. This suggests that these sleep problems could be managed and are not entirely caused by not being able to sleep more. A cross-sectional study suggested that nighttime media use is a factor, since associations between more nighttime media use and less sleep as well as an increase in depressive symptoms were found in people with ADHD (Becker & Lienesch, 2018).

Methodological Issues

Overall, the studies included in this SR were of a high quality compared with many of the studies referred to in earlier reviews, such as those of Meinzer et al. (2014), Daviss (2008) and Thapar et al. (2023), due to the inclusion criteria in this SR of studies being longitudinal, case-control, retrospective, and experimental, as well as participants having clinical levels of ADHD. However, the following methodological issues still existed in the included studies: gender distribution and a lack of mediation analyses. These issues are discussed further in the following subsections.

Gender Distribution

Overall, the participants of the included studies were heavily weighted toward males, with only 31.7% of the participants being female. Most studies controlled for gender in their analysis, but few considered the genders potential impact on the variable of interest. Those who did, found suggestions, that gender interact with the effect of subtypes of ADHD (Øie et al., 2018) and peer influence (Roy et al., 2015). Future research must focus on initially disentangling gender influence as a confounder or a moderator, and implement this finding in the analysis, to avoid incorrect findings (Shapiro et al.,2021).

Lack of Mediation Analyses

Only a few of the included studies (Semeijn et al., 2014, Eadeh et al., 2017, Feldman et al., 2017) used a mediation analysis, establishing that the investigated factors work as a mediator between ADHD and depression. The lack of a mediation analysis makes it more difficult to determine whether the investigated factor was a product of the ADHD diagnosis as well as whether the factor explained the effect from ADHD to depression.

Future Research

Recommendations for future research on each factor investigated have been presented individually in each section. Overall recommendations for future research are to include more female participants as well as a greater focus on mediation analyses in longitudinal research. Lastly, the investigated factors in this research do not constitute a full list of factors of interest; many other factors have been proposed and only investigated cross-sectionally or in community samples. Examples of relevant areas not included in this review include emotion regulation, attachment type, and loneliness. Thus, more longitudinal research is required in these areas.

Limitations

This SR had some limitations. First, just one author performed the search, sorting process, and quality assessment alone, and therefore, a consensus was not established. Thus, it is possible that others could interpret the inclusion and exclusion criteria as well as the quality assessment definitions differently. Second, the peer-reviewed criteria could mean that studies that have found no results are less representative due to them not being as likely to seek publication. This is called the "file drawer" effect, which would leave the impression that more studies find effects than is actually the case. Lastly, the results of this SR are limited in that it did not include other somatic and

psychological comorbidities, which could potentially develop from ADHD and lead to later depression.

Conclusion

To summarize the results of this review, a range of factors related to ADHD seems of importance in the development of depression in the ADHD-population. Where most consensus exists regarding; (1) a negative effect of having; the ADHD-IN subtype, decreasing self-perception, sleep problems, maternal psychopathology, traumatic events, and social difficulties; (2) no effect of ADHD medication and performance EF. Mixed findings exist regarding ADHD symptoms, academic difficulties, and the family environments influence.

However, some uncertainty still exists whether these factors act as direct and indirect factors of the ADHD diagnosis. Likewise, investigation of possible gender differences is lacking on most areas.

Conflict of interest

There are no conflicts of interests to disclose

Supplementary tables

Table S1 modified Newcastle-Ottawa Quality Assessment

Full Quality Assessment on included cohort and case-control studies according to the modified Newcastle-Ottawa Quality Assessment (See appendix 2)

	Cohort studies								
Study/author	Selection				Comparability	Outcome			Global
	Representativeness	Non-exposed	Ascertainment of exposure	Outcome T1		Assessment of outcome	Follow-up time	Follow-up cohort	
Bagwell (2006)	C	N/A	B*	B	*	B*	A*	B*	Poor
Becker (2015)	A*	N/A	B*	A*	**	C	B	B*	Fair
Biederman (2008)	B*	N/A	B*	A*	*	A*	A*	A*	Good
Chang (2021)	C	N/A	B*	A*	**	C	B	A*	Poor
Chang (2016)	B*	N/A	A*	A*	**	B*	B	A*	Good
Chronis-Tuscano (2010)	B*	N/A	B*	B	**	B*	A*	A*	Fair
Drabick (2006)	B*	N/A	C	B	**	C	A*	C	Poor
Dvorsky (2019)	B*	N/A	B*	B	**	B*	B	B*	Fair
Eadeh (2017)	A*	N/A	B*	A*	**	B*	B	N/D	Poor
Eyre (2019)	B*	N/A	B*	A*	**	C	A*	B*	Good
Feldman (2017)	B*	N/A	B*	A*	**	B*	B	A*	Good
Guendelman (2016)	B*	A*	B*	A*	**	B*	A*	B*	Good
Jerrell (2015)	B*	N/A	A*	B?	**	A*	A*	A*	Good
Lee (2015)	A*	N/A	A*	A*	**	A*	A*	A*	Good
McQuade (2010)	C	N/A	C	A*	*	B*	A*	B*	Poor
McQuade (2014)	B*	N/A	C	A*		B*	B	B*	Poor
Mrug (2012)	B*	N/A	C	A*	**	B*	A*	B*	Fair
Øie (2018)	B*	N/A	B*	A*	*	B*	B	B*	Good
Semeijn (2014)	A*	N/A	C	B	*	B*	A*	A*	Poor
Staikova (2010)	D	A*	B*	B	*	B*	A*	D	Fair
Tallberg	C	N/A	B*	A*	*	B*	A*	B*	Fair

Case-control studies

	Selection				Comparability	Exposure			Global
	Case-definition	Case representa-tiveness	Selection of controls	Definition of controls		Ascertainment of ex-posure	Same method	Non-response rate	
Blackman (2005)	A*	A*	A*	N/D		C	A*	C	Poor
Daviss et al. (2008)	B	A*	A*	A*	**	C	A*	A*	Fair
Fischer (2006)	B	A*	A*	A*		C	A*	A*	Poor
Harris (2006)	A*	A*	A*	N/D		C	A*	A*	Poor
Mitchell (2013)	A*	A*	A*	N/D	*	C	A*	N/D	Poor

Note *, Appropriate score influencing global score (see appendix); N/A, Not Applicable; N/D, No Description; A, B and C, different meaning according to component, however A is considered best and C worst (see appendix 2)

References

Agnew-Blais J.C., Polanczyk, G.V., Danese, A., Wertz, J., Moffitt, T.E., Arseneault, L. (2016) Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood. *JAMA Psychiatry.*;73(7):713–720. doi:10.1001/jamapsychiatry.2016.0465

Alfano, C. A. & Gamble, A. L. (2009). The Role of Sleep in Childhood Psychiatric Disorders. Child and Youth Care Forum., 38(6), 327–340. https://doi.org/10.1007/s10566-009-9081-y

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *40*(1), 57-87. https://doi.org/10.1111/1469-7610.00424

Asherson, P., & Agnew-Blais, J. (2019). Annual Research Review: Does late-onset attention-deficit/hyperactivity disorder exist? *Journal of Child Psychology and Psychiatry*, *60*(4), 333-352. https://doi.org/10.1111/jcpp.13020

Bagwell, C. L., Molina, B. S. G., Kashdan, T. B., Pelham, W. E., & Hoza, B. (2006). Anxiety and Mood Disorders in Adolescents With Childhood Attention-Deficit/Hyperactivity Disorder. Journal of Emotional and Behavioral Disorders, 14(3), 178–187. https://doi.org/10.1177/10634266060140030501

Bakker, M. P., Ormel, J., Verhulst, F. C., & Oldehinkel, A. J. (2010). Peer Stressors and Gender Differences in Adolescents' Mental Health: The TRAILS Study. Journal of Adolescent Health, 46(5), 444–450. https://doi.org/10.1016/j.jadohealth.2009.10.002

Barber, S., Grubbs, L., & Cottrell, B. (2005). Self-Perception in Children with Attention Deficit/Hyperactivity Disorder. Journal of Pediatric Nursing, 20(4), 235–245. https://doi.org/10.1016/j.pedn.2005.02.012

Becker, S. P., Langberg, J. M., & Evans, S. W. (2015). Sleep problems predict comorbid externalizing behaviors and depression in young adolescents with attention-deficit/hyperactivity disorder. European Child & Adolescent Psychiatry, 24(8), 897–907. https://doi.org/10.1007/s00787-014-0636-6

Becker, S. P., & Lienesch, J. A. (2018). Nighttime media use in adolescents with ADHD: links to sleep problems and internalizing symptoms. Sleep Medicine, 51, 171–178. https://doi.org/10.1016/j.sleep.2018.06.021

Becker, S. P., Tamm, L., Epstein, J. N., & Beebe, D. W. (2020). Impact of sleep restriction on affective functioning in adolescents with attention-deficit/hyperactivity disorder. Journal of Child Psychology and Psychiatry, 61(10), 1160–1168. https://doi.org/10.1111/jcpp.13235

Biederman, J., Ball, S. W., Monuteaux, M. C., Mick, E., Spencer, T. J., McCreary, M., ... & Faraone, S. V. (2008). New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(4), 426-434. https://doi.org/10.1097/CHI.0b013e31816429d3

Biederman, J., Faraone, S., Mick, E., & Lelon, E. (1995). Psychiatric comorbidity among referred juveniles with major depression: fact or artifact?. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*(5), 579-590.

Blackman, G. L., Ostrander, R., & Herman, K. C. (2005). Children with ADHD and depression: a multisource, multimethod assessment of clinical, social, and academic functioning. *Journal of Attention Disorders*, *8*(4), 195-207. https://doi.org/10.1177/108705470527877

Bryant, A., Schlesinger, H., Sideri, A., Holmes, J., Buitelaar, J., & Meiser-Stedman, R. (2022). A meta-analytic review of the impact of ADHD medications on anxiety and depression in

children and adolescents. European Child & Adolescent Psychiatry. https://doi.org/10.1007/s00787-022-02004-8

Catalá-López, F., Hutton, B., Page, M. J., Driver, J. A., Ridao, M., Alonso-Arroyo, A., ... & Tabarés-Seisdedos, R. (2022). Mortality in persons with autism spectrum disorder or attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *JAMA pediatrics*, e216401-e216401. https://doi.org/10.1186/s13643-017-0581-9

Chang, Chen, Y.-M., Hsiao, R. C., Chou, W.-J., & Yen, C.-F. (2021). Did affiliate stigma predict affective and behavioral outcomes in caregivers and their children with attention-deficit/hyperactivity disorder? International Journal of Environmental Research and Public Health, 18(14). https://doi.org/10.3390/ijerph18147532

Chang, C., D'Onofrio, B. M., Quinn, P. D., Lichtenstein, P., & Larsson, H. (2016). Medication for attention deficit/hyperactivity disorder and risk for depression: A nationwide longitudinal cohort study. Biological Psychiatry (1969), 80(12), 916–922. https://doi.org/10.1016/j.biopsych.2016.02.018

Chen, T. J., Ji, C. Y., Wang, S. S., Lichtenstein, P., Larsson, H., & Chang, Z. (2016). Genetic and environmental influences on the relationship between ADHD symptoms and internalizing problems: A Chinese twin study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *171*(7), 931-937. https://doi.org/10.1002/ajmg.b.32411

Cheung, K., Aberdeen, K., Ward, M. A., & Theule, J. (2018). Maternal Depression in Families of Children with ADHD: A Meta-Analysis. Journal of Child and Family Studies, 27(4), 1015–1028. https://doi.org/10.1007/s10826-018-1017-4

Jacobs, R. H., Reinecke, M. A., Gollan, J. K., & Kane, P. (2008). Empirical evidence of cognitive vulnerability for depression among children and adolescents: A cognitive science and

developmental perspective. *Clinical psychology review*, *28*(5), 759-782. https://doi.org/10.1016/j.cpr.2007.10.006

Chronis-Tuscano, A., Molina, B. S., Pelham, W. E., Applegate, B., Dahlke, A., Overmyer, M., & Lahey, B. B. (2010). Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. *Archives of general psychiatry*, *67*(10), 1044-1051 doi:10.1001/archgenpsychiatry.2010.127

Pollak, Y., Dekkers, T. ., Shoham, R., & Huizenga, H. . (2019). Risk-Taking Behavior in Attention Deficit/Hyperactivity Disorder (ADHD): a Review of Potential Underlying Mechanisms and of Interventions. Current Psychiatry Reports, 21(5), 33–33. https://doi.org/10.1007/s11920-019-1019-y

Cole, J., Ball, H. A., Martin, N. C., Scourfield, J., & Mcguffin, P. (2009). Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(11), 1094-1101. https://doi.org/10.1097/CHI.0b013e3181b7666e

Colomer, C., Wiener, J., & Varma, A. (2020). Do Adolescents With ADHD Have a Self-Perception Bias for Their ADHD Symptoms and Impairment? Canadian Journal of School Psychology, 35(4), 238–251. https://doi.org/10.1177/0829573520936457

Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993). The enduring psychosocial consequences of mania and depression. *The American Journal of Psychiatry, 150*(5), 720–727. https://doi.org/10.1176/ajp.150.5.720

Daviss, W. B., Birmaher, B., Diler, R. S., & Mintz, J. (2008). Does Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder Predict Risk of Later Major Depression? Journal of Child and Adolescent Psychopharmacology, 18(3), 257–264. https://doi.org/10.1089/cap.2007.0100

Daviss, W. B. (2008). A Review of Co-Morbid Depression in Pediatric ADHD: Etiologies, Phenomenology, and Treatment. Journal of Child and Adolescent Psychopharmacology, 18(6), 565–571. https://doi.org/10.1089/cap.2008.032

Deault, L. C. (2010). A Systematic Review of Parenting in Relation to the Development of Comorbidities and Functional Impairments in Children with Attention-Deficit/Hyperactivity Disorder (ADHD). Child Psychiatry and Human Development, 41(2), 168–192. https://doi.org/10.1007/s10578-009-0159-4

Diamantopoulou, S., Henricsson, L., & Rydell, A.-M. (2005). ADHD symptoms and peer relations of children in a community sample: Examining associated problems, self-perceptions, and gender differences. International Journal of Behavioral Development, 29(5), 388–398. https://doi.org/10.1080/01650250500172756

Drabick,D. A. G., Gadow, K. D., & Sprafkin, J. (2006). Co-occurrence of conduct disorder and depression in a clinic-based sample of boys with ADHD. Journal of Child Psychology and Psychiatry, 47(8), 766–774. https://doi.org/10.1111/j.1469-7610.2006.01625.x

Dunn, E. C., Brown, R. C., Dai, Y., Rosand, J., Nugent, N. R., Amstadter, A. B., & Smoller, J. W. (2015). Genetic determinants of depression: recent findings and future directions. *Harvard review of psychiatry*, *23*(1), doi: 10.1097/HRP.0000000000000054

Dvorsky, M. R., Langberg, J. M., Becker, S. P., & Evans, S. W. (2019). Trajectories of Global Self-Worth in Adolescents with ADHD: Associations with Academic, Emotional, and Social Outcomes. Journal of Clinical Child and Adolescent Psychology, 48(5), 765–780. https://doi.org/10.1080/15374416.2018.1443460

Eadeh, H., Bourchtein, E., Langberg, J. M., Eddy, L. D., Oddo, L., Molitor, S. J., & Evans, S. W. (2017). Longitudinal Evaluation of the Role of Academic and Social Impairment and Parent-Adolescent Conflict in the Development of Depression in Adolescents with ADHD.

Journal of Child and Family Studies, 26(9), 2374–2385. https://doi.org/10.1007/s10826-017-0768-7

Erskine, H. E., Norman, R. E., Ferrari, A. J., Chan, G. C., Copeland, W. E., Whiteford, H. A., & Scott, J. G. (2016). Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: a systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(10), 841-850. https://doi.org/10.1016/j.jaac.2016.06.016

Eyre, O., Langley, K., Stringaris, A., Leibenluft, E., Collishaw, S., & Thapar, A. (2017). Irritability in ADHD: Associations with depression liability. *Journal of Affective Disorders*, *215*, 281-287. https://doi.org/10.1016/j.jad.2017.03.050

Eyre, O., Riglin, L., Leibenluft, E., Stringaris, A., Collishaw, S., & Thapar, A. (2019). Irritability in ADHD: association with later depression symptoms. *European child & adolescent psychiatry*, *28*(10), 1375-1384. https://doi.org/10.1007/s00787-019-01303-x

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular psychiatry*, *24*(4), 562-575. https://doi.org/10.1038/s41380-018-0070-0

Faraone, S.V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine, 36*(2), 159-165. doi:10.1017/S003329170500471X

Feldman, J. S.,Tung, I., & Lee, S. S. (2017). Social Skills Mediate the Association of ADHD and Depression in Preadolescents. Journal of Psychopathology and Behavioral Assessment, 39(1), 79–91. https://doi.org/10.1007/s10862-016-9569-3

Fenesy, M. C. & Lee, S. S. (2022). Childhood ADHD and Executive Functioning: Unique Predictions of Early Adolescent Depression. Journal of Abnormal Child Psychology, 50(6), 753–770. https://doi.org/10.1007/s10802-021-00845-6

Fischer, A. G., Bau, C. H. ., Grevet, E. H., Salgado, C. A. ., Victor, M. M., Kalil, K. L. ., Sousa, N. O., Garcia, C. R., & Belmonte-de-Abreu, P. (2006). The role of comorbid major depressive disorder in the clinical presentation of adult ADHD. Journal of Psychiatric Research, 41(12), 991–996. https://doi.org/10.1016/j.jpsychires.2006.09.008

Fishman, P. A., Stang, P. E., & Hogue, S. L. (2007). Impact of comorbid attention deficit disorder on the direct medical costs of treating adults with depression in managed care. *Journal of Clinical Psychiatry*, *68*(2), 248-253. https://doi.org/10.4088/jcp.v68n0210

Ford, J. D., Racusin, R., Ellis, C. G., Daviss, W. B., Reiser, J., Fleischer, A., & Thomas, J. (2000). Child Maltreatment, other Trauma Exposure, and Posttraumatic Symptomatology among Children with Oppositional Defiant and Attention Deficit Hyperactivity Disorders. Child Maltreatment, 5(3), 205–217. https://doi.org/10.1177/1077559500005003001

Foster, G.C., Lane, D., Scott, D., Hebl, M., Guerra, R., Osherson, D., & Zimmer, H. (2018). introduction to psychological statistics. University of Missouri - St. Louis.

Frame, K., Kelly, L., & Bayley, E. (2003). Increasing Perceptions of Self-Worth in Preadolescents Diagnosed with ADHD. Journal of Nursing Scholarship., 35(3), 225–229. https://doi.org/10.1111/j.1547-5069.2003.00225.x

Garey, L., Olofsson, H., Garza, T., Rogers, A. H., Kauffman, B. Y., & Zvolensky, M. J. (2020). Directional effects of anxiety and depressive disorders with substance use: a review of recent prospective research. *Current Addiction Reports*, *7*(3), 344-355. https://doi.org/10.1007/s40429-020-00321-z

Gillberg, I., Rasmussen, P., Kadesjo, B., Soderstrom, H., Rastam, M., Johnson, M., Rothenberger, A., & Niklasson, L. (2004). Co-existing disorders in ADHD - implications for diagnosis and intervention. European Child & Adolescent Psychiatry, 13(S1), 80–92. https://doi.org/10.1007/s00787-004-1008-4

Goethe, J. W., & Fischer, E. H. (1995). Functional impairment in depressed inpatients. Journal of Affective Disorders, 33(1), 23–29. https://doi.org/10.1016/0165-0327(94)00069-L

Guendelman, M. D., Owens, E. B., Galán, C., Gard, A., & Hinshaw, S. P. (2016). Early adult correlates of maltreatment in girls with attention-deficit/hyperactivity disorder: Increased risk for internalizing symptoms and suicidality. Development and Psychopathology, 28(1), 1–14. https://doi.org/10.1017/S0954579414001485

Gustavson, K., Torvik, F. A., Eilertsen, E. M., Ask, H., McAdams, T. A., Hannigan, L. J., ... & Gjerde, L. C. (2021). Genetic and environmental contributions to co-occurring ADHD and emotional problems in school-aged children. *Developmental Psychology*, *57*(8), 1359. https://doi.org/10.1037/dev0001229

Harris, K., Boots, M., Talbot, J., & Vance, A. (2006). Comparison of psychosocial correlates in primary school age children with attention deficit/hyperactivity disorder- combined type, with and without dysthymic disorder. Child Psychiatry and Human Development, 36(4), 419–426. https://doi.org/10.1007/s10578-006-0012-y

Hawkey, E. J., Tillman, R., Luby, J. L., & Barch, D. M. (2018). Preschool Executive Function Predicts Childhood Resting-State Functional Connectivity and Attention-Deficit/Hyperactivity Disorder and Depression. Biological Psychiatry : Cognitive Neuroscience and Neuroimaging, 3(11), 927–936. https://doi.org/10.1016/j.bpsc.2018.06.011

Hodgkins, P., Arnold, L. E., Shaw, M., Caci, H., Kahle, J., Woods, A. G., & Young, S. (2012). A Systematic Review of Global Publication Trends Regarding Long-Term Outcomes of ADHD. Frontiers in Psychiatry., 2. https://doi.org/10.3389/fpsyt.2011.00084

Humphreys, K. L., Katz, S. J., Lee, S. S., Hammen, C., Brennan, P. A., & Najman, J. M. (2013). The association of ADHD and depression: Mediation by peer problems and parent–child

difficulties in two complementary samples. *Journal of Abnormal Psychology, 122*(3), 854–867. https://doi.org/10.1037/a0033895

Jaffee, S. R., & Price, T. S. (2012). The implications of genotype–environment correlation for establishing causal processes in psychopathology. Development and Psychopathology, 24(4), 1253–1264. https://doi.org/10.1017/S0954579412000685

James, A., Lai, F. H., & Dahl, C. (2004). Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatrica Scandinavica, 110(6), 408–415. https://doi.org/10.1111/j.1600-0447.2004.00384.x

Jensen, C., & Steinhausen, H.C. (2015). Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. Attention Deficit and Hyperactivity Disorders., 7(1), 27–38. https://doi.org/10.1007/s12402-014-0142-1

Jerrell, J. M., McIntyre, R. S., & Park, Y.-M.M. (2015). Risk factors for incident major depressive disorder in children and adolescents with attention-deficit/hyperactivity disorder. European Child & Adolescent Psychiatry, 24(1), 65–73. https://doi.org/10.1007/s00787-014-0541-z

Johnston, C. (1996). Parent characteristics and parent-child interactions in families of nonproblem children and ADHD children with higher and lower levels of oppositional-defiant behavior. Journal of Abnormal Child Psychology., 24(1), 85–104. https://doi.org/10.1007/BF01448375

Karalunas, S. L., Gustafsson, H. C., Fair, D., Musser, E. D., & Nigg, J. T. (2019). Do we need an irritable subtype of ADHD? Replication and extension of a promising temperament profile approach to ADHD subtyping. Psychological Assessment, 31(2), 236–247. https://doi.org/10.1037/pas0000664

Kendall, K. M., Van Assche, E., Andlauer, T. F. M., Choi, K. W., Luykx, J. J., Schulte, E. C., & Lu, Y. (2021). The genetic basis of major depression. *Psychological Medicine*, *51*(13), 2217-2230. https://doi.org/10.1017/S0033291721000441

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., Faraone, S. V., Greenhill, L. L., Howes, M. J., Secnik, K., Spencer, T., Ustun, T. B., Walters, E. E., & Zaslavsky, A. M. (2006). The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication. The American Journal of Psychiatry, 163(4), 716–723. https://doi.org/10.1176/ajp.2006.163.4.716

Kita, Y., & Inoue, Y. (2017). The Direct/Indirect Association of ADHD/ODD Symptoms with Self-esteem, Self-perception, and Depression in Early Adolescents. Frontiers in Psychiatry, 8, 137–137. https://doi.org/10.3389/fpsyt.2017.00137.

Laursen, T. M., Musliner, K. L., Benros, M. E., Vestergaard, M., & Munk-Olsen, T. (2016). Mortality and life expectancy in persons with severe unipolar depression. Journal of Affective Disorders., 193, 203–207. https://doi.org/10.1016/j.jad.2015.12.067

Lee, M., Yang, K.-C., Shyu, Y.-C., Yuan, S.-S., Yang, C.-J., Lee, S.-Y., Lee, T.-L., & Wang, L.-J. (2015). Corrigendum to “Attention-deficit hyperactivity disorder, its treatment with medication and the probability of developing a depressive disorder: A nationwide population-based study in Taiwan” [J. Affect. Disord. 189 (2016) 110–117]. Journal of Affective Disorders, 190, 122–122. https://doi.org/10.1016/j.jad.2015.10.017

Libutzki, B., Ludwig, S., May, M., Jacobsen, R., Reif, A., & Hartman, C. (2019). Direct medical costs of ADHD and its comorbid conditions on basis of a claims data analysis. *European Psychiatry, 58*, 38-44. doi:10.1016/j.eurpsy.2019.01.019

Luderer, M., Reinhard, I., Richter, A., Kiefer, F., & Weber, T. (2020). ADHD Is Associated with a Higher Risk for Traumatic Events, Self-Reported PTSD, and a Higher Severity of PTSD

Symptoms in Alcohol-Dependent Patients. European Addiction Research, 26(4-5), 245–253. https://doi.org/10.1159/000508918

Martin, A. J. (2006.). Attention-Deficit/Hyperactivity Disorder (ADHD), Perceived Competence, and Self-Worth: Evidence and Implications for Students and Practitioners. In Hollar, D. (2012) Handbook of Children with Special Health Care Needs / (pp. 47–72). Springer New York,. https://doi.org/10.1007/978-1-4614-2335-5_3

Mayer, J. S., Bernhard, A., Fann, N., Boxhoorn, S., Hartman, C. A., Reif, A., & Freitag, C. M. (2021). Cognitive mechanisms underlying depressive disorders in ADHD: A systematic review. *Neuroscience and Biobehavioral Reviews.*, *121*, 307–345. https://doi.org/10.1016/j.neubiorev.2020.12.018

McQuade, J. D., Hoza, B., Murray-Close, D., Waschbusch, D. A., & Owens, J. S. (2010). Changes in Self-Perceptions in Children With ADHD: A Longitudinal Study of Depressive Symptoms and Attributional Style. Behavior Therapy, 42(2), 170–182. https://doi.org/10.1016/j.beth.2010.05.003

McQuade, J. D., Vaughn, A. J., Hoza, B., Murray-Close, D., Molina, B. S. G., Arnold, L. E., & Hechtman, L. (2014). Perceived Social Acceptance and Peer Status Differentially Predict Adjustment in Youth With and Without ADHD. Journal of Attention Disorders, 18(1), 31–43. https://doi.org/10.1177/1087054712437582

Meinzer, M. C., Pettit, J. W., & Viswesvaran, C. (2014). The co-occurrence of attention-deficit/hyperactivity disorder and unipolar depression in children and adolescents: a meta-analytic review. *Clinical psychology review*, *34*(8), 595-607. https://doi.org/10.1016/j.cpr.2014.10.002

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., ... & Swendsen, J. (2010). Lifetime prevalence of mental disorders in US adolescents: results from the

National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(10), 980-989. https://doi.org/10.1016/j.jaac.2010.05.017

Meyer, A. (2005). Cross-cultural issues in ADHD research. Journal of Psychology in Africa (South of the Sahara, the Caribbean, and Afro-Latin America)

Michielsen, M., Comijs, H. C., Semeijn, E. J., Beekman, A. T. ., Deeg, D. J. ., & Sandra Kooij, J. . (2012). The comorbidity of anxiety and depressive symptoms in older adults with attention-deficit/hyperactivity disorder: A longitudinal study. Journal of Affective Disorders, 148(2-3), 220–227. https://doi.org/10.1016/j.jad.2012.11.063

Milberger, S., Biederman, J., Faraone, S. V., Murphy, J., & Tsuang, M. T. (1995). Attention deficit hyperactivity disorder and comorbid disorder: Issues of overlapping symptoms. *The American journal of psychiatry*. https://doi.org/10.1176/ajp.152.12.1793

Mitchell, J. T., Benson, J. W., Knouse, L. E., Kimbrel, N. A., & Anastopoulos, A. D. (2013). Are Negative Automatic Thoughts Associated with ADHD in Adulthood? Cognitive Therapy and Research, 37(4), 851–859. https://doi.org/10.1007/s10608-013-9525-4

Moos, R. H., & Moos, B. S. (1987). Family environment scale. *Handbook of measurements for marriage and family therapy*, *82*.

Mrug, S., Molina, B. S. G., Hoza, B., Gerdes, A. C., Hinshaw, S. P., Hechtman, L., & Arnold, L. E. (2012). Peer Rejection and Friendships in Children with Attention-Deficit/Hyperactivity Disorder: Contributions to Long-Term Outcomes. Journal of Abnormal Child Psychology, 40(6), 1013–1026. https://doi.org/10.1007/s10802-012-9610-2

Øie, M., Hovik, K. T., Andersen, P. N., Czajkowski, N. O., & Skogli, E. W. (2018). Gender Differences in the Relationship Between Changes in ADHD Symptoms, Executive Functions, and Self- and Parent-Report Depression Symptoms in Boys and Girls With

ADHD: A 2-Year Follow-Up Study. Journal of Attention Disorders, 22(5), 446–459. https://doi.org/10.1177/1087054716664407

Ostrander, R., & Herman, K. C. (2006). Potential cognitive, parenting, and developmental mediators of the relationship between ADHD and depression. *Journal of Consulting and Clinical Psychology, 74*(1), 89–98. https://doi.org/10.1037/0022-006X.74.1.89

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A.. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4

Owens, J. S., & Hoza, B. (2003). The role of inattention and hyperactivity/impulsivity in the positive illusory bias. *Journal of Consulting and Clinical Psychology, 71*(4), 680–691. https://doi.org/10.1037/0022-006X.71.4.680

Ozaslan, A. & Yildirim, M. (2021). Internalized stigma and self esteem of mothers of children diagnosed with attention deficit hyperactivity disorder. Children's Health Care, 50(3), 312–324. https://doi.org/10.1080/02739615.2021.1891071

Page M.J., McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. (2020) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Journal of Clinical Epidemiology 2021 https://doi.org/10.1186/s13643-021-01626-4

Parr, Shochet, I. M., Cockshaw, W. D., & Kelly, R. L. (2020). General Belonging is a Key Predictor of Adolescent Depressive Symptoms and Partially Mediates School Belonging. School Mental Health, 12(3), 626–637. https://doi.org/10.1007/s12310-020-09371-0

Platt, B., Kadosh, K. C., & Lau, J. Y. F. (2013). THE ROLE OF PEER REJECTION IN ADOLESCENT DEPRESSION. Depression and Anxiety, 30(9), 809–821. https://doi.org/10.1002/da.22120

Polanczyk, G. V., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. The American Journal of Psychiatry, 164(6), 942–948. https://doi.org/10.1176/appi.ajp.164.6.942

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A., & Rohde, L. A. (2015). Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of child psychology and psychiatry*, *56*(3), 345-365.https://doi.org/10.1111/jcpp.12381

Pollak, Y., Dekkers, T. J., Shoham, R., & Huizenga, H. M. (2019). Risk-taking behavior in attention deficit/hyperactivity disorder (ADHD): A review of potential underlying mechanisms and of interventions. *Current psychiatry reports*, *21*(5), 1-11. https://doi.org/10.1007/s11920-019-1019-y

Powell, V., Riglin, L., Hammerton, G., Eyre, O., Martin, J., Anney, R., Thapar, A., & Rice, F. (2020). What explains the link between childhood ADHD and adolescent depression? Investigating the role of peer relationships and academic attainment. European Child & Adolescent Psychiatry, 29(11), 1581–1591. https://doi.org/10.1007/s00787-019-01463-w

Renouf, A. G., & Harter, S. (1990). Low self-worth and anger as components of the depressive experience in young adolescents. *Development and Psychopathology*, *2*(3), 293-310. https://doi.org/10.1017/S095457940000078X

Rohde, P., Clarke, G. N., Lewinsohn, P. M., Seeley, J. R., & Kaufman, N. K. (2001). Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(7), 795-802. https://doi.org/10.1097/00004583-200107000-00014

Ros, R., & Graziano, P. A. (2018). Social Functioning in Children With or At Risk for Attention Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Journal of Clinical Child and Adolescent Psychology, 47(2), 213–235. https://doi.org/10.1080/15374416.2016.1266644

Roy, A., Hartman, C. A., Veenstra, R., & Oldehinkel, A. J. (2015). Peer dislike and victimisation in pathways from ADHD symptoms to depression. European Child & Adolescent Psychiatry, 24(8), 887–895. https://doi.org/10.1007/s00787-014-0633-9

Rudolph, K. D. & Conley, C. S. (2005). The Socioemotional Costs and Benefits of Social-Evaluative Concerns: Do Girls Care Too Much? Journal of Personality, 73(1), 115–138. https://doi.org/10.1111/j.1467-6494.2004.00306.x

Rydell, M., Taylor, M. J., & Larsson, H. (2017). Genetic and environmental contributions to the association between ADHD and affective problems in early childhood—A Swedish population-based twin study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *174*(5), 538-546. https://doi.org/10.1002/ajmg.b.32536

Shapiro, J. R., Klein, S. L., & Morgan, R. (2021). Stop 'controlling'for sex and gender in global health research. *BMJ Global Health*, *6*(4), e005714. http://dx.doi.org/10.1136/bmjgh-2021-005714

Segrin. C. (1990). A meta-analytic review of social skill deficits in depression. Communication Monographs, 57(4), 292–308. https://doi.org/10.1080/03637759009376204

Semeijn, E. J., Comijs, H., Kooij, J. J., Michielsen, M., Beekman, A. T., & Deeg, D. J. . (2014). The role of adverse life events on depression in older adults with ADHD. Journal of Affective Disorders, 174, 574–579. https://doi.org/10.1016/j.jad.2014.11.048

Seymour, K. E., Chronis-Tuscano, A., Iwamoto, D. K., Kurdziel, G., & MacPherson, L. (2014). Emotion regulation mediates the association between ADHD and depressive symptoms in a

community sample of youth. *Journal of abnormal child psychology, 42*(4), 611-621. https://doi.org/10.1007/s10802-013-9799-8

Shorey, S., Ng, E. D., & Wong, C. H. J. (2022). Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis. British Journal of Clinical Psychology, 61(2), 287–305. https://doi.org/10.1111/bjc.12333

Simmons, J. A., & Antshel, K. M. (2021). Bullying and Depression in Youth with ADHD: A Systematic Review. Child and Youth Care Forum., 50(3), 379–414. https://doi.org/10.1007/s10566-020-09586-x

Sobanski, E., Brüggemann, D., Alm, B., Kern, S., Deschner, M., Schubert, T., Philipsen, A., & Rietschel, M. (2007). Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). European Archives of Psychiatry and Clinical Neuroscience, 257(7), 371–377. https://doi.org/10.1007/s00406-007-0712-8

Sobanski, E. (2006). Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). European Archives of Psychiatry and Clinical Neuroscience, 256(1), i26–i31. https://doi.org/10.1007/s00406-006-1004-4

Spinath, B., Eckert, C., & Steinmayr, R. (2014). Gender differences in school success: What are the roles of students' intelligence, personality and motivation?. *Educational Research, 56*(2), 230-243. https://doi.org/10.1080/00131881.2014.898917

Staikova, E., Marks, D. J., Miller, C. J., Newcorn, J. H., & Halperin, J. M. (2010). Childhood Stimulant Treatment and Teen Depression: Is There a Relationship? Journal of Child and Adolescent Psychopharmacology, 20(5), 387–393. https://doi.org/10.1089/cap.2009.0107

Tallberg, P., Svanberg, K., Hallin, A.-L., Rastam, M., Gustafsson, P., & Perrin, S. (2022). The three-year outcome of emotional symptoms in clinically referred youth with ADHD and

their relationship to neuropsychological functions. Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 10(1), 72–86. https://doi.org/10.2478/sjcapp-2022-0008

Thapar, A., Livingston, L. A., Eyre, O., & Riglin, L. (2023). Practitioner Review: Attention-deficit hyperactivity disorder and autism spectrum disorder–the importance of depression. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/jcpp.13678

Torske, T., Nærland, T., Øie, M. G., Stenberg, N., & Andreassen, O. A. (2018). Metacognitive aspects of executive function are highly associated with social functioning on parent-rated measures in autistic children disorder. Frontiers in Behavioral Neuroscience, 11, 258–258. https://doi.org/10.3389/fnbeh.2017.00258

Wells G.A., Shea, B., O'Connell D., Peterson, J., Welch, V., Losos, M., et al.The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2022 Nov 9] https://www.ohri.ca//programs/clinical_epidemiology/oxford.asp

Wichstrøm, L., Belsky, J., & Steinsbekk, S. (2017). Homotypic and heterotypic continuity of symptoms of psychiatric disorders from age 4 to 10 years: a dynamic panel model. *Journal of Child Psychology and Psychiatry*, *58*(11), 1239-1247. https://doi.org/10.1111/jcpp.12754

World Health Organization (WHO). Depression. 2012 [27-11-2014].www.who.int/mediacentre/factsheets/fs369/en/.

Yoshimasu,K., Barbaresi, W.., Colligan, R. ., Voigt, R. ., Killian, J. ., Weaver, A. ., & Katusic, S. . (2016). Adults with persistent ADHD: Gender and psychiatric comorbidities – a population-based longitudinal study. European Psychiatry, 33(S1), S136–S137. https://doi.org/10.1016/j.eurpsy.2016.01.219

Zapata, M. A. (2022). Negative High School Experiences Predict Internalizing Symptomatology among Employed U.S. Adults with LD and ADHD. Journal of Adult Development, 29(3), 218–227. https://doi.org/10.1007/s10804-022-09401-y

Zarei, K., Xu, G., Zimmerman, B., Giannotti, M., & Strathearn, L. (2021). Adverse childhood experiences predict common neurodevelopmental and behavioral health conditions among US children. *Children*, *8*(9), 761. https://doi.org/10.3390/children8090761

Del 3 Implikationer for Praksis

Denne del vil omhandle forebyggende strategier og behandlingen af depression hos personer med ADHD. Som beskrevet tidligere er der evidens for en øget tilbøjelighed for personer med ADHD til at udvikle depression, hvorfor det kan være relevant at se på særlige forebyggelsestiltag til denne gruppe. Sektionen vil primært fokusere på børn og unge, fordi fundene fra det SR centrerer sig om denne gruppe. Først vil de overordnede retningslinjerne for behandling af mentale lidelser hos børn og unge i Danmark foreligges. Dette følges af en redegørelse og diskussion af en række mulige tiltag med udgangspunkt i forskningen på området, kliniske retningslinjer og de fund, der blev gjort i det SR, inddelt efter om behandlingerne er farmakologiske eller non-farmakologiske. Slutligt fulgt af yderligere implikationer fra det SR.

Behandling af Mentale Lidelser hos Børn i Danmark

I Danmark findes de Nationale Kliniske retningslinjer (NKR), som sikrer, at sundhedspersonalet har mulighed for at træffe beslutninger på baggrund af den samlede aktuelt bedste forskningsbaserede viden (*Kliniske retningslinjer*, n.d.) I forbindelse med behandling af psykiske lidelser hos børn og unge, fremgår det af en vejledning, at ikke-farmakologisk behandling er førstevalg (Sundhedsministeriet, 2019, p. 2f). I tilfælde hvor de non-farmakologiske tiltag vurderes utilstrækkelige efter relevant, rimelig karakter, omfang og varighed af behandling, kan farmakologiske tiltag iværksættes – dog kun i kombination med en anden relevant non-farmakologisk behandling (Sundhedsministeriet, 2019, p.2f). Der eksisterer dog ikke en NKR eller National Institute for Health and Care Excellence (NICE) guideline for behandling af depression ved specifikt børn og unge eller specifikt ved depression komorbidt med ADHD (Thapar et al., 2023). De NKR anvender ”en stærk anbefaling for, når de samlede fordele ved interventionen, vurderes at være klart større end ulemperne.” (Sundhedsstyrelsen, 2006, p.5) Samt ”en svag anbefaling for interventionen, når [de] vurderer, at fordelene ved interventionen er større end ulemperne, eller den tilgængelig evidens ikkekan udelukke en væsentlig fordel ved interventionen, samtidig med at det vurderes, at skadevirkningerne er få eller fraværende.” (Sundhedsstyrelsen, 2006, p.5).

Non-farmakologisk Behandling

I denne del vil non-farmakologiske behandlinger/præventionstiltag diskuteres.

Selvopfattelse og Tankemønstre

I det SR blev selvværd, selvopfattelse og negative automatiske tanker fundet at forudsige depressive symptomer i en ADHD-population. Dette støtter således et fokus på disse tankemønstre, både præventivt og som intervention.

Kognitiv Adfærds Terapi (KAT) er i den forbindelse relevant, og både nævnt som svag anbefaling af behandling af depression i NKR (Sundhedsstyrelsen, 2016, p .20) og som en svag anbefaling til både børn og voksne med ADHD, hvor netop angst og depression nævnes, som aspekter denne terapi kan forebygge (Sundhedsstyrelsen, 2017, p. 56; 2021, pp. 62-68). KAT programmer udviklet til ADHD populationen består både i udvikling af coping-strategier til bedre håndtering af ADHD-symptomer, men også i at identificere og monitorere dysfunktionelle tankemønstre (Antshel et al., 2012, p. 335f). Der vil således blive interveneret mod de negative automatiske tanker og forringet selvværd, som netop findes relevant i det SR. Derudover virker terapien ved at forsøge at nedsætte antallet af nederlag (Sundhedsstyrelsen, 2021, p. 62). Denne tilgang går i led med en kognitiv-adfærds model som netop fremsætter at det forringede selvværd og de negative tankemønstre opstår på baggrund af en historik af nederlag og sociale problematikker hos ADHD-populationen og i sidste ende leder til negative emotioner heriblandt depression (Newark & Stieglitz, 2010, p. 59,63). Et SR fandt ligeledes, at KAT gav forbedringer på selvevaluerede ADHD-symptomer og både selv-evaluerede og kliniker-evalueret depressive symptomer i en voksen ADHD-population (Jensen et al., 2016, p. 3). Der er dog indikationer for, at KAT er mere effektiv hos voksne og teenagere end hos pre-teenagere og børn (Antshel et al, 2012, p. 335f). Dette støttes af en nyere metaanalyse der fandt at KAT var effektiv i behandling af depression hos voksne, men ikke hos børn (Guo et al., 2022). På baggrund af dette er det min anbefaling, at KAT prioriteres ved ældre børn og kun anvendes ud fra en vurdering af, at barnet har kompetencer til at indgå meningsfuldt i forløbet.

Mindfulness (MBT) En bølge af den kognitive adfærdsterapi, som inddrager mindfulness, nævnes også som en mulig behandlingsform for depression. Denne terapiform er i en metaanalyse fundet at give et fald i depressive symptomer hos voksne med ADHD (Poissant et al., 2020, p.2669). En anden meta-analyse finder dog ingen effekter af MBT på depressive symptomer, hos hverken børn eller voksne med ADHD. På baggrund af dette kan denne behandlingsform ikke anbefales til børn og unge på nuværende tidspunkt.

Psyko-Edukationelle Tiltag Et anden område at sætte ind på kunne være at forhindre dannelsen af de negative tankemønstre, inden de opstår. I den forbindelse omtaler Martin (2006, p.57) en række psykologiske og pædagogiske tiltag, som kan iværksættes i læringsmiljøet for at mindske oplevelser af utilstrækkelighed. Eksempler på disse vil blive nævnt i det følgende.

Her foreslås et fokus på en konstruktiv tilgang til ADHD. Denne indebærer en række forskellige elementer såsom tilpasning af klassemiljøet, regler og omstændigheder i opgaver, tidlig intervention og hjælp fremfor at vente på fiasko, samt fokus på at ADHD ikke påvirker personens værd, og at et tæt lærer-elev-forhold er muligt, men at respekt for læreren opnås igennem lærerens respekt for individet (Lougy et al. 2007; Martin, 2006, p. 58).

Et andet element omhandler frygten for at fejle, som er særligt udbredt i denne population. Dette bør ifølge Martin (2006, p. 58) tilpasses igennem to tilgange. Den første omhandler måden, hvorpå fejl vurderes, hvor det er væsentligt, at de anses som en vigtig information om, hvordan man kan løse problemet næste gang. Den andet komponent omhandler at adskille fejlen fra individet ved at have et større fokus på strategi og proces (Martin, 2006, p. 58), også kendt som procesrettet ros, fremfor produktrettet ros (Cain & Dweck, 1995). Der er dog også indikationer for at denne procesrettet ros skal omhandle kvaliteten af processen fremfor kvantitet i starten, da der også kan opstå en trussel for selvværdet ved en langvarig indsats, som ikke lykkes.

Derudover foreslås det, at individet sammenlignes med sig selv frem for andre for nemmere at opleve og opnå fremgang, da disse personer med læringsvanskeligheder ofte konsekvent vil præstere under gennemsnittet i de overordnede sammenligninger, selvom de forbedrer sig (Martin, 2006, p. 59f).

Slutligt bør betydningen af at tilpasse opgaven efter elevens kompetencer nævnes (Martin, 2006, p. 60). Dette går i led med Vygotskys teori angående ’zonen for nærmeste udvikling’, som netop omhandler at ramme det felt, hvor et barn kan løse opgaven med lidt støtte, da dette argumenteres for at være det felt, hvor der er størst potentiale for læring (Vygotsky, 1978, p. 87). Dette felt forsøges ofte opnået igennem stilladsering, hvor opgavernes sværhedsgrad og rammer tilpasses til det enkelte barn (Margolis, 2020, p. 17).

Der eksisterer altså en række tiltag, som med fordel kan implementeres i skolevæsenet, og som muligvis kan forebygge udviklingen af lavt selvværd og

negative automatiske tanker, samtidig med at de giver øgede læringsmuligheder. Dette går også overens med anbefalinger fra NICE guidelines, hvor det fremsættes, at læringsmæssige problemer må behandles sekventielt eller sideløbende (NICE, 2022, p. 49). Disse tiltag vil dog, udover mulige kulturændringer, også ofte kræve mere personale og flere timer pr. elev, hvilket kan gøre det til en større udfordring at få implementeret.

Sociale Færdigheder

Fundene fra det SR viste overordnet set gode indikationer for, at forringede sociale færdigheder forudsagde en øget risiko for depression hos en ADHD-population. I NICE guidelines fremsættes det også, at sociale problematikker, der er komorbid med depression, bør interveneres på (NICE, 2022, p. 49). I de NKR fremsættes social færdighedstræning med en svag anbefaling til behandling af ADHD. Denne svage anbefaling fremkommer på baggrund af, at der ikke er evidens for, at sociale færdigheder forbedres. Der findes dog lav evidens for effekt på ADHD kernesymptomer og lave indikationer for skadelige virkninger (Sundhedsstyrelsen, 2021, pp.40-44). Interventionen vurderes ikke i relation til prævention eller behandling af komorbide depressive symptomer i NKR. Det vil derfor være relevant også at evaluere effekten af sociale færdighedstrænings-interventioner i henhold til at forebygge senere depressive symptomer eller som en ekstra behandling hos personer der allerede har udviklet depression. En forebyggelse af depression vil dog teoretisk set indebære, at der ses en forbedring af sociale færdigheder, som der netop ikke er sikkerhed omkring ifølge de NKR (Sundhedsstyrelsen, 2021, pp.40-44). Dette program er således ikke så effektivt som man kunne håbe, men har ingen indikationer for skadevirkninger og kan derfor godt forsøges. Klinikere bør holde fast i at forsøge at afhjælpe sociale problematikker, lige såvel som at det fremsættes, at anti-mobningstiltag bør implementeres i tilfælde, hvor dette kan have relation til depressionen (NICE, 2022, p. 49).

Familiedomænet

Forældretræning er stærkt anbefalet i de NKR, hvor dette er fundet muligvis at forbedre barnets overordnede funktionsniveau, ADHD kerne-symptomer samt sandsynligvis at forbedre forældrenes oplevede forældrekompetence (Sundhedsstyrelsen, 2021, pp. 44-54). De NKR nævner dog ikke komorbide depressive symptomer som et undersøgt udfald (Sundhedsstyrelsen, 2021, p.45). Der

er således et behov for at undersøge depression som udfald for at afgøre effekter på dette område. I det følgende vil logikken for anvendelse af forældretræningsprogrammer vurderes i lyset af de effekter, der er fundet og undersøgt, i kombination med fund fra det SR.

Familiemiljø I det SR er der uklarhed omkring betydningen af familiemiljøet, men der er indikationer for, at dette kunne være af betydning. En sådan mekanisme er i det SR foreslået at være relateret til de negative forældrereaktioner, som kan provokeres af den forstyrrende adfærd fra barnet, som ofte er forbundet med at have ADHD. Disse negative attituder/metoder fra forældrene er dernæst formodet at påvirke den øgede risiko for depressive symptomer, hvilket er fundet i et SR af studier af normalpopulationen (Gorostiaga et al., 2019). Det er derfor muligt, at disse forældretræningsprogrammer indirekte kan forebygge depressive symptomer hos barnet igennem både forbedringerne hos barnet og forældrenes oplevelse af kompetence, som kunne give en mere harmonisk forældre-barn relation og et mere harmonisk familiemiljø overordnet set. I et dansk studie af et af disse forældreprogrammer New Forest Parenting Programme (NFPP), fandt man også, at netop stress i familien blev reduceret udover fald i ADHD-symptomer og forbedrede forældrekompetencer (Lange et al., 2018). Effekter blev ligeledes fundet i de otte studier inkluderet i metaanalysen af de NKR, som undersøgte forældres stress (Sundhedsstyrelsen, 2021, pp. 48ff). En forebyggende effekt på komorbid depression må dog på nuværende tidspunkt anses som en positiv sideeffekt, som muligvis kunne opstå ved en behandling, som iværksættes på baggrund af tiltagets evidens på disse andre områder, da der ikke er sikkerhed omkring familiemiljøet betydning for depression, og hvorvidt denne forældretræning nedsætter depressive symptomer hos barnet.

Forældres Mentale Helbred Et andet aspekt, der er væsentligt at diskutere i relation til denne forældretræning, er forældrenes og herunder særligt mødrenes mentale helbred, som der i det SR findes at påvirke børnenes depressive symptomer. Det er derved et vigtigt skridt i forebyggelsen at fokusere på forældrenes mentale helbred, hvilket både kan gøres gennem øget opmærksomhed og screening for depression hos forældrene af børn med ADHD, men også ved forbyggende indsatser som et forældreprogram. Netop behovet for behandling af depression hos forældre fremsættes som et område, der må være opmærksomhed på i NICE guidelines (NICE, 2022, p. 49). Som omtalt i ovenstående, så er der indikationer for, at

forældretræning afhjælper stress hos forældre. Der synes dog at være tvetydighed omkring NFPP-indflydelse på mødres mental helbred, hvor et studie ikke finder effekt på mødres depression (Thompson et al., 2009), og et andet studie finder forbedringer på mødres mentale helbred (Sonuga-Barke et al., 2001). Et studie af et andet forældretræningsprogram (Triple- P) finder også et fald i depressive symptomer, stress og angst hos mødrene (Aghebati et al., 2014), og der bliver ligeledes fundet positive effekter på forældrenes stress og depression ved et online forældreprogram (Franke et al., 2016).

Overordnet set tyder det på, at disse forældretræningsprogrammer kan have en positiv effekt på både familiemiljø og forældres mentale helbred, samtidig med at der i forvejen eksisterer en høj anbefaling for programmerne på baggrund af positive effekter på ADHD-kernesymptomer og oplevelse af forældrekompetencer. På baggrund af dette vil sådanne programmer være fordelagtige at implementere, selvom effekten på netop depression på nuværende tidspunkt er uvis. Udover dette, bør klinikere være opmærksomme på at en mulig depression hos forældre bør screenes for og behandles sideløbende.

Søvn

I henhold til søvn var der konsensus angående, at problemer forudsiger depression i en ADHD-population i det SR, men usikkerhed omkring årsagen dertil. Dette, i kombination med at op mod 70% af børn med ADHD vurderes af forældre til at have søvnproblemer (Sung et al., 2008), betyder, at søvn bør være et fokusområde at monitorere og intervenere på. Påvirkningen af depressive symptomer er ikke et stort fokus inden for forskningen i søvn og ADHD, og derfor må målet i første omgang være at finde interventioner, som forbedrer søvnen. Dernæst kan effekten på depressive symptomer undersøges senere.

I de NKR fremgår søvnhygiejniske tiltag som førstevalg. Disse tiltag nævnes også i behandlingen af depression i NICE guidelines (NICE, 2022, p. 50). Disse indebærer blandt andet at elektronik slukkes senest 1 time før sengetid (Sundhedsstyrelsen, 2022, p. 9). Dette kan relateres til indikationer for, at mediebrug om natten er en årsag til mindre søvn, samt øget depressive symptomer hos en ADHD-population (Becker & Lienesch, 2018), hvilket vil modvirkes ved et sådant tiltag. En andet non-farmakologisk tiltag, der er relateret til søvn, er brugen af en kugledyne, som vurderes som god praksis at tilbyde ved manglende effekt af søvnhygiejniske tiltag (Sundhedsstyrelsen, 2021, p. 58-62) hos børn med ADHD.

Anbefalingen om kugledyne er er baseret på klinisk erfaring og konsensus, men der er ingen studier, som undersøger dette. Det vurderes dog, at der ikke er nogen, kendte skadelige virkninger. Kugledynen formodes at virke ved, at brugen heraf forkorter indsovningstiden og giver færre opvågninger, hvilket derigennem giver barnet en forbedret søvn (Sundhedsstyrelsen, 2021, pp. 58-62). Et andet tiltag, som fremgår af de NKR ved manglende effekt af søvn-hygiejniske tiltag, er den farmakologiske behandling med melatonin, som der fremgår en svag anbefaling af - også ved grupper med komorbiditet. Det er vurderet, at det muligvis forkorter indsovningstiden og det medfører sandsynligvis ikke fremkomsten af alvorlige bivirkninger. Der er dog usikkerheder angående melatonins effekt på generelle søvnvanskeligheder, ADHD-kerne symptomer og funktionsniveau (Sundhedsstyrelsen, 2022, p.25).

Forskningen inden for søvn hos ADHD-populationen har været stigende de seneste år (Becker, 2020, p.50). I et review angives adfærdsinterventioner at være førstevalg ved søvnløshed i en ADHD-population på trods af manglende randomiserede kontrollerede (RCT) studier (Cortese et al., 2013, p.789ff). Adfærdsinterventionerne karakteriseres ved førnævnte søvnhygiejniske tiltag, som specialtilpasses til børn med ADHD, ved at der f.eks. skal påmindes om sengetid flere gange. I relation hertil er senere fundet gode effekter af 'Brief Behavioural Sleep interventions' sammenlignet med standardbehandling i RCT-studier, hvor der er fundet en forbedring af søvn, livskvalitet og daglig funktionalitet i ADHD-populationer (Sciberras et al., 2011, p.934; Hiscock et al., 2015, p.5). Disse interventioner anvender udover søvnhygiejniske tiltag en række adfærdsstrategier, såsom brug af søvn dagbog, begrænsninger for anmodning om vand, historielæsning mm, afslappende strategier, tjekke barnet på bestemte tider, og gradvis justering af sengetider (Sciberras et al., 2011, p.934). Der er således noget, der tyder på, at implementering af en række adfærdsstrategier kan fungere som en fordelagtig støtte til de søvnhygiejniske råd.

Overordnet set findes en række mulige tiltag med indikationer for større eller mindre forbedring af søvnen. Overordnet set må disse interventioner anses som mindre ressourcekrævende, da det omhandler et enkelt produkt/medikament eller korte interventioner, som mest af alt har en informerende karakter. Sammenholdt med de lave indikationer for alvorlige bivirkninger er der altså gode indikationer for at anvende disse på trods af usikkerhed omkring, hvor stor effekten er.

Farmakologisk Behandling

I dette afsnit vil den farmakologiske behandling af depression hos ADHD-populationen diskuteres ud fra medicin udviklet til depression, medicin udviklet til ADHD, samt deres brug i kombination med non-farmakologiske tiltag eller i kombination med hinanden.

Medicinering af Depression

Den farmakologiske behandling af depression i Danmark kan bestå i Selektive serotoningenoptagshæmmere (SSRI), Serotonin-noradrenalin-genoptagshæmmere (SNRI), Noradrenalingenoptagshæmmere (NaRI), Noradrenalin og specifikke serotonin-antidepressiva (NaSSA), Melatoninagonister og i visse tilfælde andre antidepressiva (Davidsen, 2019; RADS, 2015). Her er SSRI førstevalg og fluoxetine er ydermere det eneste godkendte SSRI til behandling af børn i DK (Sundhedsministeriet, 2019, p.5). Som omtalt tidligere vil disse dog, i Danmark, altid udbydes efter forsøg med non-farmakologiske tiltag og altid samtidig med non-farmakologiske tiltag, når der er tale om børn og unge (Sundhedsministeriet, 2019, p. 2f).

I flere studier er effekten af medicin mod depression sammenlignet med KAT eller en kombinationsbehandling undersøgt i hele eller delvise ADHD-populationer. I et studie, havde 24% af deltagerne *'disruptive disorder'* komorbid med depression og 14% havde ADHD komorbid med depression. Her fandt man, at KAT ikke virkede bedre end placebo, men at fluoxetine havde en effekt. Kombination af KAT og fluoxetine gav dog de bedste resultater (March et al. 2004, p. 816f). Dette implicerer, at en kombinationsbehandling er mest effektiv. Studiet skriver dog intet omkring mulige forskelle baseret på, hvorvidt der er en komorbiditet eller forskelle imellem komorbidetets kombinationerne. I et andet studie fandt man ligeledes, at KAT alene ingen effekt havde på depression (Curry et al. 2006, p.1452ff). Kombinationen af KAT og fluoxetine viste sig at have bedre effekter i gruppen med de mindst alvorlige udgaver af depression i forhold til fluoxetine alene. Fluoxetine alene viste dog bedre effekter end kombinationsbehandlingen ved alvorlige tilfælde af depression. Disse fund tolkes som, at depressive symptomer må sænkes til et vist niveau, for at personerne bliver modtagelige for KAT-behandlingen. Dette kan være relevant i gruppen med comorbid ADHD og depression, da der netop oftere ses svære tilfælde af depression i denne gruppe. Disse behandlinger blev dog fundet overordnet set at have lavere effekter i grupper med mere end én komorbid lidelse (Curry et al. 2006,

p. 1436), hvilket støtter Biederman et al.'s (2008) fund omkring lavere effekter af behandling ved comorbid ADHD og depression.

Medicinering af ADHD

Hvad angår medicinsk behandling, kan der også være tale om ADHD-medicin, som igennem behandlingen af ADHD-symptomer muligvis ville kunne formindske risikoen for depression. I behandlingen ad ADHD- kernesymptomer fremkommer stærke anbefalinger for brug af methylphenidat, lisdexamfetamine/dexamfetamine og atomoxine, hos børn og unge med væsentlige funktionsnedsættelser i modsætningen til ikke væsentlige funktionsnedsættelse, hvor der fremgår en svag anbefaling for præparaterne (Sundhedsstyrelsen, 2021, p. 68-85). Disse præparater er dog anbefalet i lyset af deres effekt på ADHD-kernesymptomer. Effekten på depression vil således være indirekte, igennem at færre ADHD- symptomer skulle mindske problemer på andre områder såsom sociale evner, som blev fundet associeret med depression. Ligeledes viste det SR tvetydigheder angående ADHD-medicins beskyttende effekter mod depression, imens der var en overvægt af enighed omkring, at medicinen ikke har negative effekter på depression. Der er således ikke noget, der taler imod brugen af ADHD-medicin i henhold til depression, men det er meget usikkert, hvorvidt denne behandling beskytter imod depression.

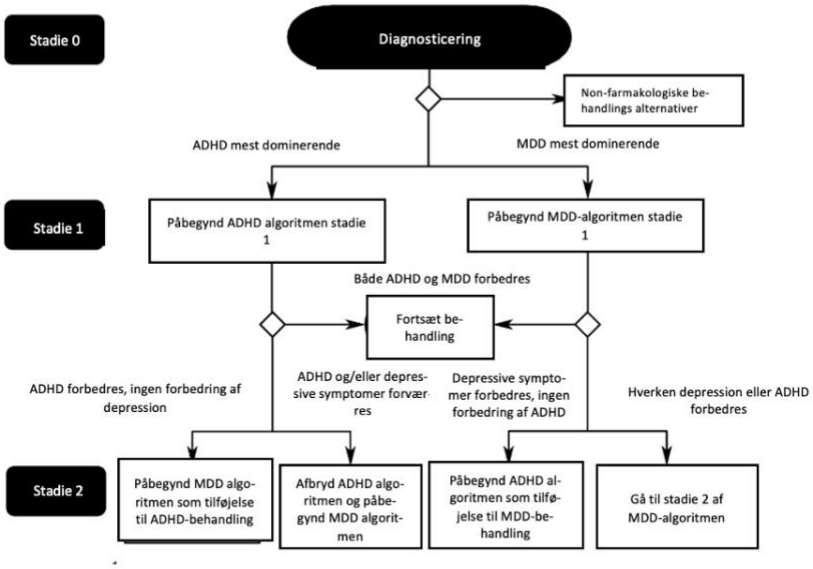
ADHD-medicin Kombineret med Depressionsmedicin

De NKR fremskriver ikke, hvorledes den farmakologiske behandling bør administreret ved tilstedeværelse af både ADHD og depression. I Texas Children's Medication Algorithm Project har man dog udviklet og opdateret en farmakologisk algoritme for behandling af ADHD og depression i kombination (se figur 2). Denne algoritme er baseret på et review af den medicinske litteratur og gruppekonsensus i et panel af klinikere og forskningseksperter (Hughes et al. 2007, p.669). I den forbindelse anbefales det først og fremmest at non-farmakologiske/psykosociale interventioners brugbarhed i den specifikke case vurderes først, da psykosociale udfordringer går på tværs af både ADHD og depression (Hughes et al. 2007, p.671f; Daviss, 2018, p. 99f). Dette går i led med de anbefalinger, der er præsenteret fra de NKR. I beslutningen om at påbegynde medicinsk behandling må det først afgøres, hvorvidt ADHD eller depression udgør den største vanskelighed, så behandlingsrækkefølgen kan vælges herudfra. Her foreskrives først, at den primære diagnose behandles ud fra en medicinsk algoritme udviklet hertil. I tilfælde af at

denne behandling kun hjælper på den primære diagnose, foreslås det, at den modsatte behandling for komorbiditeten tilføjes som supplement (Daviss, 2018, p. 99f; Hughes, 2007, p.674ff). Derudover nævnes det, at det skal forsøges med én medicinsk forandring ad gangen for at forbedre fortolkningen af behandlingsresponsen. Ydermere anbefales en løbende evaluering af både ADHD-symptomer og depressionssymptomer gennem forældre og selv-rapporterede rating skalaer for netop at kunne følge algoritmen, som er afhængig af responsens på medicinen (Daviss, 2018, p. 99f; Hughes, 2007, p.679).

Figur 2

Medicinsk algoritme for behandling af komorbid ADHD og depression



Note. Medicinsk algoritme for behandling af børn og unge som møder DSM-IV kriterier for major depressive disorder (MDD) og ADHD. Oversat efter: Hughes, C. W., Emslie, G. J., Crismon, M. L., Posner, K., Birmaher, B., Ryan, N., ... & DEPRESSIVE, M. T. O. C. M. (2007). Texas children's medication algorithm project: update from Texas consensus conference panel on medication treatment of childhood major depressive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(6), 667-686.

Denne guideline taler altså for, at både præparater til depression og ADHD kan være effektfulde, og at det skal afgøres fra individ til individ hvilken behandling, der bør iværksættes først, og hvorledes den følges op (Hughes, 2007, p. 670ff). Anbefalingen om kombineret farmakologisk behandling går dog imod RADS (2016) anbefalinger i Danmark, som fremsætter at SSRI og ADHD-medicin ikke synes at bedre depression, og ydermere at kombinationen med atomoxine giver stigning i blodtryk og hjertefrekvens.

Opsummerende giver dette indikationer for, at medicin med fordel kan anvendes i kombination med de non-farmakologiske tiltag, og at den primære diagnose bør behandles medicinsk først og fremmest. Der eksisterer dog uenighed angående at blande de to typer medicin, og det bør derfor overvejes nøje, inden denne kombination med de nævnte bivirkninger gives, samt monitoreres hvis det gives.

Yderligere Implikationer

Dette afsnit har til hensigt at udfolde implikationer for praksis, som kan udledes fra resultaterne af det SR, og som ikke indgår i ovenstående afsnit.

Traumatiske Begivenheder

Et aspekt, som blev fundet af betydning i det SR, men som ikke er blevet behandlet i ovenstående tiltag, er traumatiske begivenheder. Resultaterne fra det SR giver indikation for, at man i praksis bør forhindre og forebygge traumatiske begivenheder i ADHD-population. På baggrund af de negative aspekter associeret med traumatiske livsbegivenheder, må vi dog gå ud fra, at dette allerede er et fokus hos klinikere, men det er en kompliceret opgave. Ud fra de nævnte mulige årsager til disse traumatiske begivenheder, nævnt i det SR, kan forslag til specifikke områder at have fokus på være: Forebyggelse af biluheld og andre ulykker, igennem psykoedukation angående statistik for ulykker og forklaring af processer som øget risikovillighed, som ligger til baggrund for denne øgede risiko. Derudover kan forsøges at intervenere på risikovilligheden. Her er fundet gode effekter af ADHD-medicin, samt gode resultater af indledende forskning på et forældre-teenagerkørselsinterventionsprogram (Pollak et al., 2019, p. 7). Ydermere kan et fokus på at facilitere stabile og positive relationer for personer med ADHD for at undgå risikomiljøer nævnes, samt et fokus på færre konflikter. Dette kan ses i relation til tidligere nævnte tiltag, hvor forældretræningsprogrammer muligvis kan bidrage til mindre forældre-barn konflikt. En forbedring af sociale evner vil sandsynligvis også bidrage til færre konflikter og dermed færre traumatiske begivenheder såsom tab af venskab. Det synes dog vanskeligt at intervenere på de sociale færdigheder i ADHD-populationen (Sundhedsstyrelsen, 2021, pp.40-44).

ADHD Subtype

I det SR blev der også fundet indikationer for, at ADHD-uopmærksomme subtype (ADHD-IN) gav større risiko for udvikling af depression end den

hyperaktiv/impulsive subtype (ADHD-HI). Det giver ikke umiddelbart mening primært at fokusere på at behandle ADHD-IN symptomer, så længe det er usikkert, hvilken rolle og hvor stor en rolle disse spiller. Ydermere er ADHD-HI symptomer fundet at have indflydelse på antallet af selvmordsforsøg, hvilket kunne hænge sammen med en øget tilbøjelighed til at følge impulser (Chronis-Tuscano, 2010, p.1048). Dette giver altså indikationer for at depression ikke må negligeres i ADHD-HI gruppen, på trods af at der synes at være højere risiko for at udvikle den i ADHD-IN. Resultaterne fra det SR bør derfor primært anvendes som et pejlemærke for den fremtidig forskning på området.

Konklusion

Dette projekt havde til hensigt at besvare den opstillede problemformulering: *Hvordan kan årsagen til en øget risiko for depression hos ADHD-populationen forklares og forstås, samt hvordan kan denne risiko forebygges og interveneres på?* I projektets første del blev det klarlagt, at associationen mellem ADHD og depression, har flere mulige forklaringsmodeller. Hvor det fremgik at associationen med stor sandsynlighed både kan forklares ud fra en fælles ætiologi bestående i genetiske og fælles miljø risikofaktorer samt yderligere kan forklares ud fra direkte og indirekte kausale mekanismer fra ADHD-diagnosen, samt at disse processer kan være komplicerede at skelne fra hinanden.

Igennem det SR blev de direkte og indirekte mekanismer undersøgt nærmere, og det blev klarlagt, at særligt selvopfattelse, søvnproblemer, psykiske lidelser hos moren, sociale vanskeligheder og ADHD-subtype synes at have en indflydelse på, at depression udvikles hos personer med ADHD. Der herskede tvetydige fund ved ADHD-symptomer, akademiske vanskeligheder og familiemiljøets betydning. Slutligt var der rimelig konsensus omkring, at ADHD-medicin og performancebaseret EF-færdigheder ikke havde nogen effekt på udviklingen af depression. Studierne i det SR er dog præget af usikkerheder omkring, hvordan faktorerne helt præcist interagere med ADHD, og derudover mangles der en forståelse af kønsforskelle. Ydermere findes flere faktorer af interesse, som ikke er inkluderet i det SR grundet undersøgelsernes design, som bør undersøges i fremtiden såsom emotionsregulering.

I projektets sidste del blev præventive tiltag og interventioner bearbejdet. I denne del kan det konkluderes, at der ikke findes mange undersøgelser af behandling

til komorbid ADHD og depression, men at mange af de tiltag, som allerede foreslås som behandling af ADHD eller depression individuelt, stemmer overens med de områder, som blev fundet at influere depression i det SR. De tiltag, der samles set anbefales til at afhjælpe eller forebygge depression inkluderer; 1) forældretræningsprogrammer og herudover screening og behandling af psykisk sygdom hos forældre til børn med ADHD; (2) søvn interventioner i form af søvnhygiejniske tiltag, adfærdsstrategier, samt evt. kugledyne og melatonin behandling; (3) kognitive adfærdsterapi for ældre børn; (4) Psyko-edukationelle tiltag i læringssituationer; (5) medicinske tiltag i tillæg til disse andre non-farmakologiske tiltag; (6)Fokus på forbedring af sociale vanskeligheder og forebyggelse af traumatiske begivenheder, herunder er der dog mangel på konkrete tiltag med evidens.

Referenceliste

Aghebati A, Gharraee B, Hakim Shoshtari M, Gohari MR. Triple p-positive parenting program for mothers of ADHD children. Iran J Psychiatry Behav Sci. 2014 Spring;8(1):59-65.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *40*(1), 57-87. https://doi.org/10.1111/1469-7610.00424

Antshel, K. M., Faraone, S. V., & Gordon, M. (2012). Cognitive behavioral treatment outcomes in adolescent ADHD. *Focus*, *10*(3), 334-345. https://doi.org/10.1177/1087054712443155

Arnold, L. E., Hodgkins, P., Kahle, J., Madhoo, M., & Kewley, G. (2020). Long-term outcomes of ADHD: academic achievement and performance. *Journal of attention disorders*, *24*(1), 73-85. https://doi.org/10.1177/1087054714566076

Bagwell, C. L., Molina, B. S., Pelham Jr, W. E., & Hoza, B. (2001). Attention-deficit hyperactivity disorder and problems in peer relations: Predictions from childhood to adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(11), (1285-1292) https://doi.org/10.1097/00004583-200111000-00008

Becker, S. P. (2020) ADHD and sleep: recent advances and future directions. Current Opinion in Psychology, 34, 50–56. https://doi.org/10.1016/j.copsyc.2019.09.006

Bhandari, P. (2022, December 05). *Correlation vs. Causation | Difference, Designs & Examples.* Scribbr. Retrieved December 14, 2022, from https://www.scribbr.com/methodology/correlation-vs-causation/

Biederman, J., Ball, S. W., Monuteaux, M. C., Mick, E., Spencer, T. J., McCreary, M., ... & Faraone, S. V. (2008). New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(4), 426-434. https://doi.org/10.1097/CHI.0b013e31816429d3

Biederman, J., Faraone, S., Mick, E., & Lelon, E. (1995). Psychiatric comorbidity among referred juveniles with major depression: fact or artifact?. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*(5), 579-590.

Birmaher, B., Ryan, N. D., Williamson, D. E., Brent, D. A., Kaufman, J., Dahl, R. E., ... & Nelson, B. (1996). Childhood and adolescent depression: a review of the past 10 years. Part I. *Journal of the American Academy of Child & Adolescent Psychiatry*, *35*(11), 1427-1439. https://doi.org/10.1097/00004583-199611000-00011

Blackman, G. L., Ostrander, R., & Herman, K. C. (2005). Children with ADHD and depression: a multisource, multimethod assessment of clinical, social, and academic functioning. *Journal of Attention Disorders*, *8*(4), 195-207. https://doi.org/10.1177/108705470527877

Boyko, E. J. (2013). Observational research—opportunities and limitations. *Journal of Diabetes and its Complications*, *27*(6), 642-648. https://doi.org/10.1016/j.jdiacomp.2013.07.007

Brinkmann, S. (2015). Forståelse og fortolkning, 69-97. In Jacobsen, M. H., Lippert-Rasmussen K., & Nedergaard, P. (Eds. Videnskabsteori - i statskundskab, sociologi og forvaltning (3nd ed., pp. 69–101). Hans Reitzel

Cain, K. M., & Dweck, C. S. (1995). The relation between motivational patterns and achievement cognitions through the elementary school years. *Merrill-Palmer Quarterly (1982-)*, 25-52.

Carrick, O & Tunick, R (2020) Kap. 9 - ADHD and Depression IN: Schonwald, A. (2020). *ADHD in Adolescents*. Springer International Publishing.

Catalá-López, F., Hutton, B., Page, M. J., Driver, J. A., Ridao, M., Alonso-Arroyo, A., ... & Tabarés-Seisdedos, R. (2022). Mortality in persons with autism spectrum disorder or attention-deficit/hyperactivity disorder: a systematic

review and meta-analysis. *JAMA pediatrics*, e216401-e216401. https://doi.org/10.1186/s13643-017-0581-9

Chen, T. J., Ji, C. Y., Wang, S. S., Lichtenstein, P., Larsson, H., & Chang, Z. (2016). Genetic and environmental influences on the relationship between ADHD symptoms and internalizing problems: A Chinese twin study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *171*(7), 931-937. https://doi.org/10.1002/ajmg.b.32411

Cole, J., Ball, H. A., Martin, N. C., Scourfield, J., & Mcguffin, P. (2009). Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(11), 1094-1101. https://doi.org/10.1097/CHI.0b013e3181b7666e

Cortese, S., Brown, T. E., Corkum, P., Gruber, R., O'Brien, L. M., Stein, M., Weiss, M., & Owens, J. (2013). Assessment and Management of Sleep Problems in Youths With Attention-Deficit/Hyperactivity Disorder. Journal of the American Academy of Child & Adolescent Psychiatry., 52(8), 784–796. https://doi.org/10.1016/j.jaac.2013.06.001

Dalmaijer, E. S. (2020). Twin studies with unmet assumptions are biased towards genetic heritability. bioRxiv. https://doi.org/10.1101/2020.08.27.270801

Davidsen, A. S. (2019) Farmakologisk behandling af unipolar depression hos voksne i almen praksis. https://www.sst.dk/da/Udgivelser/2019/Rationel-Farmakoterapi-9-2019/Farmakologisk-behandling-af-depression

Daviss, W. B. (2008). A Review of Co-Morbid Depression in Pediatric ADHD: Etiologies, Phenomenology, and Treatment. Journal of Child and Adolescent Psychopharmacology, 18(6), 565–571. https://doi.org/10.1089/cap.2008.032

Daviss, W. B. (2018). Depressive disorders and ADHD. *Moodiness in ADHD*, 91-109. Springer, Cham. https://doi.org/10.1007/978-3-319-64251-2_7

Di Lorenzo, R., Balducci, J., Poppi, C., Arcolin, E., Cutino, A., Ferri, P., . . . Filippini, T. (2021). Children and adolescents with ADHD followed up to adulthood: A systematic review of long-term outcomes. *Acta Neuropsychiatrica, 33*(6), 283-298. doi:10.1017/neu.2021.23

Erskine, H. E., Norman, R. E., Ferrari, A. J., Chan, G. C., Copeland, W. E., Whiteford, H. A., & Scott, J. G. (2016). Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: a systematic review and

meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(10), 841-850. https://doi.org/10.1016/j.jaac.2016.06.016

Fagudvalget for medicinsk behandling af ADHD under RADS (Rådet for Anvendelse af Dyr Sygehusmedicin), 2015. Behandlingsvejledning for medicinsk behandling af ADHD. Version 1.

Fagudvalget for medicinsk behandling af unipolar depression under RADS (Rådet for Anvendelse af Dyr Sygehusmedicin), 2015. Behandlingsvejledning inklusiv lægemiddelrekommandation for medicinsk behandling af unipolar depression. Version 1.

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular psychiatry*, *24*(4), 562-575. https://doi.org/10.1038/s41380-018-0070-0

Felson, J. (2014). What can we learn from twin studies? A comprehensive evaluation of the equal environments assumption. *Social science research*, *43*, 184-199. https://doi.org/10.1016/j.ssresearch.2013.10.004

Field-Fote, E. (2019). Mediators and Moderators, Confounders and Covariates: Exploring the Variables That Illuminate or Obscure the "Active Ingredients" in Neurorehabilitation. Journal of Neurologic Physical Therapy, 43(2), 83–84. https://doi.org/10.1097/NPT.0000000000000275

Fishman, P. A., Stang, P. E., & Hogue, S. L. (2007). Impact of comorbid attention deficit disorder on the direct medical costs of treating adults with depression in managed care. *Journal of Clinical Psychiatry*, *68*(2), 248-253. https://doi.org/10.4088/jcp.v68n0210

Frame, K., Kelly, L., & Bayley, E. (2003). Increasing Perceptions of Self-Worth in Preadolescents Diagnosed with ADHD. Journal of Nursing Scholarship., 35(3), 225–229. https://doi.org/10.1111/j.1547-5069.2003.00225.x

Franke, N., Keown, L. J., & Sanders, M. R. (2020). *An RCT of an Online Parenting Program for Parents of Preschool-Aged Children With ADHD Symptoms.* Journal of Attention Disorders, 24(12), 1716–1726. https://doi.org/10.1177/1087054716667598

Garber, J., & Hollon, S. D. (1991). What can specificity designs say about causality in psychopathology research?. *Psychological Bulletin*, *110*(1), 129. https://doi.org/10.1037/0033-2909.110.1.129

Gelfand, D. M., & Teti, D. M. (1990). The effects of maternal depression on children. *Clinical psychology review*, *10*(3), 329-353 https://doi.org/10.1016/0272-7358(90)90065-I

Geoffray, M. B., & Simonsen, E. (2017). 29. ADHD hos voksne. In Simonsen, E., & Møhl, B. (2017). Grundbog i psykiatri (2. udg., pp. 609-613). *København: Hans Reitzel*.

Gorostiaga, A., Aliri, J., Balluerka, N., & Lameirinhas, J. (2019). Parenting styles and internalizing symptoms in adolescence: A systematic literature review. *International journal of environmental research and public health*, *16*(17), 3192. **https://doi.org/10.3390/ijerph16173192**

Guo, C., Assumpcao, L., & Hu, Z. (2022). Efficacy of non-pharmacological treatments on emotional symptoms of children and adults with attention-deficit/hyperactivity disorder: a meta-analysis. *Journal of Attention Disorders*, *26*(4), 508-524. https://doi.org/10.1177/10870547211001953

Harpin, V., Mazzone, L., Raynaud, J. P., Kahle, J., & Hodgkins, P. (2016). Long-term outcomes of ADHD: a systematic review of self-esteem and social function. *Journal of attention disorders*, *20*(4), 295-305. https://doi.org/10.1177/1087054713486516

Hinshaw, S. P., Owens, E. B., Zalecki, C., Huggins, S. P., Montenegro-Nevado, A. J., Schrodek, E., & Swanson, E. N. (2012). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *Journal of consulting and clinical psychology*, *80*(6), 1041 https://doi.org/10.1037/a0029451

Hinshaw, S. P., Owens, E. B., Zalecki, C., Huggins, S. P., Montenegro-Nevado, A. J., Schrodek, E., & Swanson, E. N. (2012). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: Continuing impairment includes elevated risk for suicide attempts and self-injury. *Journal of Consulting and Clinical Psychology, 80*(6), 1041–1051. https://doi.org/10.1037/a0029451

Hiscock, H., Sciberras, E., Mensah, F., Gerner, B., Efron, D., Khano, S., & Oberklaid, F. (2015). Impact of a behavioural sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental

mental health: randomised controlled trial. BMJ (Online), 350(jan20 1), h68–h68. https://doi.org/10.1136/bmj.h68

Hughes, C. W., Emslie, G. J., Crismon, M. L., Posner, K., Birmaher, B., Ryan, N., ... & DEPRESSIVE, M. T. O. C. M. (2007). Texas children's medication algorithm project: update from Texas consensus conference panel on medication treatment of childhood major depressive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(6), 667-686. https://doi.org/10.1097/chi.0b013e31804a859b

Jacobsen, M. H., Lippert- Rasmussen K., & Nedergaard, P. (2015) Introduktion. Hvad er videnskabsteori? 13-26, In Jacobsen, M. H., Lippert- Rasmussen K., & Nedergaard, P. (Eds.), Videnskabsteori - i statskundskab, sociologi og forvaltning (3nd ed., pp. 69–101). Hans Reitzel

Jaffee, S. R., & Price, T. S. (2012). The implications of genotype–environment correlation for establishing causal processes in psychopathology. Development and Psychopathology, 24(4), 1253–1264. https://doi.org/10.1017/S0954579412000685

Jensen, C.M, Amdisen, B. L., Jørgensen, K. J., & Arnfred, S. M. H. (2016). Cognitive behavioural therapy for ADHD in adults: systematic review and meta-analyses. Attention Deficit and Hyperactivity Disorders, 8(1), 3–11. https://doi.org/10.1007/s12402-016-0188-3

Jeppesen, P., Obel, C., Lund, L., Madsen, K. B., Nielsen, L., & Nordentoft, M. (2020). Mental sundhed og sygdom hos børn og unge i alderen 10-24 år-forekomst, udvikling og forebyggelsesmuligheder. Kapitel 5.1 – Opmærksomheds- og hyperaktivitetsforstyrrelser (181-192) København*: Vidensråd for Forebyggelse*.

Kendall, K. M., Van Assche, E., Andlauer, T. F. M., Choi, K. W., Luykx, J. J., Schulte, E. C., & Lu, Y. (2021). The genetic basis of major depression. *Psychological Medicine*, *51*(13), 2217-2230. https://doi.org/10.1017/S0033291721000441

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (2010). Stressful life events, genetic liability, and onset of an episode of major depression in women. *Focus*, *8*(3), 459-470. https://doi.org/10.1176/foc.8.3.foc459

Kessing, L. V. & Miskowiak, K. (2017). 16. Affektive lidelser. In Simonsen, E., & Møhl, B. (2017). Grundbog i psykiatri (2. udg., pp. 347-381). *København: Hans Reitzel*.

Kliniske retningslinjer. (n.d.). https://www.kl.dk/kommunale-opgaver/sundhed/kliniske-retningslinjer/

Kratochvil, C. J., Newcorn, J. H., Arnold, L. E., Duesenberg, D., Emslie, G. J., Quintana, H., Sarkis, E. H., Wagner, K. D., Gao, H., Michelson, D., & Biederman, J. (2005). Atomoxetine Alone or Combined With Fluoxetine for Treating ADHD With Comorbid Depressive or Anxiety Symptoms. Journal of the American Academy of Child and Adolescent Psychiatry, 44(9), 915–924. https://doi.org/10.1097/01.chi.0000169012.81536.38

Lange, A. M., Daley, D., Frydenberg, M., Houmann, T., Kristensen, L. J., Rask, C., Sonuga-Barke, E., Søndergaard-Baden, S., Udupi, A., & Thomsen, P. H. (2018). Parent Training for Preschool ADHD in Routine, Specialist Care: A Randomized Controlled Trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *57*(8), 593–602. https://doi.org/10.1016/j.jaac.2018.04.014

Laursen, T. M., Musliner, K. L., Benros, M. E., Vestergaard, M., & Munk-Olsen, T. (2016). Mortality and life expectancy in persons with severe unipolar depression. *Journal of affective disorders*, *193*, 203-207 https://doi.org/10.1016/j.jad.2015.12.067

Lervåg, A. (2019). Correlation and causation: to study causality in psychopathology. *Journal of Child Psychology and Psychiatry*, *60*(6), 603-605. https://doi.org/10.1111/jcpp.13074

Libutzki, B., Ludwig, S., May, M., Jacobsen, R., Reif, A., & Hartman, C. (2019). Direct medical costs of ADHD and its comorbid conditions on basis of a claims data analysis. *European Psychiatry, 58*, 38-44. doi:10.1016/j.eurpsy.2019.01.019

Litt, J. S., Minich, N., Taylor, H. G., & Tiemeier, H. (2020). The inter-relationships of extremely low birth weight, asthma, and behavior: a study of common cause, mediation, and moderation. *Academic pediatrics*, *20*(7), 975-982. https://doi.org/10.1016/j.acap.2020.05.010

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., Burns, B., Domino, M., McNulty, S., Vitiello, B., & Severe, J. (2004). Fluoxetine,

Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression: Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial. JAMA : the Journal of the American Medical Association, 292(7), 807–820. https://doi.org/10.1001/jama.292.7.807

Margolis, A. A. (2020). Zone of proximal development, scaffolding and teaching practice. *Cultural-Historical Psychology*, *16*(3), 15-26. doi:10.17759/chp.2020160303

Martin, A. J. (2006.). Attention-Deficit/Hyperactivity Disorder (ADHD), Perceived Competence, and Self-Worth: Evidence and Implications for Students and Practitioners. In Hollar, D. (2012) Handbook of Children with Special Health Care Needs / (pp. 47–72). Springer New York,. https://doi.org/10.1007/978-1-4614-2335-5_3

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological methods*, *12*(1), 23. https://doi.org/10.1037/1082-989X.12.1.23

McKay, E., Cornish, K., & Kirk, H. (2022). Impairments in Emotion Recognition and Positive Emotion Regulation Predict Social Difficulties in Adolescent With ADHD. *Clinical Child Psychology and Psychiatry*, 13591045221141770. https://doi.org/10.1177/1359104522114177

Meinzer, M. C., Pettit, J. W., & Viswesvaran, C. (2014). The co-occurrence of attention-deficit/hyperactivity disorder and unipolar depression in children and adolescents: a meta-analytic review. *Clinical psychology review*, *34*(8), 595-607. https://doi.org/10.1016/j.cpr.2014.10.002

Meyer A. (2005) Cross-cultural issues in ADHD research. Journal of Psychology in Africa 101-106

Milberger, S., Biederman, J., Faraone, S. V., Murphy, J., & Tsuang, M. T. (1995). Attention deficit hyperactivity disorder and comorbid disorder: Issues of overlapping symptoms. *The American journal of psychiatry*. https://doi.org/10.1176/ajp.152.12.1793

Møhl, B. & Simonsen, E. (2017). 1. Med mennesket i centrum. In Simonsen, E., & Møhl, B. (2017). Grundbog i psykiatri (2. udg., pp. 29-61). *København: Hans Reitzel*.

National Institute for Health and Care Excellence. (2022. *Depression in children and young people: identification and management* (NICE guideline NG134). *https://www.nice.org.uk/guidance/ng134*

Newark, P. E., & Stieglitz, R. D. (2010). Therapy-relevant factors in adult ADHD from a cognitive behavioural perspective. *ADHD Attention Deficit and Hyperactivity Disorders*, *2*(2), 59-72. https://doi.org/10.1007/s12402-010-0023-1

Olsen L, Mortensen E, Bech P. Prevalence of major depression and stress indicators in the Danish general population. Acta Psychiatr Scand. 2004;109(2):96-103. https://doi.org/10.1046/j.0001-690X.2003.00231.x

Orri, M., Pingault, J. B., Turecki, G., Nuyt, A. M., Tremblay, R. E., Côté, S. M., & Geoffroy, M. C. (2021). Contribution of birth weight to mental health, cognitive and socioeconomic outcomes: two-sample Mendelian randomisation. *The British Journal of Psychiatry*, *219*(3), 507-514.

Ostrander, R., Crystal, D. S., & August, G. (2006). Attention deficit-hyperactivity disorder, depression, and self-and other-assessments of social competence: a developmental study. *Journal of Abnormal Child Psychology*, *34*(6), 772-786. https://doi.org/10.1007/s10802-006-9051-x

Park, S., Kim, B. N., Kim, J. W., Shin, M. S., Yoo, H. J., Lee, J., & Cho, S. C. (2014). Associations between maternal stress during pregnancy and offspring internalizing and externalizing problems in childhood. *International Journal of Mental Health Systems*, *8*(1), 1-8. https://doi.org/10.1186/1752-4458-8-44

Petticrew, M., & Roberts, H. (2006). *Systematic reviews in the social sciences: a practical guide*. Blacwell Publishing. Kap. 1-9 (1-265)

Poissant, H., Moreno, A., Potvin, S., & Mendrek, A. (2020). A Meta-analysis of Mindfulness-Based Interventions in Adults with Attention-Deficit Hyperactivity Disorder: Impact on ADHD Symptoms, Depression, and Executive Functioning. Mindfulness, 11(12), 2669–2681. https://doi.org/10.1007/s12671-020-01458-8

Pollak, Y., Dekkers, T. J., Shoham, R., & Huizenga, H. M. (2019). Risk-taking behavior in attention deficit/hyperactivity disorder (ADHD): A review of potential underlying mechanisms and of interventions. *Current psychiatry reports*, *21*(5), 1-11. https://doi.org/10.1007/s11920-019-1019-y

Rohde, P., Clarke, G. N., Lewinsohn, P. M., Seeley, J. R., & Kaufman, N. K. (2001). Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(7), 795-802. https://doi.org/10.1097/00004583-200107000-00014

Roth, D. L. & MacKinnon, D. P. (2012) 6 - Mediation analysis with longitudinal data: In Newsom, Jones, R. N., & Hofer, S. M. . *Longitudinal data analysis : a practical guide for researchers in aging, health, and social sciences* (1st edition). Routledge. https://doi.org/10.4324/9780203814208

Rudolph, K. D., Kurlakowsky, K. D., & Conley, C. S. (2001). Developmental and social–contextual origins of depressive control-related beliefs and behavior. *Cognitive Therapy and Research*, *25*(4), 447-475. https://doi.org/10.1023/A:1005538704056

Rydell, M., Taylor, M. J., & Larsson, H. (2017). Genetic and environmental contributions to the association between ADHD and affective problems in early childhood—A Swedish population-based twin study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *174*(5), 538-546. https://doi.org/10.1002/ajmg.b.32536

Safren, S. A. (2006). Cognitive-behavioral approaches to ADHD treatment in adulthood. *Journal of clinical Psychiatry*, *67*, 46.

Schrodek, E., & Swanson, E. N. (2012). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: Continuing impairment includes elevated risk for suicide attempts and self-injury. *Journal of Consulting and Clinical Psychology, 80*(6), 1041–1051. https://doi.org/10.1037/a0029451

Sciberras, E., Fulton, M., Efron, D., Oberklaid, F., & Hiscock, H. (2011). Managing sleep problems in school aged children with ADHD: A pilot randomised controlled trial. Sleep Medicine, 12(9), 932–935. https://doi.org/10.1016/j.sleep.2011.02.006

Shaw, M., Hodgkins, P., Caci, H., Young, S., Kahle, J., Woods, A. G., & Arnold, L. E. (2012). A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC medicine, 10*(1), 1-15. https://doi.org/10.1186/1741-7015-10-99

Sonuga-Barke, E. J., Daley, D., Thompson, M., Laver-Bradbury, C., & Weeks, A. (2001). Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(4), 402-408. https://doi.org/10.1097/00004583-200104000-00008

Steinberg, E. A., & Drabick, D. A. (2015). A developmental psychopathology perspective on ADHD and comorbid conditions: The role of emotion regulation. *Child Psychiatry & Human Development*, *46*(6), 951-966. https://doi.org/10.1007/s10578-015-0534-2

Storebø, O. J., Elmose Andersen, M., Skoog, M., Joost Hansen, S., Simonsen, E., Pedersen, N., Tendal, B., Callesen, H. E., Faltinsen, E., & Gluud, C. (2019). Social skills training for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years. The Cochrane Database of Systematic Reviews., 2019(6). https://doi.org/10.1002/14651858.CD008223.pub3

Sundhedsministeriet (2019) Vejledning om medikamentel behandling af børn og unge med psykiske lidelser https://www.retsinformation.dk/eli/retsinfo/2019/9726

Sundhedsstyrelsen, (2016) National klinisk retningslinje for non-farmakologisk behandling af unipolar depression https://www.sst.dk/da/Udgivelser/2016/NKR-Non-farmakologisk-behandling-af-unipolar-depression

Sundhedsstyrelsen, (2017) Udredning og behandling af ADHD hos voksne – national klinisk retningslinje https://www.sst.dk/da/udgivelser/2017/nkr-udredning-og-behandling-af-adhd-hos-voksne

Sundhedsstyrelsen, (2021) Udredning og behandling af ADHD hos børn og unge – national klinisk retningslinje https://www.sst.dk/da/udgivelser/2021/nkr-adhd-hos-boern-og-unge

Sundhedsstyrelsen, (2022) National klinisk retningslinje for behandling med melatonin ved søvnforstyrrelser hos børn og unge https://www.sst.dk/da/Udgivelser/2022/NKA_-Behandling-med-melatonin-ved-soevnforstyrrelser-hos-boern-og-unge

Sung, V., Hiscock, H., Sciberras, E., & Efron, D. (2008). Sleep Problems in Children With Attention-Deficit/Hyperactivity Disorder: Prevalence and the Effect on

the Child and Family. Archives of Pediatrics & Adolescent Medicine, 162(4), 336–342. https://doi.org/10.1001/archpedi.162.4.336

Thapar, A., Livingston, L. A., Eyre, O., & Riglin, L. (2023). Practitioner Review: Attention-deficit hyperactivity disorder and autism spectrum disorder–the importance of depression. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/jcpp.13678

Thompson, M. J., Laver-Bradbury, C., Ayres, M., Le Poidevin, E., Mead, S., Dodds, C., Psychogiou, L., Bitsakou, P., Daley, D., Weeks, A., Brotman, L. M., Abikoff, H., Thompson, P., & Sonuga-Barke, E. J. (2009). A small-scale randomized controlled trial of the revised new forest parenting programme for preschoolers with attention deficit hyperactivity disorder. *European child & adolescent psychiatry*, *18*(10), 605–616. https://doi.org/10.1007/s00787-009-0020-0

Uchida, M., Spencer, T. J., Faraone, S. V., & Biederman, J. (2018). Adult outcome of ADHD: an overview of results from the MGH longitudinal family studies of pediatrically and psychiatrically referred youth with and without ADHD of both sexes. *Journal of attention disorders*, *22*(6), 523-534. https://doi.org/10.1177/1087054715604360

Vygotsky, L. S. (1978). Mind in society: the development of higher psychological processes. 6. Interaction between learning and development. (79-92), Harvard University Press.

Wichstrøm, L., Belsky, J., & Steinsbekk, S. (2017). Homotypic and heterotypic continuity of symptoms of psychiatric disorders from age 4 to 10 years: a dynamic panel model. *Journal of Child Psychology and Psychiatry*, *58*(11), 1239-1247. https://doi.org/10.1111/jcpp.12754

World Health Organization. Depression. 2012 [27-11-2014].www.who.int/mediacentre/factsheets/fs369/en/.

Wozniak, J., Biederman, J., Kiely, K., Ablon, J. S., Faraone, S. V., Mundy, E., & Mennin, D. (1995). Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*(7), 867-876. https://doi.org/10.1097/00004583-199507000-00010

Wu, X., Bastian, K., Ohinmaa, A., & Veugelers, P. (2018). Influence of physical activity, sedentary behavior, and diet quality in childhood on the incidence of

internalizing and externalizing disorders during adolescence: a population-based cohort study. *Annals of Epidemiology*, *28*(2), 86-94. https://doi.org/10.1016/j.annepidem.2017.12.002