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The Child and Adolescent Twin Study in Sweden (CATSS)

Henrik Anckarsäter,[1,2] Sebastian Lundström,*[2,3] Linnea Kollberg,[4] Nora Kerekes,[1,3] Camilla Palm,[4] Eva Carlström,[4] Niklas Långström,[3,4] Patrik K. E. Magnusson,[4] Linda Halldner,[4,5] Sven Bölte,[5,6] Christopher Gillberg,[7,8] Clara Gumpert,[9] Maria Råstam,[7,10] and Paul Lichtenstein[4]

[1] Institute of Neuroscience and Physiology, Forensic Psychiatry, University of Gothenburg, Sweden
[2] Department of Clinical Sciences, Forensic Psychiatry, Lund University, Sweden
[3] Swedish Prison and Probation Service, R&D Unit, Norrköping, Sweden
[4] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[5] Karolinska Institutet Center of Neurodevelopmental Disorders (KIND), Stockholm, Sweden
[6] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[7] Institute of Neuroscience and Physiology, Gillberg Neuropsychiatry Centre, University of Gothenburg, Sweden
[8] Department of Child and Adolescent Psychiatry, University of Glasgow, United Kingdom
[9] Section of Forensic Psychiatry, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[10] Department of Clinical Sciences, Child and Adolescent Psychiatry, Lund University, Sweden
* Performed all statistical analyses in the article.

The Child and Adolescent Twin Study in Sweden (CATSS) is an ongoing longitudinal twin study targeting all twins born in Sweden since July 1, 1992. Since 2004, parents of twins are interviewed regarding the children's somatic and mental health and social environment in connection with their 9th or 12th birthdays (CATSS-9/12). By January 2010, 8,610 parental interviews concerning 17,220 twins had been completed, with an overall response rate of 80%. At age 15 (CATSS-15) and 18 (CATSS-18), twins and parents complete questionnaires that, in addition to assessments of somatic and mental health, include measures of personality development and psychosocial adaptation. Twin pairs in CATSS-9/12 with one or both twins screening positive for autism spectrum disorders, attention deficit/hyperactivity disorder, tic disorders, developmental coordination disorder, learning disorders, oppositional defiant disorder, conduct disorder, obsessive–compulsive disorder, and/or eating problems have been followed with in-depth questionnaires on family, social environment and personality, and subsequently by clinical assessments at age 15 together with randomly selected population controls, including 195 clinically assessed twin pairs from the first 2 year cohorts (CATSS-15/DOGSS). This article describes the cohorts and study groups, data collection, and measures used. Prevalences, distributions, heritability estimates, ages at onset, and sex differences of mental health problems in the CATSS-9/12, that were analyzed and found to be overall comparable to those of other clinical and epidemiological studies. The CATSS study has the potential of answering important questions on the etiology of childhood mental health problems and their role in the development of later adjustment problems.

∎ **Keywords:** neuropsychiatry, genetics, epidemiology, childhood, age at onset, twins

The longitudinal Child and Adolescent Twin Study in Sweden (CATSS), launched in 2004, was designed to establish a longitudinal, nation-wide database on somatic and mental health problems in twins during childhood and adolescence. The overall scientific hypothesis for the study is that childhood-onset neurodevelopmental problems (NDPs), defined as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASDs), tic disorders (TDs), developmental coordination disorder (DCD), and learning disorders (LDs), play important roles in the development of mental health problems and psychosocial maladaptation during teenage and young

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adulthood. The study is ongoing and has up until January 2010 included 17,220 children aged 9 and 12 years (80% of all twins in the targeted consecutive birth cohorts born in Sweden from July 1992 and onwards). Published papers based on the CATSS have dealt with distributions and factor structure of mental health problems (Anckarsäter et al., 2008a), genetic and environmental overlaps across the NDPs (Lichtenstein et al., 2010), autistic symptoms (Ronald et al., 2011), autistic-like traits (Lundström et al., 2011), and paternal age as a risk factor for ASDs (Lundström et al., 2010), but the overall study design has not been previously described.

The childhood-onset problems in focus here are referred to as 'neurodevelopmental' as they are all highly heritable (Lichtenstein et al., 2010), over-represented in medical conditions affecting brain functioning (Gillberg, 1995), and first manifested during childhood. They frequently occur together, are more common in boys than in girls, and are thought to express extremes in functions that vary dimensionally in the population, such as the capacities for learning, empathy, and impulse control (Anckarsäter et al., 2008a). Using established diagnostic criteria, at least 5% of all children are diagnosed with NDPs in severe forms (Kadesjö, 2000), and these problem constellations often continue to give considerable functional and psychosocial impairments in adult age (Biederman et al., 2006), including increased mortality (Jokela et al., 2009).

Specific NDPs — for example, ADHD and LDs — have been shown in numerous longitudinal studies to be associated with the development of oppositional defiant disorder (ODD) and conduct disorder (CD), subsequently linked to antisocial personality disorder (ASPD), societal maladjustment (Hofvander et al., 2009), and an increased risk for virtually every type of adult mental disorder (Kim-Cohen et al., 2003). It is less well established how the ASDs are associated with these risks (Gilmour et al., 2004), as studies of the ASDs in relation to outcomes such as substance abuse and criminality have mainly been cross-sectional (Anckarsäter et al., 2008b; Einarsson et al., 2009; Siponmaa et al., 2001). In adults, however, both ADHD and ASDs have been linked to a hampered development of regulatory personality traits, such as self-directedness and cooperativeness, which are known to be deficient in mental disorders across diagnostic categories (Anckarsäter et al., 2006; Svrakic et al., 1993). Based on the empirical evidence available today, it may be concluded that far from being rare childhood conditions that will 'grow away', NDPs need to be systematically addressed in all scientific studies of mental health problems across the life-span.

The CATSS was designed to allow assessments of the relevance of NDPs for health and adaptation during adolescence and adulthood, including systematic assessments of NDPs at baseline (9 or 12 years of age) and renewed symptom ratings in further phases. This article gives an overview of the study, including the development of the assessment tool used for NDPs at baseline, and presents data on the distribution, prevalence, heritability, gender differences, and ages at onset of NDPs and other child mental health problems.

Subjects and Methods

CATSS-9/12: TELEPHONE INTERVIEW

In this phase of the study, which has been ongoing since July 2004, parents of all Swedish 9-year-old twins (i.e., born July 1995 and onwards) are identified through the Swedish Twin Registry and asked to participate in telephone interviews on somatic and mental health. During the first 3 years of the study, 12-year-old twins (i.e., born July 1992 to June 1995) were also included. The reason for choosing these age groups was that most of the major child psychiatric problem constellations have been established by this age, while the problems associated with puberty most often have not yet emerged. The telephone interviews are carried out by interviewers from a professional company, 'Intervjubolaget', who, after a brief introduction in child and adolescent psychiatry and twin research, use a computerized version of the interviews.

As of January 2010, 8,610 informants had responded for 17,220 individual twins; in 87.5% of the cases the mother, in 12.2% the father, and in 0.3% another member of the family. The overall response rate in the study is 80%. Systematic analyses for differences between non-responders and responders (i.e., children for whom parents declined or consented to interviews) were performed on the basis of an anonymized merge between the CATSS database for the first 11,222 participants and official files such as the National Board of Health and Welfare database on socio-economic circumstances, in- and outpatient diagnostics, and pharmacological treatment. Non-responders to the CATSS 9/12 telephone interviews were more likely than responders to have: a parent treated in psychiatric settings (9.6% of the non-responders vs. 6.3% of the responders), a father convicted of a felony (11.2% vs. 7.2%), a mother convicted of a felony (1.6% vs. 0.7%), a divorced mother (16.4% vs. 12.5%), a divorced father (16.4% vs. 12.4%), or to belong to low socio-economic strata (26.6% vs. 21.9%). Non-responders to the telephone interviews also had 2.1% ADHD as compared to 1.6% among responders, 0.95% ASD versus 0.84%, 2.0% LDs versus 0.99%. Among non-responders, 1.8% had been prescribed psychopharmacological treatment for ADHD as compared to 1.4% of the responders.

The main instruments used in the various CATSS phases are provided in Table 2, together with references. The telephone interview was designed to collect information on a wide range of health issues. The child's medical history is specifically addressed by questions on delivery, health care controls (mandatory in Sweden during

TABLE 1

Birth Cohorts and Participants in Each Phase of the CATSS

	Birth cohorts									
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
CATSS-9/12	1042	2304	2136	2088	1950	2050	1864	2002	1784	[b]
CATSS-9/12 Quest	190	246	240	350	178	196	234	232	279	[b]
CATSS-9 Clinical	—	—	—	—	—	—	—	—	—	[a]
CATSS-15			1263	1255	[a]	[a]	[a]			
CATSS-15/DOGSS	—	200	190	[b]						
CATSS-18	[b]	[b]	[a]	[a]	[a]					

Note: [a]planned, [b]ongoing.

infancy, at age 4, and at school start) and other contacts with the health care system, systematically addressing more than 50 different conditions and a vast number of subconditions; for example, many different types of epilepsy or asthma/allergies. For both twins, parenting, childhood traumas, pregnancy, perinatal circumstances, socio-economic situation, schooling, and peer interactions are also assessed.

Mental retardation, epilepsy, brain damage, and chromosomal aberrations are included among the diagnoses specifically addressed in each telephone interview. In addition, parents are given the opportunity to describe any 'other' medical condition diagnosed in their child. This free-text information is screened by a physician to identify cases with either inborn or early brain damage syndromes or chromosomal syndromes, epilepsy and mental retardation. Thus, it is possible to exclude twin pairs with one or several of these factors from analyses if they are inappropriate for the scientific question; for example, monozygotic twin pairs with autism in the presence of shared fragile X, or dizygotic pairs discordant for ADHD with a history of neonatal asphyxia or brain tumor in the affected twin. The prevalences of chromosomal aberrations (0.1%) and brain damage (0.9%) reported in the cohort seem reasonable (Lichtenstein et al., 2010). Prescription drugs during the last 30 days are asked for.

TABLE 2

Instruments Measuring the DSM-IV Axis System in the Phases of the CATSS

	CATSS-9/12 Tel	CATSS-9/12 Quest	CATSS-9 Clin	CATSS-15	CATSS-15/ DOGSS	CATSS-18
Axis I						
A-TAC (Hansson et al., 2005; Larson et al., 2010)	X					
The Mood Disorder Questionnaire (Hirschfeld et al., 2000)		X				X
Child Behavior Check List (Achenbach, 1991)		X				X
ASDI (Gillberg et al., 2001)			X		X	
K-SADS-PL (Kaufman, 2000)			X		X	
Child Mania Rating Scale (CMRS-P-10, Pavuluri et al., 2006)				X		
Eating Disorder Inventory-2 (Garner 1991).						X
ADHD Self-Report Scale (Kessler et al., 2005)						X
Alcohol Use Disorder Identification Test (AUDIT, Babor et al., 1992)				X	X	X
Drug Use Disorder Identification Test (DUDIT, Berman et al., 2005)				X	X	X
Axis II						
TCI (Brändström et al., 1998)				X	X	X[a]
Junior TCI (Kerekes et al., 2010)		X				
WISC-IV (Wechsler et al., 2007)			X		X	
Youth Psychopathy Inventory (Andershed et al., 2008)				X	X	
Axis III						
Internally developed checklist (as described above)	X				X	
P.A.R.I.S. (Gillberg & Coleman, 2002)			X		X	
Axis IV						
Child Monitoring Scale (Stattin & Kerr, 2000)	X			X	X	
Live Events Checklist (Johnson et al., 1980)		X		X		X
Environment Survey (Granlund et al., 2000)		X		X	X	
Parent–Child Relationship (Hetherington & Clingenpeel, 1992)				X	X	X
Axis V						
Child Global Assessment Scale (C-GAS, Lundh et al., 2010)			X		X	

Note: [a]Self-Directedness and Cooperativeness only.

Mental health problems, including the defined NDPs, are assessed by the 'Autism — Tics, AD/HD and other Comorbidities inventory (A-TAC)', an instrument specifically developed for the CATSS to measure possible problems on the basis of telephone ratings conducted by lay interviewers. Since the A-TAC is essential for defining the cases in the longitudinal CATSS, an extensive description of this measure, including two validation studies, is provided below. The data collected during the first four months (July-October 2004, 368 interviews concerning 736 children born during these months in 1992 or 1995) was used as a pilot study to guide the final design of the instruments.

THE A-TAC
Background and Module Structure
The A-TAC inventory was designed for use in large-scale epidemiological research as an easy-to-administer, dimensional, and comprehensive parental interview that can be carried out by lay interviewers over the phone (Hansson et al., 2005; Larson et al., 2010). The A-TAC covers all major clinical diagnostic criteria in child- and adolescent psychiatry, starting with the ASDs and systematically exploring the other NDPs shown to overlap with the ASDs (ADHD, TDs, DCD, and LDs) and most other problem areas in child- and adolescent psychiatry. Questions were worded to assess DSM-IV-definitions of symptoms and diagnostic criteria by a group of experts at the Department of Child and Adolescent Psychiatry at the University of Gothenburg. The instrument is freely available as additional web material to the second validation study (Larson et al., 2010). Items are organized in modules (e.g. Concentration & attention, Impulsiveness & activity, Social interaction, Language). Modules and problem categories are assessed without diagnostic hierarchies or exclusion criteria.

Questions and Scoring
Each module starts with a reminder that the questions refer to a lifetime perspective, in comparison to peers, and that the questions addressing specific symptoms or characteristics may be answered by the response categories *No* (score 0), *Yes, to some extent* (score 0.5), and *Yes* (score 1.0). As alternatives, *Do not know* or *Do not wish to answer* are given, both of which are coded as 'missing'. For each module in which at least one item is endorsed, the parents are also asked whether or not problems associated with the endorsed symptoms have led to (1) dysfunction at school, among peers, or at home, or (2) suffering on the part of the child. Finally, for each symptom/problem endorsed, age of onset and persistence are asked for.

Preliminary Version and First Validation Study
A preliminary version of the instrument, consisting of 178 symptom questions, was tested before the start of the CATSS. Items were worded to contain all symptoms listed

in the DSM-IV (American Psychiatric Association, 1994) symptom criteria of the NDPs, a selection of DSM-IV symptoms listed for other psychiatric disorders, and additional items including symptoms listed in the Gillberg and Gillberg algorithm for Asperger syndrome (Gillberg & Gillberg, 1989), and questions included in published questionnaires for screening or diagnostics of ASD and general psychiatric disorders, such as the Asperger Syndrome Screening Questionnaire (ASSQ; Ehlers et al., 1999), the Asperger Syndrome Diagnostic Interview (ASDI; Gillberg et al., 2001), and the Five to Fifteen questionnaire (Kadesjö et al., 2004).

The first validation study compared 111 blind evaluations of 84 children on the waiting list for neuropsychiatric assessments and 27 controls (Hansson et al., 2005). Interrater agreement was generally excellent for all modules ($ICC_{2,1} > 0.90$), and the test-retest reliability for new interviews after 6–8 weeks good to excellent ($ICC_{2,1} > 0.70$). Subsequent clinical diagnoses of ASDs and ADHD were predicted with 'excellent' combined sensitivity and specificity (Areas Under Receiver Operating Characteristics [ROC] Curves [AUCs] around or above 0.90), and diagnoses of DCD, TD, and LD with moderate to good sensitivity and specificity (AUCs > 0.70, Hansson et al., 2005). However, the number of children with other diagnoses was not sufficient to extend the validation beyond these five diagnoses. It was also noted that despite the excellent validity for ASDs, discrimination was poor between clinical subtypes, such as Asperger syndrome or high-functioning autism.

Development of the Full Version (A-TAC: FV) and Second Validation Study
After the first validation study, before starting up the CATSS, more items were added from the clinical literature and the authors' clinical experience in order to improve the specificity. New modules were also introduced to assess possible overlaps between problem constellations. At the start of the CATSS, the interview contained 327 items, comprising 227 assessing symptoms (as compared to the 178 items in the previous version) and 100 additional questions assessing dysfunction and/or suffering, age at onset, and duration of problems. A systematic reduction of the number of items without loss of sensitivity was seen as essential in the long-term screening of the general population. Based on the 736 individuals interviewed in the CATSS-9/12 pilot study, the consistency (Cronbach's α) of the modules was assessed, and the instrument was pruned by removing 59 items that either reduced module internal consistency or yielded inconsistent answers. Remaining items were organized according to a 'gate' structure, meaning that all parents are asked the 'gate' questions, and whenever one item is endorsed fully or partially, the additional questions addressing more specific clinical traits are added. The gate questions were systematically identified as the items needed to identify all cases reporting impaired functioning and/or suffering

related to the module. Some items that were uncorrelated with the proposed module but provided clinically specific information (such as food fads or severe overweight) were kept and assembled under a new heading, 'Miscellaneous'. Consistency was good to excellent for all modules except Tics/Compulsions and Oppositional/Conduct. For the Tics/Compulsions module, an orthogonal factor analysis constrained to two factors confirmed the heterogeneity of the constellation, yielding one factor corresponding to 'tics' and another corresponding to 'Compulsions' (data not shown). The module was therefore split into two. Based on the overall poor internal consistency, the 'Conduct' module was split into 'Opposition' and 'Conduct', but the 'gate items' for Opposition are also used for the Conduct module, as it is clinically motivated to assess conduct problems in children with oppositional defiant traits. Questions relating to the age at remission of problems were answered inconsistently and therefore omitted. The final version of the A-TAC (Full Version, FV) thus consists of (1) 96 'gate' items, organized in 19 modules and the 'Miscellaneous' section; (2) 90 additional items tapping into more specific symptoms; and (3) 76 items (4 in each module) addressing psychosocial dysfunction and subjective suffering associated with the particular problem area, age at onset, and whether the problems are still present or in remission. Items corresponding to the DSM-IV criteria for ASD and ADHD were all included in the screening algorithms regardless of psychometric considerations.

For each module, several different scores are provided and tested psychometrically. Three or more items answered with *Do not know* or *Do not want to respond* in the same module exclude the module as 'missing'. Three types of symptom scores have been calculated, the *total symptom score* based on all symptom questions in the module, the *gate score* based on the questions above the gates, and the *DSM-IV score* including the DSM-based items only.

The *problem load* score, in contrast to the symptom scores, is not calculated by the symptom questions but as the sum of the two items that assess dysfunction and suffering (thus ranging from 0 to 2). A score of ≥ 1, indicating either that one of the problem questions was fully endorsed or that both items were endorsed 'to some extent', has been assumed to correspond to 'significant problems' due to the symptoms presented in the module.

To validate the A-TAC: FV, interviews with a new group of parents of 91 children waiting for clinical neuropsychiatric diagnostic assessments and of 319 children for whom the parents had reported clinical diagnoses assigned by the child and adolescent psychiatric health services were compared to 366 control children without previous diagnoses (Larson et al., 2010). In this validation, the total symptom, gate, and DSM scores were tested against final clinical diagnoses. The screening properties previously reported for ASDs, ADHD, TDs, DCDs, and LDs (Hansson et al.,

2005) were replicated and shown to work in both genders. The three types of symptom scores also worked almost equally well to identify diagnoses, but the best sensitivities and specificities as compared to optimal inflection points on ROC curves were provided by the gate scores, which were used to define two cut-offs for each score, the highest score giving a sensitivity ≥ 0.90 (≥ 0.95 for ASDs and ADHD) and the lowest score to give a specificity ≥ 0.90 (≥ 0.95 for ASDs and ADHD). The higher cut-off scores are given in Table 3.

In order to compare prevalences between genders and overlaps between problem types, cut-off values were defined for eating problems, obsessive compulsive disorder (OCD), generalized anxiety disorder, separation anxiety disorder, ODD, and CD based on preliminary data from the reported validation study (Larson et al., 2010) and on the distribution of scores in relation to estimated prevalences for these disorders. Due to the lack of validation data for anxiety and mood disorders in the A-TAC, these modules were replaced by the Screen for Child Anxiety Related Disorder (generalized anxiety disorder, Hale et al., 2005) and the short Mood and Feelings Questionnaire (mood disorders, Thapar & McGuffin, 1998) in July 2007. From this time, questions under the gates were also omitted due to budgetary restrictions, so that only the gate and problem load scores are available from the remaining modules.

CATSS 9/12: QUESTIONNAIRES

Questionnaires are used to provide background information relevant to health problems, such as psychosocial environment (the Parent Perceptions of Child's Peers, Hetherington et al., 1994), the Family Environment Scale (FES; Moos & Moos, 1994), the Dyadic Adjustment Scale (DAS; Spanier, 1976), parent-rated child personality (the Junior Temperament and Character Inventory (J-TCI; Kerekes et al., 2010), and school problems, vaccinations, migration, and psychiatric family history. Further information on the child's mental health is obtained by means of the instruments listed in Table 2. The questionnaire phase of the study is a follow-up of telephone interviews indicating some type of mental health problem and of randomly selected screen-negative controls. During the first 2 months of the pilot study, the response rate was comparatively low (46%). After this, we took extra care to inform the parents of the follow-up questionnaires during the initial telephone interviews, and we reduced the number of items in the questionnaires, which resulted in a response rate of 61% during the following months. After the pilot study, the questionnaires were further slimmed by exclusion of several instruments, and since then, families where one or both of the twins screen positive for an NDP and/or ODD, CD, OCD, and/or eating problem and control families have received the questionnaires.[1] As of January 1, 2010, 1,065 questionnaires concerning 2,130 individuals, representing 649 screen-positive twins, 455

TABLE 3

Cumulative Percentile Proportion of Diagnosed Children Detected for Each Gate Score in the A-TAC Modules

A-TAC module	Max. score	Cronbach's α	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5–5	5.5–6	6.5–7	7.5–8	8.5
ASD	17	.86	53.9	70.1	81.8	87.4	91.2	93.3	94.9	96	96.7	97.6	98.2	98.7	99.0	100[1]
Language	6	.66	75.6	87.9	94.4	96.8	98.2	98.7	99.2	99.4	99.7	99.9	100			
Social interaction	6	.77	75.2	89.1	94.7	96.7	97.8	98.5	99.0	99.3	99.6	99.9	100			
Flexibility	5	.70	76.7	88.4	94.3	96.6	98.0	98.7	99.2	99.5	99.7	100				
ADHD	19	.92	42.5	52.8	60.7	66.7	71.2	75.7	79.1	82	84.4	88.4	91.2	93.5	95.0	100[2]
Conc., attention	9	.90	55.6	66.1	73.6	78.9	83.3	86.6	89.3	91.4	93.2	95.9	97.4	98.5	99.3	100[3]
Impulsiveness and activity	10	.87	55.5	67.5	76.4	81.8	86	89	91.4	93.2	94.7	96.7	97.7	98.6	99.2	100[4]
Tics	3	.57	84.1	91.5	96.7	97.6	99.2	99.5	100							
Motor control	1	*	91.6	98	100											
Learning	3	*	74.9	84.5	91.7	94.7	97.2	98.4	100							
Eating problems	2	*	88.4	95.1	99.5	99.7	100									
Compulsions	2	*	96	98.4	99.5	99.7	100									
Separations	5	.58	78.8	90	95.7	97.6	98.9	99.3	99.7	99.9	99.9	100				
Anxiety	3	*	94.5	98.1	99.4	99.7	99.9	100	100							
Opposition	5	.75	67.3	79.1	88.5	92.5	95.5	97.2	98.4	99	99.5	100				
Conduct	5	.61	90.4	96.1	98.3	99.1	99.5	99.7	99.9	99.9	100	100				
Memory	3	*	72.5	86.3	93.5	96.3	98.4	99.3	100							
Perception	5	.62	74.5	87.4	94.2	96.5	98.l2	98.7	99.4	99.6	99.8	100				
Planning and organizing	2	*	71.6	88.5	96.7	98.4	100									

Note: [1] 8.5 = 99.21, 9 = 99.30, 9.5 = 99.39, 10 = 99.48, 10.5 = 99.58, 11 = 99.65, 11.5 = 99.71, 12 = 99.77, 13 = 99.87, 13.5 = 99.89, 14 = 99.93, 14.5 = 99.94, 15–15.5 = 99.97, 16 = 99.99, 17 = 100

[2] 8.5 = 95.49, 9 = 96.03, 9.5 = 96.46, 10 = 96.91, 10.5 = 97.33, 11 = 97.62, 11.5 = 97.60, 12 = 98.11, 12.5 = 98.40, 13 = 98.65, 13.5 = 98.79, 14 = 98.95, 14.5 = 99.17, 15 = 99.31, 15.5 = 99.42, 16 = 99.56, 16.5 = 99.64, 17 = 99.71, 17.5 = 99.80, 18 = 99.88, 18.5 = 99.93, 19 = 100.

[3] 8.5 = 99.56, 9 = 100

[4] 8.5 = 99.41, 9 = 99.63, 9.5 = 99.77, 10 = 100.

* α was not calculated for modules with < four items

screen-negative co-twins, and 692 controls, have been collected, including those from the two pilot studies. The overall response rate for the questionnaire phase is 1,065 of 1,756 sent out questionnaires (60.6%). For the CATSS 9/12 questionnaires, eligible non-responders were overrepresented for ADHD (9.1% vs 6.2%) and ASDs (4.4% vs 3.4%) as compared to responders. The prevalence of learning disabilities was 3.4% among non-responder and 3.5% among responders. Finally, pharmacological treatment for ADHD had been prescribed for 7.0% of the non-responders and for 6.1% of the responders.

CATSS 9: CLINICAL

Planned for 2011 is a clinical validation of 9-year-old children found to be screen-positive for an NDP, CD, ODD, and/or eating problem (according to the same algorithm as that used for the CATSS-9/12 questionnaires) in the telephone interviews. Families living in the regions of Skåne, Västra Götaland, or Stockholm (about 50% of the Swedish population) with one or both twins screen-positive, and control families, will be asked to participate in clinical investigations. We will also assess previous contacts that the families have had with the health care system. Furthermore, this study will identify types of problems or symptoms that predict contact with the health care system, in particular the

child and adolescent psychiatric services. It will provide a population-based, clinical validation of the A-TAC instrument. This study has initial funding and is planned for a 3-year period.

CATSS-15

When the twins have reached 15 years of age, families are again contacted with questionnaires measuring risk factors and outcomes. The aims of the follow-ups at age 15 is to study the effect of NDPs on primarily four outcomes: social marginalization, substance abuse, criminality, and the onset of new mental health problems. Parents and twins fill out separate questionnaires. This part of the study, scheduled to start in 2008, was delayed for practical reasons until the winter 2009–2010 and started with the cohorts born in 1994 and 1995. The CATSS-15 database currently includes self-reports from 2,501 individual twins, 2,378 of whom in pairs with both twins responding responding (giving an overall response rate at 48%). Parent-supplied data is available for 2,550 individual twins, all in pairs with data on both twins (overall response rate at 50%). For 2,321 individual twins (44%), data is available both from the twin and a parent. These subjects were thus all screen-negative and had not been approached clinically (as described below). The comparatively low

response rate in this phase of the study is currently being analyzed in order to improve future data collection. As all measures in CATSS-15 had also been collected from twins included in the CATSS-15/DOGSS clinical assessments, a final merge of databases from CATSS-15 and CATSS-15/DOGSS will yield somewhat higher response rates.

CATSS-15/DOGSS

Families with same-sex twins, one or both of whom were screen-positive (as defined above for the questionnaires) in the telephone interviews in CATSS-9/12 or selected as random controls for the CATSS-9/12 questionnaire are contacted for the CATSS-15/DOGSS (Developmental Outcomes in a Genetic twin Study in Sweden). Consenting families have a clinical examination at one of three sites: in Stockholm (about 50 pairs yearly), in Malmö (about 20 pairs yearly), and in Gothenburg (about 30 pairs yearly). The study started with the 1993 birth cohort in 2008 and includes 195 twin pairs from the first 2-year cohorts, with a response rate > 60%. Starting with the cohort born in 1995, the number of included twin pairs was reduced, and only twin pairs with one or both children screen-positive for ASD and/or ADHD are included together with controls, in all corresponding to about half the cohorts examined in the previous years.

In addition to all the measures collected in CATSS-15, the clinical examinations in CATSS-15/DOGSS are specifically designed to provide a comprehensive psychiatric work-up according to all five axes of the DSM-system by the instruments described in Table 2. Cognitive function is assessed by the Wechsler scales for children (WISC-IV) and the QB-test (Qb-Tech, 2008). Somatic health is assessed by the P.A.R.I.S. proforma (Gillberg & Coleman, 1996). A wide range of questionnaires is used to obtain information that cannot be observed clinically — for example, peer relations, family relations, spare-time activities, bullying, criminality, substance and alcohol abuse.

Two specially trained psychologists, blind to all previous information and to the results of the examination of the co-twin, perform separate clinical interviews with each teenager and the parent(s). Results are compared with medical records, which are collected from previous contacts with somatic and/or psychiatric health services. The results of the psychiatric diagnostic interviews are validated by a clinical expert (senior child psychiatrist). All discrepancies are assessed and noted by the clinical researchers.

CATSS-18
Web Questionnaire

In a currently ongoing follow-up phase, all twins turning 18 years between July 2010 and 2015 (and thus previously included in the CATSS-9/12, CATSS-15, and/or CATSS-15/DOGSS studies) and their parents are asked to participate in a web-based follow-up shortly after reaching legal majority (18 years of age). The web questionnaire is designed to provide longitudinal information on the development of NDP-associated symptoms, and to capture prodromal symptoms of major mental disorders.

The NDPs are measured by internally developed DSM-IV-based questionnaires for ASDs and TDs corresponding to the A-TAC scales, and by the ADHD Self Report Scale (Kessler et al., 2005). Mental health problems are assessed by the depression module in the Development and Well-Being Assessment (DAWBA, Goodman et al., 2000), the Screen for Child Anxiety Related Emotional Disorders (Hale et al., 2005), the Brief Social Phobia Scale, and the Eating Disorder Inventory (Garner, 1991) together with prodromal symptoms of schizophrenia and bipolar disorder (Pavuluri, 2007). Personality development and its disorders are to be measured by the Temperament and Character Inventory (TCI) (Cloninger, 1994; Brändström 1998) and the Youth Psychopathic Traits Inventory (Andershed et al., 2008). Substance abuse is assessed by the Alcohol Use Disorder Identification Test (AUDIT, Babor et al., 1992) and the Drug Use Disorder Identification Test (DUDIT, Berman et al., 2005) questionnaires, and psychosocial marginalization by questionnaires concerning employment, friendships, and civil status. Finally, criminality and aggression will be assessed by the Life History of Aggression questionnaire (LHA, Coccaro et al., 1997) and the Self Reported Delinquency scale (Elliot et al., 1985).

CATSS-DNA

DNA is currently collected from all participants in the CATSS. Directly after the 9/12 telephone interview, a kit is sent home to the twins for DNA collection with saliva (Oragene®). This procedure was introduced in April 2008, and previous year-cohorts are currently re-contacted in order to complete the CATSS biobank, which today includes 7,114 individuals. In the CATSS-15/DOGSS study, biomaterial is also retrieved from the twins through capillary tests and from both parents by saliva.

Zygosity is definitively determined by a panel of 48 single nucleotide polymorphisms (SNPs) derived for zygosity analyses (Hannelius et al., 2007). For twins without DNA samples or before results from molecular genetic assessments are available, an algorithm based on five questions on twin similarity derived from 571 pairs of twins with known zygosity is used. Only twins with more than 95% probability of being correctly classified have been assigned a zygosity by this method.

Statistical Methods

Statistical analyses for this article were based on the CATSS 9/12 A-TAC interviews data ($n = 17,220$, population characteristics provided above) and performed in the SAS 9.1, SPSS 17.0 or MX soft-wares. Intra-class (for continuous data) and tetrachoric (for categorical data) correlations were calculated with the PROC CORR procedure. Internal consistency was measured by Cronbach's α in modules

with ≥ four items. Standard univariate structural equation models were conducted in Mx (Neale et al., 2003). Analyses were performed first in the total study group, then by gender.

Ethical Considerations

Subjects are protected by the informed consent process, in which they are informed of what is being collected and repeatedly given the option to withdraw their consent and discontinue their participation. The CATSS-9/12 study has ethical approval from the Karolinska Institute Ethical Review Board: Dnr 03-672 and 2010/507-31/1, CATSS-9 – clinical 2010/1099-31/3 CATSS-15 Dnr: 2009/1599-32/5, CATSS-15/DOGSS Dnr: 03-672 and 2010/1356/31/1, and CATSS-18 Dnr: 2010/1410/31/1.

Results

Dimensional Assessments of Mental Health Problems

The cumulative percentile proportion of children with each gate score for the respective A-TAC modules is given in Table 3 together with the maximum score and the Cronbach's α for the scale. The internal consistency was good to excellent for all modules with more than four items. For the composite scores of ASDs (consisting of the Language, Social interaction, and Flexibility modules), α was 0.86 (17 items), and for ADHD (consisting of the Concentration & attention and Impulsivity & activity modules) 0.92 (19 items). All problem types assessed by the A-TAC were dimensionally distributed and highly skewed, with a majority of children for whom no problems were reported, followed at each increasing level of problem assessment by a monotonously decreasing proportion of the children.

Intra-class correlations for MZ and same-sex DZ twins, and estimates of the proportion of the variance ascribable to genetic effects (A), shared environment (C), and unique environment (E) were calculated (Table 4). All types of mental problems had both genetic and unique environmental susceptibilities but no shared environmental effects except for conduct problems in girls, in whom the genetic effects were lower than for other types of problems, reflecting a significant shared environmental effect. Generally, hereditary effects had larger explanatory value among boys than among girls, with the notable exception of eating problems.

Categorical Assessments of Mental Health Problems

Prevalences of the assessed problem definitions are listed in Table 5 together with age at onset and tetrachoric correlations. For all types of problems except anxiety and eating problems, boys scored significantly higher than girls (Mann-Whitney U tests all $p < .0001$). Overall, 7% of the study group reached the high cutoff (proxies for clinical diagnoses) for one or more mental disorders according to

A-TAC. Furthermore, for all problem types, boys had similar or earlier age at onset as compared to girls. Similar to the dimensional assessments, correlations for MZ twins were stronger than for DZ twins. The overlap between the different problem types is given in Table 6.

Discussion

This study is one of the most comprehensive twin studies of childhood mental and somatic health problems ever performed. It has a high response rate (80%). Non-responders, no matter how few, are more likely than responders to be socially disadvantaged and to have different types of health problems. Through anonymized merges with official databases it was possible to analyze prevalences of such factors among non-responders as compared to responders, showing that even if problems were more common among non-responders in both the telephone interviews and the questionnaires at age 9/12, they were nevertheless clearly all represented also in the responding group, and the differences were overall so small that it is unlikely that any results could not be generalized to the total population, even on, for instance, parental criminality or poor socio-economic circumstances, with the possible exception of children with severe LDs, who are clearly under-represented in this study. It will also be possible to adjust specific results to known patterns of study participation.

At the time of writing (January 2010), data has been collected at ages 9/12 and 15 from a baseline cohort of 17,220 twins included so far, and the process of including new twins and conducting further follow-ups in early adulthood continues. All types of mental health problems measured in the study have dimensional distributions, and the most commonly reported problem type is ADHD. The prevalences for the NDPs were overall similar to those seen in other studies, although on the conservative side (standard prevalence estimates are at or even above 1% for ASDs and about 5% for ADHD, DCD, and ODD: Gillberg, 2010). The lower prevalence for ADHD found in our study may be ascribed to the fact that the cut-off required problems in both the inattention and hyperactivity areas, while the DSM definition allows for a diagnosis with problems in one area only. For the A-TAC, we have also validated two more inclusive cut-off points yielding prevalences more consistent with modern studies (5.7% and 10.3%: Larson et al., 2010). Of course, if we assume that mental disorders arise in the extreme tails of normally distributed abilities (e.g., autism as the expression of the lowermost end of empathy and socio-communicative abilities) and have dimensional distributions, cut-off values are arbitrary (do not correspond to natural categories) and will ultimately depend on definitions other than just the number of symptoms. One clear example is tic disorders, with prevalence estimates ranging from 1% for Tourette's syndrome (Comings, 1990) to 15% of all chil-

dren presenting with simple tics at some stage of development (Gillberg, 2010). With problems having such wide distributions, it has to be decided whether the number of problems, their functional impact, or other measures of severity should be the denominators for assigning diagnoses. Nevertheless, the figures presented based on the validated and/or defined A-TAC algorithms and cut-offs appear reasonable in view of the scientific literature (Gillberg, 2010) and may thus serve to crudely assess how common the different types of problems are, their age at onset, their overlaps, and gender differences. As expected, boys had higher prevalences of all types of mental problems than girls, with the exception of eating problems. In this general population study; however, the sex ratios were less skewed than in some previous clinical studies (e.g., Kadesjö, 2000).

Our results also clearly demonstrate that in child psychiatry one problem type seldom comes alone. The distributions of the collapsed ASD and ADHD scores show that the most affected children generally have problems from all areas included in these umbrella diagnoses, and it has been reported elsewhere that the risk for co-existing heterotypical problems rise sharply in children with the highest ASD symptom load (Lundström et al., 2011). Children with NDPs are thus more often than not affected in more than one area of functioning, even to the extent that hierarchies of mutually excluding categorical diagnoses have to be considered as conflicting with scientific evidence. This has important clinical implications, as it clearly speaks against the development of sub-specialized services targeting, for example, only children with 'pure' ASDs (Gillberg, 2010), and is compatible with the

TABLE 4

Intra-class Correlations for MZ and Same-Sexed DZ Twins and ACE Models for Both Genders (all), for Girls , and for Boys

A-TAC module	Intraclass correlations						Estimates of genetic and environmental effects (95% Confidence Intervals)								
	MZ			DZ			A			C			E		
	All	♀	♂	All	♀	♂	All	♀	♂	All	♀	♂	All	♀	♂
ASD	0.65	0.53	0.70	0.25	0.29	0.23	0.68 (.66–.68)	0.59 (.53–.63)	0.72 (.71–.75)	0 (.00–.00)	0 (.00–.05)	0 (.00–.01)	0.32 (.31–.32)	0.41 (.37–.44)	0.28 (.25–.31)
Language	0.63	0.55	0.66	0.23	0.23	0.22	0.62 (.60–.64)	0.57 (.52–.60)	0.63 (.60–.66)	0 (.00–.01)	0 (.00–.03)	0 (.00–.02)	0.38 (.36–.40)	0.43 (.40–.47)	0.37 (.34–.40)
Social interaction	0.51	0.52	0.57	0.19	0.22	0.16	0.55 (.52–.58)	0.47 (.39–.47)	0.59 (.55–.63)	0 (.00–.00)	0 (.00–.06)	0 (.00–.01)	0.45 (.42–.48)	0.54 (.49–.58)	0.41 (.37–.45)
Flexibility	0.59	0.45	0.65	0.18	0.18	0.17	0.63 (.63–.66)	0.54 (.50–.59)	0.66 (.62–.69)	0 (.00–.00)	0 (.00–.03)	0 (.00–.00)	0.37 (.35–.38)	0.46 (.41–.50)	0.34 (.31–.38)
ADHD	0.65	0.59	0.67	0.20	0.18	0.19	0.66 (.64–.68)	0.61 (.58–.65)	0.67 (.63–.70)	0 (.00–.01)	0 (.00–.01)	0 (.00–.01)	0.34 (.32–.36)	0.39 (.35–.42)	0.33 (.30–.37)
Concentration and attention	0.57	0.52	0.58	0.11	0.08	0.11	0.55 (.55–.58)	0.5 (.47–.55)	0.55 (.51–.60)	0 (.00–.01)	0 (.00–.01)	0 (.00–.01)	0.45 (.42–.47)	0.5 (.46–.54)	0.44 (.40–.49)
Impulsiveness and activity	0.64	0.55	0.69	0.15	0.08	0.14	0.65 (.64–.65)	0.57 (.53–.61)	0.68 (.67–.71)	0 (.00–.00)	0 (.00–.01)	0 (.00–.00)	0.35 (.34–.35)	0.43 (.39–.47)	0.32 (.29–.35)
Tics	0.38	0.28	0.42	0.11	0.07	0.12	0.36 (.35–.39)	0.26 (.20–.31)	0.39 (.34–.44)	0 (.00–.01)	0 (.00–.04)	0 (.00–.02)	0.64 (.60–.67)	0.74 (.69–.79)	0.61 (.56–.66)
Motor control	0.38	0.32	0.41	0.06	0.03	0.06	0.35 (.31–.39)	0.28 (.23–.33)	0.39 (.33–.44)	0 (.00–.01)	0 (.00–.01)	0 (.00–.01)	0.65 (.61–.68)	0.72 (.67–.77)	0.61 (.56–.66)
Learning	0.66	0.62	0.68	0.14	0.14	0.13	0.64 (.62–.67)	0.63 (.59–.66)	0.65 (.61–.68)	0 (.00–.00)	0 (.00–.01)	0 (.00–.01)	0.36 (.34–.38)	0.37 (.33–.41)	0.35 (.32–.39)
Eating problems	0.41	0.43	0.37	0.18	0.21	0.13	0.41 (.38–.45)	0.47 (.41–.51)	0.35 (.29–.40)	0 (.00–.02)	0 (.00–.04)	0 (.00–.04)	0.58 (.55–.61)	0.53 (.49–.57)	0.65 (.60–.70)
Compulsions	0.31	0.22	0.36	0.12	0.16	0.09	0.31 (.00–.35)	0.3 (.21–.36)	0.33 (.28–.37)	0 (.00–.00)	0 (.00–.06)	0 (.00–.03)	0.69 (.65–.72)	0.69 (.64–.75)	0.67 (.62–.72)
Separations	0.50	0.43	0.55	0.22	0.26	0.18	.49 (.44–.52)	0.45 (.30–.52)	0.51 (.46–.58)	0 (.00–.00)	0.02 (.00–.13)	0 (.00–.04)	0.51 (.47–.54)	0.53 (.48–.59)	0.49 (.44–.53)
Anxiety	0.40	0.28	0.55	0.11	0.08	0.14	.37 (.33–.41)	0.24 (.14–.29)	0.54 (.49–.59)	0 (.00–.02)	0 (.00–.08)	0 (.00–.02)	0.63 (.59.66)	0.76 (.71–.81)	0.56 (.41–.51)
Opposition	0.55	0.47	0.6	0.27	0.24	0.28	0.58 (.54–.59)	0.51 (.44–.55)	0.59 (.55–.62)	0 (.00–.02)	0 (.00–.04)	0 (.00–.03)	0.42 (.40–.45)	0.49 (.45–.53)	0.41 (.38–.44)
Conduct	0.54	0.43	0.61	0.36	0.43	0.32	0.60 (.55–.60)	0.24 (.13–.36)	0.64 (.61–.67)	0.03 (.00–.09)	0.27 (.17–.35)	0 (.00–.02)	0.37 (.36–.38)	0.49 (.45–.54)	0.36 (.33–.38)
Memory	0.59	0.53	0.62	0.16	0.13	0.17	0.58 (.55–.60)	0.52 (.48–.57)	0.61 (.57–.65)	0 (.00–.01)	0 (.00–.01)	0 (.00–.01)	.42 (.39–.44)	0.48 (.44–.52)	0.39 (.35–.46)
Perception	0.51	0.47	0.54	0.20	0.21	0.18	0.54 (.52–.57)	0.51 (.50–.55)	0.58 (.54–.62)	0 (.00–.09)	0 (.00–.00)	0 (.00–.01)	0.45 (.42–.48)	0.49 (.49–.50)	0.42 (.39–.46)
Planning and organizing	0.49	0.46	0.52	0.18	0.18	0.18	0.51 (.48–.53)	0.47 (.42–.51)	0.53 (.49–.57)	0 (.00–.01)	0 (.00–.03)	0 (.00–.01)	0.49 (.46–.52)	0.53 (.49–.57)	0.47 (.43–.51)

TABLE 5

Prevalences, Gender Differences, Mean Age at Onset and Tetrachoric Correlations for MZ and DZ Twin Pairs

| A-TAC module | Cutoff | Prevalence | | | Mann-Whitney M:F p value | Mean age at onset (year All/B/G) | MZ: tetrachoric all/boys/girls | DZ: tetrachoric all/boys/girls |
		All	Boys	Girls				
ASD	8.5	1.0%	1.4%	0.5%	< .0001	3.2/2.2/2.4	.81/.84/.68	.51/.46/.61
ADHD	12.5	1.9%	2.6%	1.1%	< .0001	3.9/3.9/4.0	.85/.81/.91	.34/.35/.25
Tics	1.5	3.1%	4.5%	1.7%	< .0001	6.0/5.9/6.5	.63/.66/.53	.28/.33/—
Motor coordination	1	2.0%	2.5%	1.5%	< .0001	2.0/2.0/2.0	.64/.68/.56	.19/.18/.17
Learning	3	1.6%	1.8%	1.4%	< .0001	5.2/5.0/5.5	.87/.89/.81	—/—/—
Eating problems	1.5	0.5%	0.5%	0.6%	< .0001	5.9/4.9/6.6	.68/—/.80	—/—/—
Separations	2.5	1.1%	1.2%	1.0%	< .0001	5.6/4.7/6.9	.76/.81/.60	.22/.35/—
Compulsions	1	1.6%	1.9%	1.4%	< .0001	6.9/6.5/7.6	.69/.80/.35	.45/.40/.51
Anxiety	1	1.9%	2.0%	1.7%	< .0001	6.7/6.6/7.4	.71/.80/.59	.31/.50/—
Opposition	3	2.8%	3.5%	2.2%	< .0001	5.1/5.1/5.1	.74/.79/.61	.39/.38/.44
Conduct	2	0.9%	1.3%	0.6%	< .0001	5.7/5.5/6.3	.68/.69/.65	.71/.65/.80
Memory	1.5	6.5%	8.2%	4.7%	< .0001	5.6/5.5/5.9	.80/.80/.79	.26/.30/.14
Perception	2.5	1.8%	2.3%	1.2%	< .0001	3.1/3.1/3.1	.69/.71/.65	.27/.23/.35
Planning and organizing	1.5	3.3%	4.2%	2.4%	< .0001	5.2/5.3/5.2	.77/.83/.68	.33/.36/.20

notion that genetic susceptibilities behind mental health problems have to be sought both in relation to specific problem types and to general dysfunction and suffering (Anckarsäter, 2010).

Estimates of the role of hereditary versus environmental liabilities behind mental health problems were based on dimensional assessments of mental problems. For ASDs, ADHD, and LDs, genetic effects explain about two-thirds of the inter-individual variance, and for ODD and CD more than half the variance, while the role of genes behind TD, OCD, and DCD was somewhat less pronounced. These estimates are consistently lower than those found when the liability for a categorical diagnosis is assessed. For example, the role of genetic factors for the liability of a research diagnosis of ASDs was 80%, for ADHD 79%, for DCD 70%, and for TD 56% in a previous publication using the CATSS cohort (Lichtenstein et al., 2010), meaning that the heritability estimates for traits related to these conditions were at least 10% lower (although with overlapping confidence intervals).

The heritability estimates from CATSS are consistent with those previously reported from large twin studies

TABLE 6

Overlap Between Problems (Per cent of Subjects With One Problem Type (Rows) Who Also Have Another (Columns))

A-TAC module	ASD	ADHD	Tics	Motor control	Learning	Eating problems	Separations	Compulsions	Anxiety	Defiance	Conduct	Memory	Perception	Planning and organizing
ASD		50.6	42.7	35.8	35.8	35.8	22.5	29.7	29.6	47.0	21.1	75.5	63.6	67.2
ADHD	25.4		25.8	18.9	17.7	2.8	13.7	16.4	19.2	44.6	20.5	68.5	29.7	57.6
Tics	13.1	21.4		8.7	7.4	1.9	7.0	13.8	10.5	18.8	6.7	29.4	16.5	19.9
Motor coordination	17.2	18.2	13.5		21.4	1.4	6.5	8.3	10.9	15.6	7.5	42.4	31.2	26.7
Learning	22.0	21.4	14.8	27.6		2.2	7.5	9.2	12.0	16.2	10.3	70.7	25.4	30.8
Eating problems	9.9	9.9	11.1	5.5	6.6		13.7	8.8	6.9	16.5	3.3	24.1	13.2	12.1
Separations	19.6	21.9	20.3	11.6	10.6	7.3		26.1	41.6	29.9	8.7	36.7	23.2	29.2
Compulsions	17.6	19.0	26.6	10.4	9.0	2.3	16.7		26.4	26.2	10.4	34.1	21.9	23.7
Anxiety	16.0	18.6	18.3	11.7	10.4	2.2	25.1	25.1		25.5	11.7	35.4	18.6	27.7
Opposition	15.8	29.6	20.7	11.1	9.0	3.1	12.4	15.0	17.7		20.0	37.3	19.7	36.6
Conduct	20.4	40.1	22.2	16.5	17.3	1.9	11.2	17.8	24.8	60.3		45	22.8	43.8
Memory	10.9	19.8	14.2	13.1	17.2	2.0	6.2	8.5	9.7	16.4	6.5		15.0	27.8
Perception	34.3	31.8	29.1	35.2	22.5	3.9	14.4	19.9	19.2	31.3	12.1	55.0		44.8
Planning and organizing	19.8	33.2	19.0	16.5	14.9	2.0	9.8	11.7	15.5	31.6	12.7	55.3	24.3	

using ratings by parents. For example, the heritability of categorically defined autism was estimated at 91% (Bailey et al., 1995) and of ASD-related traits at 82% in large English studies (Ronald et al., 2008). For ADHD, the heritability of the categorical condition was estimated at 91% (Levy et al., 1997), that of both the category and the trait at 75% according to a meta-analysis (Faraone et al., 2005), and that of ADHD-related traits in a large Dutch study by parent reports at 75% (Hudziak et al., 2005). For motor coordination problems (referred to as 'clumsiness'), a lower heritability estimate (34%) has also been reported previously (Moruzzi et al., 2011), just as for compulsions (40%, van Grootheest et al., 2009). Heritability estimates very similar to ours have previously been reported for conduct problems (70%, Spatola et al., 2007). In studies assessing NDPs by self-rate instruments, considerably lower heritability has been estimated (typically in the range of about half of the population variance, e.g. Ronald et al., 2008; Lundström et al., 2011).

All disorders except eating problems are more influenced by genetic factors in boys than in girls. In contrast, the influence of shared environment (i.e., family environment and other shared exposures that make twins more similar) was overall negligible, the one exception being conduct problems in girls. However, since conduct problems in 9-year-old girls are rare, this result should be viewed with caution. Using an instrument that assesses each mental problem specifically without pre-defined diagnostic hierarchies in a population-based cohort such as ours will give a different pattern of overlaps between various problem types as compared to clinical assessments by instruments calibrated to achieve as specific diagnoses as possible.

Traditionally, NDPs are clinical diagnoses that are difficult to study in large population-based cohorts. By the validation of the A-TAC, we have access to a screening instrument that yields data that can be used as proxies for clinical diagnoses in such studies. As conditions with a marked heritability and increased prevalence in medical conditions with a known etiology, such as chromosomal disorders or brain damage, the NDPs hold promise as possible endophenotypes in the search for molecular genetic mechanisms involved in mental disorders. At the same time, it seems improbable that today's heterogeneous diagnostic categories would be appropriate for describing and defining these problems in the kind of studies that will be made possible by the emerging genome-wide, molecular genetic techniques. For research, multivariate twin analyses of large cohorts with measures of all types of mental disorders may yield empirically defined phenotypes based on population data for molecular genetic and other etiological studies.

To sum up, this study will be one of the most comprehensive twin studies of childhood mental health problem ever performed with a very high overall response rate (80%) and the possibility to analyze the total population

through anonymized merges with official databases. At the time of writing, data has been collected at ages 9/12 and 15, while the 18-year follow-up is planned to start in 2011. In this paper, we have reported baseline data from the first 17,220 twins, and new twins are continuously included. Several clinical and longitudinal follow-ups are ongoing/planned. However, some limitations should also be mentioned. The most important is probably that the baseline data collection is by means of parental reports. Though the A-TAC instrument used for these interviews has been thoroughly validated (Hansson et al., 2005; Larson et al., 2010), clinical interviews with each child would, of course, have been preferable but were not feasible in view of the number of subjects involved. However, the two clinical studies (CATSS-9 — clinical and CATSS-15/DOGSS) will add to the understanding of the biases inferred by the parent interviews and of the differences that are inherent between groups derived by systematic screening of the population and by specialized clinics. The A-TAC has not yet been validated against clinical diagnoses of eating disorders, generalized anxiety disorders, separation anxiety disorder, or mood disorders, but some such validations are underway. So far, our data yields prevalences and distributions that are comparable to those of clinical studies. Further, sex distributions, overlap between problem types, and heritability estimates were reasonable in view of the scientific literature on child and adolescent psychiatry. Thus, the CATSS study has the potential to continue to answer important questions on the etiology of NDPs as well as the development of childhood NDP-problems into later adjustment problems.

Acknowledgments

Endnotes

1   The exact algorithm to select candidates for the questionnaire study were a DSM A-TAC score for ADHD ≥ 8, ASDs ≥ 4.5, Conduct ≥ 1, Opposition ≥ 2, Compulsions ≥ 1, Tics ≥ 1, Eating problems ≥ 1 AND an endorsement of dysfunction and/or suffering related to the symptoms (a problem score of ≥ 1), or had a parentally reported clinical diagnosis of one or more of these conditions, in total corresponding to 7% of the children in 13% of the twin pairs, and a random sample of control twin pairs (1 in 20 interviews). Since November 2008, with access to new validation information, the questionnaires have also been sent to pairs in which one or both twins scored ≥ 8 in ADHD, ≥ 4.5 in ASDs, ≥ 1.5 in Eating problems, ≥ 3 in

Oppositional/Conduct ≥ 2 in Tics, ≥ 1 in Compulsions, ≥ 1 in Motor control or ≥ 3 in Learning using the DSM score regardless of whether they indicated dysfunction or suffering related to the problems or characteristics.

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