**Supplementary information**

**Online Resource 1.** Additional information on participants.

The data used in this study originate from the Lifelines Cohort Study [1,2]. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. All individuals aged between 25 and 50, living in the three Northern provinces of the Netherlands, were invited through their general practitioners (GPs); note that in the Netherlands every resident is registered at a general practice. Individuals were not eligible if they had a severe psychiatric or physical illness, limited life expectancy, or insufficient knowledge of the Dutch language. Inhabitants of the Northern provinces that were not invited by their GP but did meet above-mentioned criteria could register themselves via the Lifelines website. At baseline measurement (2006–2013), the Lifelines cohort consisted of 167,729 participants and included children from 6 months, elderly people up to 93 years, and somewhat more women than men (57.9% vs. 42.1%). Over two-thirds of the participants had at least one family member participating in Lifelines. For more information about the Lifelines Cohort Study see [1–3].

The data used in the current study were obtained from an add-on study implemented in Lifelines that was collected from 2017 to 2019. This add-on study was performed as part of the research conducted by the EU-funded CoCA consortium: Comorbid Conditions of ADHD as described in the main text.

**Online Resource 2.** Additional information on measures.

*Attention-Deficit/Hyperactivity Disorder.* Among all participants, ADHD symptoms were assessed with the Dutch version of the ADHD DSM-IV questionnaire [4,5]. The questionnaire consists of 11 inattention items and 12 hyperactivity items that are scored from 0 ‘’never or rarely present’’ to 3 ‘’very often present’’. These 23 items indicate the presence or absence of each of the 18 DSM-IV ADHD symptoms (some symptoms are measured by two items) during the past six months. A symptom is considered present when one of the corresponding items is rated 2 or higher which results in a sum score ranging from 0 to 18. The Dutch version of the ADHD DSM-IV questionnaire has been shown good psychometric properties [4].

*Aggressive behaviour.* In childhood and adolescence, aggressive behaviour was assessed with the Child Behaviour Checklist (CBCL) [6,7]. The aggressive behaviour subscale of the CBCL includes 18 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 36. The score indicates the severity of aggressive behaviour problems during the past six months. In adulthood, aggressive behaviour was assessed with the Adult Self Report (ASR) [7]. The aggressive behaviour subscale of the ASR includes 15 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 30. The score indicates the severity of aggressive behaviour problems during the past six months. The CBCL and ASR have been shown good psychometric properties [6,7].

*Depression.* In childhood and adolescence, depression was assessed with the CBCL [6,7]. The DSM-IV affective problems subscale of the CBCL includes 13 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 26. The score indicates the severity of affective problems during the past six months. In adulthood, Major Depressive Disorder and Dysthymia were assessed with the Dutch version of the Mini-international Neuropsychiatric Interview (MINI-S) [8]. The MINI is a standardized diagnostic interview that indicates the severity of DSM-IV Major Depressive Disorder during the past year and Dysthymia during the past two years. Interview skips (i.e., previous versions of the MINI contained interview skips when participants answered no to the presence of core symptoms) were removed so that we had full information on all possible symptoms. The MINI has been shown good psychometric properties [8,9].

*Anxiety.* In childhood and adolescence, the presence of anxiety was assessed with the CBCL [6,7]. The DSM-IV anxiety problems subscale of the CBCL includes 6 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 12. The score indicates the severity of anxiety problems during the past six months. In adulthood, Anxiety Disorders were assessed with the MINI-S [8]. The MINI indicates the severity of DSM-IV Panic Disorder, Social Phobia, and Generalized Anxiety Disorder (GAD) during the past year.

*Autism spectrum problems.* In childhood and adolescence, Autism Spectrum Disorder problems were assessed with the Child Social Behaviour Questionnaire (CSBQ) [10]. The CSBQ consists of 49 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 98. The score indicates problems among seven subdomains during the past three months: reduced contact, reduced social insight, reduced empathy, violation of social conventions, resistance to change, stereotyped behaviour, and violation of communication rules. In adulthood, Autism Spectrum Disorder problems were assessed with the Adult Social Behaviour Questionnaire (ASBQ) [11]. The ASBQ consists of 44 items that are scored from 0 ‘’never or rarely present’’ to 2 ‘’very often present’’ and result in a sum score ranging from 0 to 88. The score indicates problems among six subdomains during the past three months: reduced contact, reduced social insight, reduced empathy, violation of social conventions, resistance to change, and stereotyped behaviour. The CSBQ and ASBQ have been shown good psychometric properties [10–12].

*Substance use.* In childhood, substance use was assessed by asking the children’s parents whether they smoked, how often they drank alcohol, and how often they used drugs during the past year. In adolescence and adulthood, substance use was assessed by asking the participants how often they smoked, how often they drank alcohol, and how often they used drugs during the past year.

For more information about how participants were classified as having neurodevelopmental and/or psychiatric problems see Online Resource 3.

**Online Resource 3.** Additional information about how participants were classified as having neurodevelopmental or psychiatric problems.

Participants were classified as having depression and/or anxiety when they met the DSM-IV criteria. MDD was considered present when one core symptom and at least four additional symptoms were present or when both core symptoms and at least three additional symptoms were present [9]. Dysthymia was considered present when all core symptoms and at least two additional symptoms were present [9]. Panic Disorder was considered present when all core symptoms and at least four additional symptoms were present [9]. Social Phobia was considered present when all core symptoms were present [9]. GAD was considered present when all core symptoms and at least three additional symptoms were present [9].

Participants were classified as substance users when they were current smokers, drank more than one and a half glasses of alcohol per day, used cannabis or magic mushrooms, or used any hard drugs (i.e., if any of the following categories was rated as “yes”: amphetamines, cocaine, heroin, or ecstasy).

The questionnaires that were used to assess ADHD, autism spectrum problems, aggressive behaviour, and depression and anxiety in childhood and adolescence only yield continuous scores. Participants were classified as having these problems when their score exceeded a cut-off score that was set to reflect the prevalence in the general population which has been established by previous research [13–19]. We used frequency tables to identify cut-off scores that most closely matched the prevalence in the general population. When two adjacent scores resulted in prevalence rates similarly close to the population prevalence, we favoured the cut-off score that resulted in the highest prevalence. The reason to favour the higher cut-off scores was the prevalence of 1% for autism spectrum problems which is quite low for model estimation. This number would be even lower if we accepted prevalence rates below 1%.

The sample prevalence of neurodevelopmental and psychiatric problems in childhood, adolescence, and adulthood is displayed in ST1.

**ST1.** Sample prevalence in CoCA add-on study in Lifelines cohort.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sample prevalence** | | |
|  | *Childhood* | *Adolescence* | *Adulthood* |
| ***ADHD*** | 4.7% | 4.1% | 2.7% |
| ***Inattention*** | 4.9% | 3.9% | 3.0% |
| ***Hyperactivity-impulsivity*** | 5.8% | 4.2% | 3.2% |
| ***ASD*** | 1.0% | 1.2% | 1.1% |
| ***Reduced contact*** | 1.0% | 1.2% | 1.3% |
| ***Reduced empathy*** | 1.7% | 1.2% | 1.1% |
| ***Violation of social conventions*** | 1.1% | 1.1% | 1.0% |
| ***Reduced social insight*** | 1.0% | 1.2% | 1.0% |
| ***Stereotyped behaviour*** | 1.0% | 1.4% | 1.1% |
| ***Resistance to change*** | 1.6% | 2.0% | 1.6% |
| ***Aggressive behaviour*** | 5.1% | 3.4% | 2.7% |
| ***Depression*** | 1.3% | 3.7% | 6.3% |
| ***Anxiety*** | 2.8% | 4.0% | 8.0% |
| ***Smoking*** | 0.0% | 1.4% | 6.7% |
| ***Alcohol consumption*** | 0.0% | 1.4% | 12.3% |
| ***Soft drug use*** | 0.0% | 4.6% | 2.9% |
| ***Hard drug use*** | 0.0% | 0.2% | 1.9% |

*Notes:* CoCA = Comorbid Conditions of ADHD; ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder.**REFERENCES**

[1] Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, et al. Universal risk factors for multifactorial diseases: LifeLines: A three-generation population-based study. Eur J Epidemiol 2008;23:67–74. https://doi.org/10.1007/s10654-007-9204-4.

[2] Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol 2015;44:1172–80. https://doi.org/10.1093/ije/dyu229.

[3] Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines Cohort Study. PLoS ONE 2015;10:1–12. https://doi.org/10.1371/journal.pone.0137203.

[4] Kooij JJS, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CAT, Hodiamont PPG. Internal and external validity of Attention-Deficit Hyperactivity Disorder in a population-based sample of adults. Psychol Med 2005;35:817–27. https://doi.org/10.1017/S003329170400337X.

[5] DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV: Checklists, norms, and clinical interpretation. New York, NY, US: Guilford Press; 1998.

[6] Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms and profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families.; 2001.

[7] Achenbach TM, Ivanova MY, Rescorla LA. Empirically based assessment and taxonomy of psychopathology for ages 1½–90+ years: Developmental, multi-informant, and multicultural findings. Compr Psychiatry 2017;79:4–18. https://doi.org/10.1016/j.comppsych.2017.03.006.

[8] Overbeek, Schruers. MINI-S for DSM-5 Dutch version. 2019.

[9] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychoatric Interview (M.I.N.I.): The Development and Valiation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–33.

[10] Hartman CA, Luteijn E, Moorlag H, de Bildt A, Minderaa RB. CSBQ, revised manual 2007. Children’s social behavior questionnaire. Amsterdam: Harcourt Test Publishers; 2008.

[11] Horwitz EH, Schoevers RA, Ketelaars CEJ, Kan CC, van Lammeren AMDN, Meesters Y, et al. Clinical assessment of ASD in adults using self- and other-report: Psychometric properties and validity of the Adult Social Behavior Questionnaire (ASBQ). Res Autism Spectr Disord 2016;24:17–28. https://doi.org/10.1016/j.rasd.2016.01.003.

[12] Hartman CA, Luteijn E, Serra M, Minderaa RB. Refinement of the Children’s Social Behavior Questionnaire (CSBQ): An instrument that describes the diverse problems seen in milder forms of PDD. J Autism Dev Disord 2006;36:325–42. https://doi.org/10.1007/s10803-005-0072-z.

[13] Gadow KD, Sprafkin J, Schneider J, Nolan EE, Schwartz J, Weiss MD. ODD, ADHD, Versus ODD+ADHD in Clinic and Community Adults. J Atten Disord 2007;11:374–83.

[14] Erskine HE, Ferrari AJ, Nelson P, Polanczyk GV, Flaxman AD, Vos T, et al. Research Review: Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. J Child Psychol Psychiatry 2013;54:1263–74. https://doi.org/10.1111/jcpp.12144.

[15] Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct Disorder and Oppositional Defiant Disorder in a national sample: Developmental epidemiology. J Child Psychol Psychiatry 2004;45:609–21. https://doi.org/10.1111/j.1469-7610.2004.00250.x.

[16] McManus S, Bankart J, Scott F, Purdon S, Smith J, Bebbington P, et al. Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry 2011;68:459–65.

[17] Lai M-C, Lombardo MV, Baron-Cohen S. Autism. Lancet 2014;383:896–910. https://doi.org/10.1007/978-1-4939-3474-4\_91.

[18] Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345–65. https://doi.org/10.1111/jcpp.12381.

[19] Polanczyk GV, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. Am J Psychiatry 2007;164:942–8. https://doi.org/10.1176/appi.ajp.164.6.942.

**Online Resource 4.** Presentation of the comorbidity, familial co-aggregation, and shared familiality of neurodevelopmental problems among each other and with aggressive behaviour, depression, anxiety, and substance use by type of index instead of problem.

Regarding the neurodevelopmental problems with each other, cross-disorder phenotypic correlations were highest between ADHD and ASD (rP = 0.51) and hyperactivity-impulsivity and stereotyped behaviour (rP = 0.47), and lowest between hyperactivity-impulsivity and reduced empathy (rP = 0.21) and inattention and reduced empathy (rP = 0.23). Recurrence risk ratios were highest for inattention with ASD (λR = 2.96 and 2.65) and ADHD with stereotyped behaviour (λR = 2.61 and 2.33), and lowest for hyperactivity-impulsivity with reduced contact (λR = 1.18) and hyperactivity-impulsivity with reduced empathy (λR = 1.23). Cross-disorder familial correlations were highest between hyperactivity-impulsivity and reduced empathy (rF = 0.76) and hyperactivity-impulsivity and resistance to change (rF = 0.75), and lowest between inattention and violation of social conventions (rF = 0.52), inattention and stereotyped behaviour (rF = 0.55), and inattention and reduced contact (rF = 0.58).

Regarding the neurodevelopmental problems with psychiatric problems, phenotypic correlations were highest between ASD and aggressive behaviour (rP = 0.58) and resistance to change and aggressive behaviour (rP = 0.56), and lowest between reduced empathy and hard drug use (rP = 0.01). Recurrence risk ratios were highest for violation of social conventions with aggressive behaviour (λR = 2.66) and ADHD with aggressive behaviour (λR = 2.56), and lowest for stereotyped behaviour with hard drug use (λR = 0.53), resistance to change with hard drug use (λR = 0.54), and reduced empathy with soft drug use (λR = 0.56). The familial correlation was highest between stereotyped behaviour and anxiety (rF = 0.84), and lowest between resistance to change and alcohol consumption (rF = -0.06).

**ST2.** Comorbidity, familial co-aggregation, and shared familiality among neurodevelopmental problems.



*Notes:*ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; CI = Confidence Interval; SE = Standard Error; \* = Significant at 0.05 level.

**ST3.** Comorbidity, familial co-aggregation, and shared familiality between neurodevelopmental problems and aggressive behaviour, depression, anxiety, and substance use.



*Notes:*ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; CI = Confidence Interval; SE = Standard Error; \* = Significant at 0.05 level.