Appendix

**Table A1**

*Methods and Results of Previous Multiple Trajectory Studies of ADHD Symptoms in Autistic Individuals*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Sample | Age at baseline (yrs): *Mean* (*SD*), Range | Age at last follow-up (yrs):*Mean* (*SD*), Range | Follow-up interval | ADHD symptoms measure | Trajectories: % of sample |
| Visser et al. (2017) | 203 children who screened positive for ASD on the Early Screening of Autistic Traits Questionnaire70% met DSM-IV criteria for ASD | 2.7 (0.5),1.0 - 3.8 | 5.6 (0.9),3.6 - 7.8 | T2: Mean of 1.4 years after baselineT3: Mean of 1.5 years later | AP standard scores of the CBCL 1.5-5 | (1) Moderate-Decreasing AP scores: 48%(2) Moderate-Stable AP scores: 22%(3) Low-Increasing AP scores: 20%(4) Low-Stable AP scores: 5%(5) Moderate-Increasing AP scores: 5% |
| McCauley et al. (2020) | 194 children referred for autism diagnosis as young children78% received a diagnosis of ASD, mostly at age 2 years | 9.4 (-),5.7 - 11.8 | 25.7 (-),23.2 - 30.1 | T2: Mean of 5.6 years after baselineT3: Mean of 2.5 years laterT4: Mean of 2.9 years laterT5: Mean of 5.5 years later | AP standard scores of the CBCL 1.5-5 and CBCL School Age | (1) Low-Decreasing AP scores: 59% (2) High-Decreasing AP scores: 41% |
| Anderson et al. (2011) | 116 children referred for autism diagnosis or with non-ASD developmental delaysa56% met criteria for an autism diagnosis23% classified as 'broader autism spectrum disorder': individuals with autism traits who did not meet criteria for an autism diagnosis | 9.7b (-), - | 18.2b (-), - | Assessments every 4 months from the age of 13 to 18 years | Hyperactivity raw scores from the ABC | (1) Low-Decreasing: 44% (2) Moderate-Decreasing: 36%(3) High-Decreasing: 11%(4) Lowest-Decreasing: 9% |

*Note.* ABC = Aberrant Behavior Checklist; ADHD = attention-deficit/hyperactivity disorder; AP = attention problems; ASD = autism spectrum disorder; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SD = standard deviation; yrs = years.

aThis sample overlapped with that of McCauley et al. (2020)

bEstimated based on data presented in Table 1 of Anderson et al. (2011)

# Evaluating stability in function and meaning of the AP scales of the CBCL

Petersen et al. (2020) specified six criteria to demonstrate stability in function and meaning of two scales. The AP scales of the CBCL 1.5 – 5 and 6 – 18 meet these criteria, listed below.

1. *the content selected for the measures is judged to reflect the same construct based on theory and adequately samples different facets of the construct (content validity)*

The AP scales were derived through factor analysis of the 99 and 118 items of the CBCL 1.5 – 5 and 6 – 18, respectively, which aimed to assess an array of behaviour problems that manifest in childhood. Importantly, scores on both AP scales differentiate between children referred for behavioural difficulties and non-referred children and correlate strongly with ADHD symptoms as assessed by other measures as well as with ADHD diagnosis (Achenbach & Rescorla, 2000, 2001).

1. *good short-term test-retest reliability of the measures’ scores*

The manuals for the CBCL 1.5 – 5 and 6 – 18 report high test-retest reliability of the AP scales (Achenbach & Rescorla, 2000, 2001). In the current study, all Pearson correlations of the AP scale total scores from one time point to the next were significant (all *p* < .001) and ranged from 0.63 to 0.82, indicating acceptable test-retest reliability.

1. *the measures’ scores show convergent validity, as well as divergent validity with measures of other constructs*

Convergent validity is supported by a strong correlation between AP scale total scores at T4 (when the CBCL 1.5 – 5 was administered) with total scores at T5 (when the CBCL 6–18 was administered; *r* = 0.63, *p* < .001). Divergent validity is supported by low correlations between AP scores and Somatic Problems scores (ranging from 0.27 to 0.38 across the eight time points). Given that several cognitive and behavioural factors evaluated in the Pathways in ASD study are expected to be related to attention problems, our assessment of divergent validity was limited.

1. *the measures’ scores have a similar but not necessarily invariant factor structure across time*

The AP scales are considered to reflect a single construct, a model found to have acceptable fit for both the CBCL 1.5 – 5 and CBLC 6 – 18. Attention Problems scale items from both questionnaires have been found to load onto a factor separable from other CBCL syndrome scales in general population samples (e.g., Deutz et al., 2016; Geeraerts et al., 2015) as well as in autistic children (Pandolfi et al., 2009, 2012; Schiltz & Magnus, 2020).

1. *the measures’ scores have high internal consistency*

The CBCL 6–18 manual reports acceptable internal consistency of the AP scale with a Cronbach alpha of 0.86 (Achenbach & Rescorla, 2001). In the current study, Cronbach alpha values for the AP scale from the CBCL 1.5 – 5 (T1 to T4) ranged from .66 to .73 and those for the CBCL 6 – 18 (T5 to T8) ranged from .83 to .85.

1. *the measures’ scores are sensitive to change and show theoretically expected developmental change*

Randomized controlled trials analyzing pre- to post-intervention CBCL AP scores have found expected decreases in scores following treatment (e.g., Abedini et al. (2021)⸻mindfulness-based cognitive therapy for children hospitalized with cancer; Schottelkorb et al. (2020) ⸻child-centered play therapy for autistic children). The CBCL AP scale has shown developmental change in general population samples (Robbers et al., 2011) and in samples of children referred for ASD at an early age (McCauley et al., 2020; Visser et al., 2017).

# Identifying psychotropic substances

**Table A2**

*List of Psychotropic Medications Reported by Caregivers*

|  |  |  |
| --- | --- | --- |
| Psychotropic medications |  | Other names provided |
| Amitriptyline |  | Elavil |   |   |   |
| Amphetamine\dextroamphetamine\* |  | Adderall | Adderall XR |   |   |
| Aripiprazole |  | Abilify |   |   |   |
| Atomoxetine |  | Strattera  |   |   |   |
| Carbamazepine |  | Carbamazepine | Tegretol |   |   |
| Chloral hydrate  |  |   |   |   |   |
| Citalopram |  | Co-citalopram |   |   |   |
| Clobazam |  | Clobazam | Apo clobazam | Frisium |   |
| Clomipramine |  |   |   |   |   |
| Clonazepam |  | Rivotril  |   |   |   |
| Dextroamphetamine\* |  | Dexedrine |   |   |   |
| Divalproex |  | Depakote | Depakote sprinkles |  |   |
| Fluoxetine |  | apo fluoxetine | Prozac  |  |   |
| Fluvoxamine |  |   |   |   |   |
| Guanfacine |  | Intuniv | intuniv IR | iIntuniv XR  |   |
| Lamotrigine |  |  |   |   |   |
| Levetiracetam |  | Keppra  |   |   |   |
| Lisdexamfetamine |  | Vyvanse |  |   |   |
| Lithium |  |   |   |   |   |
| Lorazepam |  | Ativan |   |   |   |
| Methylphenidate  |  | Methylphenidate HCL | Ritalin | Biphentin | Concerta |
| Nortriptyline |  | Aventyl |   |   |   |
| Oxcarbazepine |  | Trileptal  |   |   |   |
| Paliperidone |  | Invega  |   |   |   |
| Paroxetine |  |   |   |   |   |
| Periciazine |  | Neuleptil  |   |   |   |
| Phenobarbital |  |   |   |   |   |
| Quetiapine |  | Seroquel  |   |   |   |
| Risperidone |  | Teva-Risperidone | Risperdal |  |   |
| Sertraline |  | Co-sertraline | Zoloft |  |   |
| Trazodone |  |   |   |   |   |
| Valproic acid |  | Valproate | Depakene |  Epival |   |

\*Generic name was not entered by any participant

## Systematic search and coding of soft psychotropics

### Search strategy and inclusion criteria

To identify studies evaluating the effectiveness of potential soft psychotropics, we searched the MEDLINE database via PubMed for articles with the substance name in the title or abstract as well as one of the following terms relating to psychotropic effects: ADHD, anxiety, attention/inattention, autism, behavior\*, bipolar, cogniti\*, compulsi\*, depress\*, hyperactiv\*, mood, obsessi\*, OCD, psychiatric, psychosis, schizophrenia, sleep. We applied the humans and meta-analysis filters. These searches were performed from September 2021 to March 2022. Title/abstract screening was performed to identify articles for full-text screening. Both stages of screening were performed by two independent reviewers. Disagreements were resolved through discussion.

Eligible studies were meta-analyses of RCTs evaluating the psychotropic effect(s) of the substances of interest relative to a placebo or another substance with previously demonstrated psychotropic effects. Eligible outcomes included cognition, psychological symptoms, behaviour, and sleep. Evaluations of the effect of a substance on biological markers of these outcomes were eligible (e.g., a study evaluating the effect of a substance on the sleep EEG). Studies had to be in English or French.

If the systematic review of meta-analyses did not provide support for the psychotropic effect(s) of a substance or no meta-analyses were identified, we ran the same search with the RCT filter instead of the meta-analysis filter. Eligible RCTs were double-blind, placebo-controlled trials or double-blind comparative trials (a) conducted after the date of the latest meta-analysis for a particular population and outcome (if any) or (b) evaluating populations or outcomes not covered by the identified meta-analyses (if any). Additional inclusion criteria were the same as for the meta-analysis search.

We categorized soft psychotropics based on the level of available evidence for their effectiveness. Substances for which a meta-analysis of randomized controlled trials (RCTs) in humans supported statistically significant effects on cognition, mood, or behaviour were classified as having “strong support”. Soft psychotropics with “moderate support” were those for which a double-blind, placebo-controlled trial or double-blind comparative trial with a substance with previously demonstrated psychotropic effects as the comparator supported their effectiveness; if more than one eligible trial was published for a particular population and outcome, the substance was classified as having moderate support when more RCTs supported the substance’s effectiveness than not. Substances for which only less methodologically rigorous clinical trials were performed or for which no trials had been published were classified as having “weak/no support”. Given the negligible concentrations of potentially active agents in homeopathic remedies, these were all classified as non-psychotropic substances.

### Results

**Table A3**

*Results of Systematic Searches of Meta-Analyses*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Substance name | Number of titles/abstracts screened | Number of full texts screened | Strong support for psychotropic effect | Reference |
| 5-hydroxytryptophan | 3 | 0 |  |  |
| **Acetyl L-carnitine** | 6 | 6 | **Yes** | (Veronese et al., 2018) |
| Alpha-lipoic acid | 3 | 0 |  |  |
| Belladonna | 0 |  |  |  |
| Bio-chelat | 0 |  |  |  |
| Calcium | 93 | 0 |  |  |
| Cat’s claw | 0 |  |  |  |
| Cannabis oil | 1 | 0 |  |  |
| **CBD oil** | 7 | 4 | **Yes** | (Kopelli et al., 2020) |
| Chlorella | 0 |  |  |  |
| Chlorophyll | 0 |  |  |  |
| Coconut oil | 0 |  |  |  |
| Coenzyme Q10 | 4 | 1 | No |  |
| **Corticosteroids** | 57 | 3 | **Yes** | (Prado & Crowe, 2019) |
| Dimercaptosuccinic acid | 0 |  |  |  |
| Dimethylglycine | 0 |  |  |  |
| Echinacea | 2 | 0 |  |  |
| **Flax (Omega-3)**a | 2 | 1 | **Yes** | (Sarris et al., 2011) |
| Folinic acid, folic acid, folateb | 3 | 3 | No |  |
| GABA | 33 | 1 | No |  |
| Glutathione | 41 | 0 |  |  |
| Henbane | 0 |  |  |  |
| Horsetail | 0 |  |  |  |
| **Iodine** | 16 | 4 | **Yes** | (Taylor et al., 2014) |
| **Iron** | 69 | 10 | **Yes** | (Cai et al., 2017) |
| Kelp | 1 | 0 |  |  |
| Lingonberry | 0 |  |  |  |
| L-glutamine | 1 | 0 |  |  |
| L-theanine | 1 | 1 | No |  |
| Magnesium | 29 | 0 |  |  |
| Malic acid | 1 | 0 |  |  |
| Manganese | 13 | 0 |  |  |
| **Melatonin** | 78 | 37 | **Yes** | (Sumsuzzman et al., 2021) |
| Omega-6 | 12 | 1 | No |  |
| Omega-9 | 0 |  |  |  |
| **Oxytocin** | 62 | 14 | **Yes** | (Chen et al., 2021) |
| Phenylbutyric acid | 0 |  |  |  |
| Phosphate/ phosphorus | 16 | 0 |  |  |
| Pinebark | 5 | 3 | No |  |
| **Probiotics** | 34 | 13 | **Yes** | (Jiang et al., 2021) |
| Red algae | 0 |  |  |  |
| Relaxin | 0 |  |  |  |
| Remicade | 10 | 2 | No |  |
| **Selenium** | 17 | 2 | **Yes** | (Toulis et al., 2010) |
| Taurine | 1 | 0 |  |  |
| Thymic protein | 0 |  |  |  |
| Trimethylglycine | 0 |  |  |  |
| Vervain | 0 |  |  |  |
| Vitamin A | 14 | 1 | No |  |
| **Vitamin B** | 11 | 6 | **Yes** | (S. Li et al., 2021) |
| Vitamin C | 20 | 1 | No |  |
| **Vitamin D** | 82 | 11 | **Yes** | (Cheng et al., 2020) |
| Vitamin E | 28 | 0 |  |  |
| **Zinc** | 50 | 6 | **Yes** | (da Silva et al., 2021) |

aSince flax is considered an omega-3 supplement, support for flax as a soft psychotropic was taken as support for other forms of omega-3 supplements.

**Table A4**

*Results of Systematic Searches of Randomized Controlled Trials (RCTs)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Substance name | Number of titles/abstracts screened | Number of full texts screened | Moderate support for psychotropic effect | Reference |
| **5-hydroxytryptophan** | 25 | 15 | **Yes** | (Yousefzadeh et al., 2020) |
| **Alpha-lipoic acid** | 13 | 2 | **Yes** | (Rezaei Kelishadi et al., 2021) |
| Belladonna | 0 |  |  |  |
| Bio-chelat | 0 |  |  |  |
| **Calcium** | 86 | 2 | **Yes** | (Ghanbari et al., 2009; Thys-Jacobs et al., 1989) |
| **Cannabis oil** | 5 | 2 | **Yes** | (Chaves et al., 2020) |
| Cat’s claw | 0 |  |  |  |
| Chlorella | 2 | 1 | No |  |
| Chlorophyll | 0 |  |  |  |
| Coconut oil | 7 | 1 | No |  |
| **Coenzyme Q10** | 23 | 9 | **Yes** | (Sawaddiruk et al., 2019) |
| Dimercaptosuccinic acid | 4 | 2 | No |  |
| Dimethylglycine | 6 | 1 | No | (Kern et al., 2001) |
| **Echinacea** | 2 | 1 | **Yes** | (Lopresti & Smith, 2021) |
| **Folinic acid, folic acid, folatea** | 248 | 35 | **Yes** | (Batebi et al., 2021; Frye et al., 2018) |
| **GABA** | 231 | 3 | **Yes** | (Hannant et al., 2021) |
| ***Glutathione*** | 108 | 3 | ***Possible b*** | (Mischley et al., 2015) |
| Henbane | 0 |  |  |  |
| Horsetail | 0 |  |  |  |
| Kelp | 0 |  |  |  |
| L-glutamine | 5 | 0 |  |  |
| Lingonberry | 0 |  |  |  |
| **L-theanine** | 28 | 20 | **Yes** | (Baba et al., 2021) |
| **Magnesium** | 126 | 18 | **Yes** | (Zhu et al., 2020) |
| Malic acid | 0 |  |  |  |
| Manganese | 2 | 0 |  |  |
| Omega-6 | 39 | 0 |  |  |
| Omega-9 | 1 | 0 |  |  |
| Phenylbutyric acid | 1 | 0 |  |  |
| Phosphate/ Phosphorus | 115 | 0 |  |  |
| **Pinebark** | 12 | 8 | **Yes** | (Hsu et al., 2021; Trebatická et al., 2006) |
| Red algae | 1 | 1 | No |  |
| Relaxin | 1 | 1 | No |  |
| **Remicade** | 21 | 10 | **Yes** | (Mansur et al., 2021) |
| **Taurine** | 17 | 4 | **Yes** | (O’Donnell et al., 2016) |
| Thymic protein | 2 | 0 |  |  |
| Trymethylglycine | 9 | 1 | No |  |
| Vervain | 0 |  |  |  |
| **Vitamin A** | 38 | 5 | **Yes** | (Bitarafan et al., 2016) |
| **Vitamin C** | 74 | 7 | **Yes** | (De Oliveira et al., 2015) |
| **Vitamin E** | 94 | 15 | **Yes** | (Bošković et al., 2016) |

aSince folinic acid and folic acid both work to increase folate, studies combining these supplements were reviewed to evaluate level of support for the psychotropic effect of any of these substances.

b Supportive study was specifically for intra-nasally administered glutathione. We coded as No moderate support.

# Missingness

Four children were excluded from the current analyses because they were found to be ineligible for the Pathways in ASD study after recruitment. One child was diagnosed with neurofibromatosis with brain lesions, one was diagnosed with a chromosomal abnormality, one did not meet research criteria for an ASD diagnosis, and one was noted to be ineligible without a recorded reason.

## Associations of missingness of AP scores with analysis variables and auxiliary variables

Missingness of AP scores at T1 was associated with higher AP scores at T3 (*p* = .04). Missing AP scores at T2 were associated with higher SER (*p* = .01) and higher caregiver depression symptoms (*p* = .03); missingness at T3 was associated with higher SER (*p* = .003), and younger age of primary caregiver (*p* = .01); missingness at T4 was associated with lower ADOS RRB-CSS (*p* = .02) and younger age of primary caregiver (*p* = .002); missingness at T6 was associated with lower child FSIQ (*p* = .001) and communication skills (*p* = .002), higher SER (*p* = .01), and younger age of primary caregiver (*p* < .001); missingness at T7 was associated with lower child FSIQ (*p* = .01) and child communication skills (*p* =.03); missingness at T8 was associated with lower child FSIQ (*p*= .002) and communication skills (*p* < .001), higher SER (*p* = .02), and younger age of primary caregiver (*p* = .04).

## Extent of missingness per variable

**Table A5**

*Extent of Missingness per Variable*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Variable | Measure | Time point | % missingness |
| Analysis variables |  |  |  |
|  | Age at diagnosis |  | T1 | 0 |
| Autism symptom severity scores | ADOS | T1 | 1.3 |
| FSIQ | M-P-R or WPPSI-III | T1 | 4.5 |
| Socio-economic risk | FBIQ | T1 | 12.7 |
| Communication skills | VABS-II | T1 | 2.5 |
| Social skills | VABS-II | T8 | 44.8 |
| Attention problems | CBCL 1.5-5 | T1 | 8.1 |
|  | CBCL 1.5-5 | T2 | 17.3 |
|  | CBCL 1.5-5 | T3 | 23.9 |
|  | CBCL 1.5-5 | T4 | 36.6 |
|  | CBCL 6-18 | T5 | 50 |
|  | CBCL 6-18 | T6 | 46.8 |
|  | CBCL 6-18 | T7 | 60.1 |
|  | CBCL 6-18 | T8 | 55.7 |
|  | Caregiver age at consent | FBIQ | T1 | 0 |
|  | Caregiver depression | SCL-90-R | T1 | 12.7 |
| Auxiliary variable |  |  |  |
|  | Caregiver employment status | FBIQ | T1 | 4.6 |

*Note.* ADOS = Autism Diagnostic Observation Schedule; CBCL = Child Behavior Checklist; FBIQ = Family Background Information Questionnaire; FSIQ = Full Scale Intelligence Quotient; GHC = General Health Questionnaire; M-P-R = Merrill-Palmer-Revised Scales of Development; SCL-90-R = Symptom Checklist-90-Revised; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence – Third Edition.

# Group-based trajectory modeling

**Table A6**

*Model Fit Indices*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Number of groups | Trajectory shape | BIC(1) | BIC(2) | Bayes factor (1) | Bayes factor (2) | Interpretation | deltaBIC (1) | deltaBIC (2) | Interpretation |
| 1 | Linear | 132.9 | 135.21 |  |  |  |  |  |  |
| 2 | Linear | 463.63 | 469.27 | 2.3216E-144 | 8.3097E-146 | Strong evidence | 661.46 | 668.12 | Very strong |
| 3 | Linear | 629.07 | 637.94 | 1.41358E-72 | 5.59178E-74 | Strong evidence | 330.88 | 337.34 | Very strong |
| 4 | Linear | 704.66 | 716.75 | 1.48484E-33 | 5.93269E-35 | Strong evidence | 151.18 | 157.62 | Very strong |
| 5a | Linear | 733.01 | 748.33 | 4.8725E-13 | 1.92744E-14 | Strong evidence | 56.7 | 63.16 | Very strong |
| 6 | Linear | 750.77 | 769.31 | 1.93611E-08 | 7.73574E-10 | Strong | 35.52 | 41.96 | Very strong |
| 7 | Linear | 774.6 | 796.37 | 4.47469E-11 | 1.77007E-12 | Strong | 47.66 | 54.12 | Very Strong |
| 5 | Quadratic(1) | 728.76 | 744.89 | *70.10541235* | *31.18695817* | *Evidence against* | - | - | - |
| 5 | Quadratic(2) | 726.38 | 742.5 | - | - | - | - | - | - |
| 5 | Quadratic(3) | 726.38 | 742.5 | - | - | - | - | - | - |
| 5 | Quadratic(4) | 729.27 | 745.4 | - | - | - | - | - | - |
| 5 | Quadratic(5) | 729.35 | 745.47 | - | - | - | - | - | - |
| 5 | Cubic(1) | 728.57 | 745.5 | *84.77494167* | *16.94546082* | Strong evidence against | - | - | - |
| 5 | Cubic(2) | 727.76 | 744.69 | - | - | - | - | - | - |
| 5 | Cubic(3) | 722.48 | 739.41 | - | - | - | - | - | - |
| 5 | Cubic(4) | 726.26 | 743.19 | - | - | - | - | - | - |
| 5 | Cubic(5) | 722.81 | 739.74 | - | - | - | - | - | - |
| 5 | Stable (1) | 733.19 | 747.71 | 0.835270211 | 1.858928042 | Weak evidence for model (i) and weak evidence for model j | 0.36 | -1.24 | Not supported |
| 5 | Stable (2) | 733.61 | 748.13 | 0.548811636 | 1.221402758 | Same as above | - | - | - |
| 5 | Stable (3) | 729.88 | 744.39 | 22.87397954 | 51.4186013 | Strong evidence for Model (i) | - | - | - |
| 5 | Stable (4) | 722.84 | 737.35 | 26108.07676 | 58688.55427 | Strong evidence for Model (i) | - | - | - |
| 5 | Stable (5) | 731.94 | 746.45 | 2.9153795 | 6.553504862 | Weak to Moderate evidence for Model (i) | - | - | - |
| 5b | Stable (1,5) | 735.7 | 749.41 | 0.067880939 | 0.339595526 | Strong - Moderate evidence for this model | 5.38 | 2.16 | Moderate |
| a This model was selected over the 4-group linear model given the similar fit and adequacy of these models and the potential clinical significance of a fifth group.b A five-group model with stable slopes for Groups 1 and 5 was selected prior to incorporation of the dropout function. |

**Figure A1**

***BIC values for linear models***

**Table A7**

***Adequacy indices***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 4 Group model: Linear  |   |   |  |  |  |
|   | APP | pi | APP/(1-APP) | pi/(1-pi) | OCC | p | pi - p | /pi-p/ |
| Grp 1 | **0.98** | 0.16274 | 49 | 0.194372 | **252.09** | 0.145 | 0.01774 | 0.0177396 |
| Grp 2 | **0.88** | 0.483232 | 7.333333 | 0.935105 | **7.84** | 0.506 | -0.02277 | 0.0227678 |
| Grp 3 | **0.83** | 0.262764 | 4.882353 | 0.356418 | **13.70** | 0.27 | -0.00724 | 0.007236 |
| Grp 4 | **0.89** | 0.091242 | 8.090909 | 0.100403 | **80.58** | 0.079 | -0.00409 | 0.004088067 |
|  |  |  |  |  |  |  | sum: | 0.012957867 |
| 5 Group model: Linear |   |   |   |   |  |  |  |
|   | APP | pi | App/(1-APP) | pi/(1-pi) | OCC | p | pi - p | /pi-p/ |
| Grp 1 | **0.97** | 0.162783 | 32.33333 | 0.194433 | **166.30** | 0.148 | 0.014783 | 0.0147828 |
| Grp 2 | **0.82** | 0.238817 | 4.555556 | 0.313745 | **14.52** | 0.254 | -0.01518 | 0.0151826 |
| Grp 3 | **0.81** | 0.352465 | 4.263158 | 0.544318 | **7.83** | 0.366 | -0.01354 | 0.0135351 |
| Grp 4 | **0.71** | 0.138581 | 2.448276 | 0.160875 | **15.22** | 0.142 | -0.00342 | 0.0034192 |
| Grp 5 | **0.89** | 0.107354 | 8.090909 | 0.120265 | **67.28** | 0.089 | 0.018354 | 0.0183541 |
|  |  |  |  |  |  |   | sum: | 0.01305476 |
|  |  |  |  |  |  |  |  |  |
| 5 Group model: Stable and Linear |   |   |   |  |  |  |
|   | APP | pi | App/(1-APP) | pi/(1-pi) | OCC | p | pi - p | /pi-p/ |
| Grp 1-Stable | **0.96** | 0.156534 | 24 | 0.185584 | **129.32** | 0.145 | 0.011534 | 0.0115336 |
| Grp 2 | **0.75** | 0.19904 | 3 | 0.248501 | **12.07** | 0.173 | 0.02604 | 0.0260396 |
| Grp 3 | **0.76** | 0.255259 | 3.166667 | 0.342749 | **9.24** | 0.267 | -0.01174 | 0.0117406 |
| Grp 4 | **0.81** | 0.315424 | 4.263158 | 0.460759 | **9.25** | 0.351 | -0.03558 | 0.0355757 |
| Grp 5-Stable | **0.88** | 0.073743 | 7.333333 | 0.079614 | **92.11** | 0.064 | 0.009743 | 0.0097431 |
|  |  |  |  |  |  |   | sum: | 0.01892652 |

# Psychotropic medication and soft psychotropic use

**Table A8**

*Frequency of Use of Psychotropic Medication and Soft Psychotropics Across Time Points*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Timepoint | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |  | Use at ≥ one time point |
| Mean age in years (*SD)* | 3.41 (0.78) | 3.99 (0.79) | 4.51 (0.76) | 7.52 (0.32) | 7.27 (0.23) | 8.73 (0.20) | 9.71 (0.22) | 10.76 (0.24) |  |  |
|  | % using psychotropic medication |
| Total sample | 3.2 | 4.5 | 4.2 | 10.1 | 18.8 | 22.7 | 27.3 | 31.7 |  |  |
|  | LS(*n* = 57) | 1.9 | 2.1 | 2.0 | 2.5 | 9.7 | 12.8 | 16.0 | 19.4 |  | 14.0 |
|  | LI(*n* = 68) | 1.8 | 5.5 | 7.3 | 10.9 | 16.2 | 15.6 | 15.2 | 22.2 |  | 19.1 |
|  | LD(*n* = 105) | 2.4 | 1.4 | 1.4 | 2.9 | 11.1 | 12.1 | 21.2 | 25.5 |  | 14.9 |
|  | MD(*n* = 138) | 3.8 | 6.3 | 4.3 | 15.9 | 25.8 | 36.1 | 40.5 | 45.1 |  | 33.1 |
|  | HS(*n* = 25) | 11.8 | 12.5 | 11.1 | 28.6 | 41.7 | 46.7 | 60.0 | 63.6 |  | 43.5 |
| ꭓ2, *p* |  |  |  |  |  |  |  |  |  | 18.86, **< .001** |
|  | % using ADHD medication |
| Total sample | 1.3 | 0.7 | 1.0 | 2.5 | 8.2 | 10.6 | 15.4 | 19.4 |  |  |
|  | LS(*n* = 57) | 0 | 0 | 0 | 0 | 3.2 | 7.7 | 11.1 | 9.7 |  | 8.8 |
|  | LI(*n* = 68) | 0 | 0 | 1.8 | 0 | 5.3 | 4.3 | 5.7 | 13.9 |  | 10.3 |
|  | LD(*n* = 105) | 1.2 | 0 | 0 | 1.4 | 4.3 | 6.7 | 8.8 | 14.8 |  | 9.9 |
|  | MD(*n* = 138) | 1.9 | 1.0 | 0 | 3.4 | 12.1 | 17.6 | 23.3 | 28.3 |  | 17.7 |
|  | HS(*n* = 25) | 5.9 | 5.9 | 10.5 | 17.6 | 25.0 | 20.0 | 50.0 | 41.7 |  | 34.8 |
| ꭓ2, *p* |  |  |  |  |  |  |  |  |  | 11.45**.02** |
|  | % using soft psychotropicsa |
| Total sample | 18.9 | 19.0 | 23.4 | 23.7 | 18.1 | 19.1 | 23.6 | 22.8 |  |  |
|  | LS(*n* = 57) | 17.0 | 20.8 | 19.6 | 22.0 | 6.5 | 17.9 | 12.0 | 12.9 |  | 38.6 |
|  | LI(*n* = 68) | 14.3 | 14.5 | 24.6 | 16.7 | 22.2 | 21.7 | 30.3 | 27.8 |  | 44.1 |
|  | LD(*n* = 105) | 18.8 | 18.9 | 20.8 | 22.5 | 13.3 | 15.0 | 21.2 | 19.2 |  | 36.6 |
|  | MD(*n* = 138) | 22.4 | 19.0 | 22.9 | 27.3 | 26.6 | 21.4 | 27.9 | 24.5 |  | 50.8 |
|  | HS(*n* = 25) | 17.6 | 29.4 | 42.1 | 37.5 | 8.3 | 20.0 | 20.0 | 41.7 |  | 60.9 |
|  | ꭓ2, *p* |  |  |  |  |  |  |  |  |  | 7.84, .10 |

*Note.* HS = High-Stable trajectory group; LS = Low-Decreasing trajectory group; LS = Low-Stable Trajectory group; MD = Moderate-Decreasing trajectory group.

% values are calculated based on number of participants with interpretable psychotropic substance data.

a Soft psychotropics with moderate to strong evidence of psychotropic effect.

# Sensitivity analysis

Sensitivity analyses examining the association of trajectory group membership with VABS Socialization scores at T8 were performed in multiply imputed datasets.

## Multiple imputation

The number of imputations (N = 40) was selected based on White et al.’s (2011) suggestion of performing a number of imputations larger than the percentage of missing data amongst the eligible participants⸺ 33% of values were missing in our analysis data set. The imputation model included all variables used in the trajectory analyses. The fully conditional specification method of imputation was applied. Missing data were sequentially imputed from variables with the least missing data to those with the most missing data. The singularity threshold was set to 10-8 (as opposed to the SPSS default of 10-12), following the recommendation of Wang and Johnson (2019). In their study, they found that setting the singularity threshold to this value (in addition to increasing the number of imputations above the default 5 in SPSS) helped to increase the replicability of findings. Pooled parameter estimates were obtained using Rubin’s rule (K. H. Li et al., 1991; Wang & Johnson, 2019).

## Results

ANCOVAs with ADOS SA-CSS, ADOS RRB-CSS, FSIQ, and VABS-II Communication Standard Score were planned. However, due to significant differences between trajectory groups in child FSIQ and VABS-II Communication Standard Score (Table A9), only ADOS SA-CSS and ADOS RRB-CSS were included as covariates (Miller & Chapman, 2001). It is worth noting that the significant group differences in VABS-II Communication Standard Score may partly be accounted for by caregivers conflating receptive language skills and attention problems.

**Table A9**

*Comparisons of Potential Covariates Across Trajectory Groups*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trajectory groups | ADOS SA-CSS | ADOS-RRB CSS | FSIQ | VABS-II Communication Standard Score |
| Low-Stable | 7.00 (1.75) | 7.65 (1.77) | 59.82 (25.81) | 82.49 (12.79) |
| Low-Increasing | 7.72 (1.69) | 7.97 (1.70) | 52.29 (28.27) | 74.66 (17.27) |
| Low-Decreasing | 7.24 (1.96) | 7.72 (1.90) | 53.94 (27.54) | 74.54 (14.22) |
| Moderate-Decreasing | 7.49 (1.84) | 8.03 (1.54) | 44.24 (28.28) | 69.41 (16.03) |
| High-Stable | 8.17 (1.79) | 7.54 (1.69) | 52.08 (36.48) | 67.00 (15.60) |
|  | *F*(4, 387) = 2.50, *p* = .04 | *F*(4,387) = 0.99, *p* = .41 | *F*(4,374) = 3.53, ***p* = .008** | *F*(4,382) = 8.59, ***p* < .001** |
|  | - | - | LS > MD | LS > LI = LD = MD = HS |

*Note.* HS = High-Stable trajectory group; LD = Low-Decreasing trajectory group; LI = Low-Increasing trajectory group; LS = Low-Stable trajectory group; MD = Moderate-Decreasing trajectory group.

The pooled estimates from ANCOVAs with T1ADOS SA-CSS and ADOS RRB-CSS as covariates and with simple contrasts to the High-Stable group indicated that the Low-Stable (*t*(388) = 4.38, *p* < .001), Low-Increasing (*t*(388) = 2.30, *p* = .02) and Low-Decreasing (*t*(388) = 3.33, *p* ≤ .001) groups have higher VABS socialization scores at T8 than the High Stable group. There was no significant difference in mean Socialization scores of the High-Stable and Moderate-Decreasing groups (*t*(388) = 0.89, *p* = .37). Neither of the included covariates was significantly associated with VABS Socialization. These results are consistent with those obtained through PROC TRAJ.

# Comparing trajectory groups on teacher-reported VABS-II Socialization scores

**Figure A2**

***VABS-II Socialization standard scores from teacher reports in each Attention Problems trajectory group with 95% confidence intervals***



*Note.* The confidence intervals of the Moderate-Decreasing and High-Stable groups do not overlap with those of the Low-Stable or Low-Decreasing groups. Confidence intervals of the Low-Increasing group do not overlap with the Low-Stable or Low-Decreasing groups.

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