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Child and Parental Characteristics of Medication Use for Attention-Deficit/Hyperactivity Disorder

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Abstract

Objectives: To investigate child and parental characteristics of medication use for attention-deficit/hyperactivity disorder (ADHD).

Methods: Participants were part of the prospective population-based Norwegian Mother, Father and Child Cohort study (MoBa) ($n = 114,500$ children, 95,000 mothers, and 75,000 fathers). This cohort was linked to the Norwegian Prescription Database (NorPD) and the Norwegian Patient Registry (NPR) to compare child and parental characteristics in children medicated and not medicated for ADHD during years 2008–2013.

Results: One thousand seven hundred and sixty-four children (74% boys) with ADHD (International Classification of Diseases [ICD-10]: F90 and F98.8) were identified. One thousand three hundred and sixty-two (77%) used medication. Boys and girls did not differ in the use of ADHD medication (both 77%). Mean age at first prescription was 9 years in both boys and girls, and age at ADHD diagnosis was 8 years in medicated and unmedicated children. Significantly more hyperkinetic conduct disorders (F90.1), and significantly fewer with attention-deficit disorder (F98.8) were found among the medicated children compared to the unmedicated children. The medicated children also had a significantly lower global functioning (Child Global Assessment Scale). Child disruptive symptoms reported in the MoBa child age 3 year questionnaire were significantly higher in children who used medication compared to the nonusers ($t = 2.2$, $p = 0.03$), and group differences in ADHD symptoms at age 3 years were close to significant ($t = 1.8$, $p = 0.07$). Other preschool child and parental characteristics were not significantly different in the two groups.

Conclusion: In this large birth cohort study, where a great majority of children with ADHD used medication, only child characteristics were significantly associated with the use of medication. We could not replicate previous findings suggesting that ''environmental factors,'' such as parental education and psychopathology, drive medication use. The small differences between medicated and unmedicated children in this cohort study, where a majority used medication, might be due to strong established clinical practices where medication is offered as a treatment option, particularly for hyperkinetic conduct disorder in an egalitarian high-income society.

Keywords: child, ADHD, methylphenidate, treatment, The Norwegian Mother, Father and Child Cohort study, MoBa

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterized by symptoms of attention deficit and hyperactivity-impulsivity. Symptoms must be present in more than one setting (e.g., home and school) and result in impairment to fulfill the criteria for a diagnosis (American Psychiatric Association (APA) 2013). Childhood ADHD has been estimated to affect 3%–4% of the general population (Polanczyk et al. 2015) and is more often diagnosed in boys (Thapar and Cooper 2016).

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A recent treatment review showed that the prioritizing and balance between psychological and medical interventions vary between national ADHD guidelines (Wong et al. 2019). Another review (Sayal et al. 2018) outlined that North American guidelines generally recommend medication as first-line treatment for ADHD. The European guidelines, on the other hand, have a more conservative approach to medication, and often suggest psychological treatment first, at least for the less severe cases (Sayal et al. 2018), despite blinded evidence not supporting these as a specific treatment for core ADHD symptoms (Daley et al. 2018). Concerning choice of medication, the American Academy of Pediatrics (AAP) underlines that the evidence is particularly strong for psychostimulant medications and sufficient, but less strong for atomoxetine, and α2-adrenergic agonists (Subcommittee on Attention-Deficit/Hyperactivity Disorder et al. 2011). The AAP does not specifically recommend an order for medication choice, while the European NICE guidelines [NG87] only recommend atomoxetine and α2-adrenergic agonists to nonresponders to psychostimulants, or when these could not be tolerated (National Institute for Health and Care Excellence 2018).

Methylphenidate, atomoxetine, and α2-adrenergic agonists have shown beneficial short-term effects on the core symptoms of ADHD (MTA Cooperative Group 2004; Banaschewski et al. 2006; Cortese et al. 2018). However, as there are large regional variations in use both between and within countries, research into the contextual factors that may influence the use of ADHD medication has been called for in the literature (Hinshaw et al. 2011; Wallach-Kildemoes et al. 2015; Furu et al. 2017). About 10 years ago, a review study (Leslie and Wolraich 2007) emphasized male gender as an important predictor of medication use, but substantial gender differences in received drug treatment for ADHD were not found in two large clinical European studies (Novik et al. 2006; Lindemann et al. 2012). Contextual predictors of medication use reported in the literature have been negative familial influence (Bird et al. 2008), social adversity (low maternal education, single parenthood, and reception of social welfare) (Hjern et al. 2010), and parental psychopathology (Lindblad et al. 2011). Furthermore, several child-related factors have been reported to influence medication use; child symptom load (both ADHD and other externalizing and internalizing symptoms) (Miller et al. 2008; Scholle et al. 2020), child academic achievement (Falissard et al. 2010); and specific developmental disorders (Scholle et al. 2020). Due to the different single factors reported in the literature, a community study sought to disentangle the factors by the use of multivariable modelling in children 3–10 years of age ($n = 1920$) (Galera et al. 2014). That study reported that questionnaire-rated ADHD symptoms, male gender, and social variables, but not child psychiatric comorbidity or parental characteristics, predicted medication use. The validity of their findings may have been limited by the fact that only questionnaire-rated ADHD symptoms were controlled for in the analyses. None of the above studies has investigated predictors of ADHD medication controlling for the influence of a clinical ADHD diagnosis *per se*, and therefore, they do not entirely address whether the predictors pertain to the ADHD diagnosis or to medication use. Their findings also differ somewhat from two clinical studies, based on German health insurance data (Garbe et al. 2012), and data from a French outpatient psychiatric clinic (Courtabessis et al. 2018), where a small, but increased risk for comorbid behavioral/emotional disorders was found in the medicated children diagnosed with ADHD compared to the unmedicated children.

Furthermore, a recent Australian community-based study illustrates the difference in questionnaire-/interview-rated diagnoses and clinical diagnoses (Efron et al. 2019). In that study, first grade children were diagnosed with ADHD by a diagnostic interview ($n = 179$), and ADHD severity and social disadvantage at age 7 years, but not comorbid disorders, were associated with ADHD medication use at ages 7 and 10 years. The authors noted, however, that only a minority of the children who were diagnosed based on the interview had received a clinical ADHD diagnosis (17% at age 7 years, rising to 38% at age 10 years), thus questioning the clinical relevance of the findings. Gender differences were investigated in a large twin registry study, where males had higher scores for all symptom domains for both diagnosis and medication of child ADHD at the population level, while a similar severity was seen in clinically diagnosed males and females (Mowlem et al. 2019). However, both ADHD and disruptive symptoms were found to be stronger predictors of medication use in girls compared to boys, suggesting that females with ADHD may be less likely to be prescribed medication unless they have prominent externalizing problems. The authors pointed to the need for replication in nontwin samples with inclusion of measures of parental characteristics, child developmental delay, or child internalizing symptoms.

In a previous article, we found that a registered clinical ADHD diagnosis at age 8–13 years was predicted by several of the same variables presented as predictors of medication use in the abovementioned medication studies (male gender, parental education, child preschool ADHD and disruptive symptoms, delayed development, and maternal psychopathology) (Oerbeck et al. 2017b). This study uses the same data source, and adds to the previous literature by investigating child and parental characteristics of the use of medication for ADHD. The paucity of studies tapping into the differences between medicated and unmedicated children is an argument for exploring a wide variety of variables and made a clear hypothesis for all investigated variables difficult. However, based on the previous literature, it was reasonable to assume the particular importance of child externalizing symptoms for the use of ADHD medication.

Methods

Participants

The Norwegian Mother, Father and Child Cohort study (MoBa) is a prospective population-based pregnancy study conducted by the Norwegian Institute of Public Health. Mothers were recruited at week 17 in pregnancy from all over Norway. The women consented to participate in 41% of the pregnancies (Magnus et al. 2016), and received questionnaires at regular intervals. The cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers. This study is based on version 8 of the quality-assured data MoBa files released for research on ADHD. Informed consent was obtained from each MoBa participant upon recruitment. The establishment and data collection in MoBa were previously based on a license from the Norwegian Data protection agency and approval from the Regional Committee for Medical Research Ethics, and is now based on regulations related to the Norwegian Health Registry Act. This study was approved by the Regional committee for Medical Research Ethics (South East Norway). We included children born from January 1, 2000, through December 31, 2008, whose mothers responded to the child age 3 year MoBa-questionnaire ($n = 57{,}986$, with a 52% response rate (MoBa 2012). This cohort was linked to the nationwide Norwegian Prescription Database (NorPD) and the Norwegian Patient Registry (NPR).

Measures

Data from the NorPD

The NorPD contains data on all prescribed medication dispensed by pharmacies to individuals in Norway from 2004 and onward

(Furu et al. 2010). Medicines in Norway are coded according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology 2016). In this study, ADHD medication included the codes methylphenidate (extended and immediate release; N06BA04), atomoxetine (N06BA09), amphetamine (N06BA01), and α2-adrenergic agonists (N02CX02 and C02AC02) with approved indication for ADHD in Norway during the study period. Participants treated with ADHD medication were identified if they had filled at least one prescription from 2008 to 2013. Age at first prescription of ADHD medication was obtained from the NorPD.

Data from the NPR

The NPR is a national health care registry that receives patient data reported from all the specialized mental health care services, including the Child and Adolescent Mental Health Services (CAMHS). The health care is free of charge for children up till age 16, and according to the Norwegian health register act and the NPR regulation passed by the Norwegian parliament in 2007, it is mandatory for the specialized health care services to report health care data to the NPR. Consequently, individual-level research data are available from 2008 onward (with personal identification numbers stored in encrypted form in the NPR). Diagnoses were reported according to the International Classification of Diseases (ICD-10) (World Health Organization (WHO) 1990). In this study, we linked the MoBa cohort with the NPR by the personal identification numbers. *Participants were identified as having ADHD if the child was registered in NPR with an ICD-10 diagnosis of Hyperkinetic disorder (F90) or Attention-Deficit Disorder (F98.8) between the years 2008–2013.* The ICD-codes F90 and F98.8 correspond to the ADHD diagnoses predominantly combined and hyperactive/impulsive presentation, and predominantly inattentive presentation, respectively, in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association (APA) 2013). We report Multiaxial Classification of Child and Adolescent Psychiatric Disorders (World Health Organization (WHO) 1996) on children diagnosed with ADHD reported by CAMHS to the NPR. The multiaxial classifications include six axes (I–VI): I: Clinical psychiatric disorders, II: Specific disorders of psychosocial development; Learning disabilities, III: Intellectual disabilities, IV: Medical conditions, V: The associated abnormal psychosocial situations (van Goor-Lambo et al. 1990), and VI: Children's Global Assessment Scale; CGAS (Shaffer et al. 1983). CGAS is a clinician-rated tool (range 0–100, higher values imply better functioning) used in research and in clinical settings to indicate the lowest overall level of the child's global functioning (at home, at school, and with peers). Moderate inter-rater reliability was found when used in a clinical setting with untrained raters (Lundh et al. 2010). CGAS is divided into 10-point intervals, with a description of the child's level of functioning for each interval. We report the frequency of the Major Impairment interval from 31 to 40 registered in the NPR. Age at first ADHD diagnosis was computed by subtracting birth year from year of diagnosis in NPR.

Data from MoBa

Child characteristics. Information on child gender and potential biological risk factors at birth (prematurity, birth weight) was obtained from the Medical Birth Registry of Norway (MBRN).

- Neurobiological risk was defined as present if the child had (1) a biological risk at birth, for example, been premature (≤ gestational week 37) and/or a birth weight <2500 g, and (2) a neurodevelopmental risk at child age 6 months as measured by ratings of ≥ two standard deviations from the mean on at least one of the motor and/or communication subscales of the Ages and Stages Questionnaire (Bricker and Squires 1999).
- Preschool motor function: At child age 3 years, mothers reported whether the child had met the criterion ''Delayed motor development or is clumsy'' with either a yes (1) or no (0).
- Preschool language functioning: At child age 3 years, mothers reported whether the child had shown ''Delayed or deviant language development'' with either a yes (1) or no (0).

Child mental disorder symptoms were assessed at child age 3 years using items from the CBCL/1½–5 year version (Achenbach and Rescorla 2000). All CBCL items were rated on a 3-point (0–2) Likert scale (Not true, Somewhat true, or Very true).

- ADHD symptoms included six items corresponding to the six items comprising the CBCL/1½–5 year DSM oriented scale for ADHD (Can't concentrate, Can't sit still, Can't stand waiting, Demands must be met immediately, Gets into everything, and Quickly shifts of activities). Cronbach's alpha in this sample was 0.76.
- Anxiety symptoms included three items from the CBCL/1½–5 year Anxious/Depressed syndrome scale (Clings to adults/too dependent, Gets too upset when separated from parents, and Too fearful). Cronbach's alpha in this sample was 0.50.
- Disruptive behavior symptoms included five items from the CBCL/1½–5 year Aggressive Behavior syndrome scale (Defiant, Gets in many fights, Hits others, Punishment doesn't change behavior, and Doesn't seem to feel guilty). Cronbach's alpha in this sample was 0.64.

Parent characteristics

- Maternal age at delivery was abstracted from the records of the MBRN.
- Parental education and marital status were obtained from the first MoBa questionnaire. Parental level of education was measured during pregnancy as the sum of mean years of education for mothers and fathers divided by two. Marital status was dichotomized to single parent versus married/cohabitating.
- Relationship satisfaction was measured using a 5-item version of the Relationship Satisfaction Scale (RSS) at child age 3 years (Roysamb et al. 2014). Each item is rated on a 6-point (1–6) Likert scale, and an average score below 4 has shown a high ability to predict future break-up/divorce (Rosand et al. 2014). Cronbach's alpha in this sample was 0.97.
- Satisfaction with life was measured by the short version of the Satisfaction With Life Scale (SWLS) (Diener et al. 1985; Pavot and Diener 2008) at child age 3 years. The five items are rated on a 7-point (1–7) Likert scale, and a high score indicates high satisfaction. Cronbach's alpha in this sample was 0.98.
- Maternal ADHD symptoms were assessed at child age 3 years with the Adult Self-Report Scale (ASRS-6) (Kessler et al. 2005). The six items were scored on a 5-point (0–4) Likert scale with high scores indicating more symptoms. Cronbach's alpha in this sample was 0.78.
- Maternal internalizing symptoms at child age 3 years were assessed using an 8-item version of the Hopkins Symptom Checklist (SCL-8), four items measuring anxiety and four items measuring depression (Strand et al. 2003). Items were scored on a 4-point (1–4) Likert scale, and a high score indicates more symptoms. Cronbach's alpha in this sample was 0.91.

- Maternal externalizing symptoms at child age 3 years were measured with the Anger subscale of The Differential Emotional Scale (DES) (Izard et al. 1993). Each subscale consists of three questions, asking how often a person experiences different feelings and scored on a 5-point (1–5) Likert scale, and a high score indicates more symptoms. Cronbach's alpha in this sample was 0.80.

Statistics

The child and parental characteristics of children with and without prescribed ADHD medication are presented as number of participants, percentage, means, and standard deviations, as appropriate. Group differences were analyzed with two-tailed chi square tests and independent *t*-tests at a 5% significance level. To assess the effect size of group differences, we estimated the standardized mean difference (*d*). A multivariable logistic regression analysis with backward elimination was performed to assess predictors for medication. The initial predictors were selected based on both statistical and clinical relevance, and include measures of child development, child symptoms, and parental characteristics and symptoms, see Table 2 for details on the predictors and Supplementary Table S1 for the univariable regression analysis. The criterion for removal of an independent variable from the model was set to *p*-value <0.20. To check for differences in gender and age at prescription (age 5–8 vs. ≥9 years), we also did stratified analyses.

Results

One thousand seven hundred and sixty-four children with ADHD were identified and 74% were boys. Among the 1764 children, 23% ($n=402$) did not use ADHD medication. There was no significant gender difference, as 77% of both boys and girls used ADHD medication. Methylphenidate was prescribed to 98% of the users, and the rest used atomoxetine, and none used amphetamine or α2-adrenergic agonists. Mean age at first prescription was 9 years, with no significant gender difference (boys: 8.9 years SD = 1.7, girls: 9.0 years SD = 1.7, $t=0.84$, $p=0.40$). Mean age at ADHD diagnosis was not significantly different in medicated and unmedicated children (8.2 years, SD = 2.0 and 8.1 years, SD = 1.7, respectively, $t=0.76$, $p=0.45$).

The ICD-10 ADHD subtype ''Disturbance of activity and attention'' (F90.0) was present in 76% of the participants. Significantly more ''Hyperkinetic conduct disorders'' (F90.1) and significantly fewer with ''Attention Deficit Disorders'' (F98.8) were registered among the medicated children compared to the unmedicated children. The medicated children had a lower global functioning (CGAS), but no other significant diagnostic group differences were found (Table 1).

Table 2 presents preschool characteristics of children with ADHD, with and without medication use. Child disruptive symptoms at age 3 years were significantly higher in those who used medication compared to the nonusers ($t=2.1$, $p=0.03$), while group differences in ADHD symptoms at age 3 years did not reach significance ($t=1.8$, $p=0.07$). Child anxiety symptoms, developmental delay, and other child characteristics were not significantly different in the two groups (Table 2). There were no significant group differences in parental characteristics between groups of children with/without medication (Table 2).

The multivariable logistic regression analysis with backward elimination resulted in three predictors contributing ($p<0.20$) to the following: parental education (odds ratio [OR] = 0.94 (95% confidential interval [CI] = 0.86–1.03), $p=0.16$), maternal ADHD symptoms (OR = 0.96 (95% CI = 0.92–1.01), $p=0.10$) and child disruptive symptoms (OR = 1.12 (95% CI = 1.01–1.25), $p=0.03$), and only the latter significantly.

Stratified analyses by gender did not reveal significant group differences with one exception, concerning disruptive behavior. Preschool disruptive symptoms were significantly different in medicated and unmedicated boys ($n=579$, mean 3.7 vs. 3.3, $p=0.05$, $d=0.20$), but not in girls ($n=208$, mean 3.6 vs. 3.3, $p=0.39$) (other results not shown). Likewise, the frequency of the registered ADHD subtype

Table 1. Diagnostic Subtypes and Comorbid Disorders in Children with Attention-Deficit/Hyperactivity Disorder,[a] With and Without Attention-Deficit/Hyperactivity Disorder Medication ($N=1764$)

NPR ICD-10 codes	*Without medication (n = 402)* % (n)	*With medication (n = 1362)* % (n)	*Statistics*
Diagnostic subtype ADHD			
Hyperkinetic conduct disorder (F90.1)	3.7 (15/402)	8.6 (117/1362)	$\chi^2=10.59$, $p=$ **0.001**, $d=-0.49$
Attention deficit disorder (F98.8)	16.4 (66/402)	2.3 (32/1362)	$\chi^2=117.09$, $p <$ **0.0001**, $d=1.16$
Comorbid disorders axis I			
Autism spectrum disorder (F84)	6.5 (26/402)	9.3 (127/1362)	$\chi^2=3.20$, $p=0.07$
Tic disorders (F95)	6.2 (25/402)	8.3 (113/1362)	$\chi^2=1.86$, $p=0.17$
Elimination disorders (F98.0–1)	4.2 (17/402)	3.8 (52/1362)	$\chi^2=0.14$, $p=0.71$
Attachment disorder (F94.1–2)	1.0 (4/402)	2.3 (32/1362)	$\chi^2=2.85$, $p=0.09$
Emotional disorders (F40–42, F92–94.0)	7.5 (30/402)	7.1 (97/1362)	$\chi^2=0.05$, $p=0.82$
Comorbid disorders axis II–VI			
II: Learning disabilities (F80–83)	20.6 (83/402)	16.7 (228/1362)	$\chi^2=3.26$, $p=0.07$
III: Intellectual disabilities (F70–79)	0.7 (3/402)	1.4 (19/1362)	$\chi^2=1.06$, $p=0.30$
IV: Somatic disorders (any)	4.2 (17/402)	5.2 (71/1362)	$\chi^2=0.63$, $p=0.43$
V: Abnormal psychosocial situations	44 (177/402)	39 (537/1362)	$\chi^2=2.73$, $p=0.10$
VI: CGAS 31–40, Major impairment	1.2 (5/402)	3.1 (42/1362)	$\chi^2=4.05$, $p=$ **0.04**, $d=-0.51$

Significant *p*-values are in bold.

[a]Registered in NPR with an ICD-10 diagnosis of Hyperkinetic disorder (F90) or Attention-Deficit Disorder (F98.8) between the years 2008 and 2013.

ADHD, attention-deficit/hyperactivity disorder; CGAS, Child Global Assessment Scale; ICD, International Classification of Diseases; NPR, Norwegian Patient Registry.

Table 2. Offspring And Parental Characteristics in Children with Attention-Deficit/Hyperactivity Disorder,[a] With and Without Attention-Deficit/Hyperactivity Disorder Medication ($N = 1764$)

MoBa questionnaires; data from the child age 3 year questionnaire	*Without medication* (n = *402*)	*With medication* (n = *1362*)	
Child development	% (n)	% (n)	*Statistics*
Neurobiological risk at birth	27.9 (112/402)	26.5 (361/1362)	$\chi^2 = 0.29$, $p = 0.59$
Age 3 Delayed motor development	3.2 (13/402)	3.4 (46/1362)	$\chi^2 = 0.20$, $p = 0.89$
Age 3 Delayed language development	6.5 (26/402)	8.4 (114/1362)	$\chi^2 = 1.54$, $p = 0.22$
Child psychiatric symptoms	*Mean (SD)*	*Mean (SD)*	t-*Test*
Age 3 ADHD (CBCL)	4.9 (2.6)	5.3 (2.8)	$t = -1.82$, $p = 0.07$
Age 3 Anxiety (CBCL)	.83 (1.0)	.95 (1.1)	$t = -1.32$, $p = 0.19$
Age 3 Disruptive (CBCL)	3.3 (1.8)	3.6 (2.0)	$t = -2.21$, $p = \mathbf{0.03}$, $d = 0.16$
Parent characteristics and symptoms			
Single parent	6.9% ($n = 24/348$)	6.3% ($n = 73/1155$)	$\chi^2 = 0.15$, $p = 0.70$
Mean years of education, both parents/2 (SD)	13.1 (2.2)	13.0 (2.2)	$t = 0.79$, $p = 0.43$
Maternal age at delivery in years, mean (SD)	28.6 (5.4)	28.3 (5.1)	$t = 0.78$, $p = 0.44$
RSS, mean (SD)	4.2 (6.4)	4.5 (6.4)	$t = -0.78$, $p = 0.44$
SWLS, mean (SD)	9.4 (12.7)	10.6 (13.1)	$t = -1.59$, $p = 0.11$
Maternal ADHD symptoms (ASRS-6), mean (SD)	7.8 (3.8)	7.7 (4.3)	$t = 0.26$, $p = 0.80$
Maternal anxiety and depression (SCL-8), mean (SD)	11.8 (4.8)	11.6 (4.2)	$t = 0.70$, $p = 0.49$
Maternal symptoms of anger (DES), mean (SD)	7.2 (2.3)	7.4 (2.3)	$t = -1.1$, $p = 0.29$

Significant p-value is in bold.

[a]Registered in the NPR with an ICD-10 diagnosis of Hyperkinetic disorder (F90) or Attention Deficit Disorder (F98.8) between the years 2008 and 2013.

ADHD, attention-deficit/hyperactivity disorder; ASRS-6, Adult Self-Report Scale; CBCL, Child Behavior Checklist; DES, Differential Emotional Scale; ICD, International Classification of Diseases; MoBa, Norwegian Mother, Father and Child Cohort study; NPR, Norwegian Patient Registry; SCL, Hopkins Symptom Checklist-8 items.

Hyperkinetic conduct disorder (F90.1) was significantly higher among the medicated children compared to the unmedicated children only in boys (10% vs. 4%, $\chi^2 = 11.35$, $p = 0.001$), not in girls (5% vs. 4%, $\chi^2 = 20$, $p = 0.66$).

Stratified analyses by age group showed that children who were medicated at ages 5–8 years had significantly higher preschool ADHD and disruptive symptoms, compared to children medicated ≥ age 9 years (ADHD symptoms: mean 6.9 vs. 5.1, $p < 0.0001$, $d = 0.64$, and disruptive symptoms: mean 3.3 vs. 2.3, $p = 0.001$, $d = 0.50$, respectively).

Discussion

In this large prospective population-based cohort study, we investigated child and parental characteristics of ADHD medication use in children with ADHD up to age 13 years.

The majority of children in this study used medication (77%), with methylphenidate prescribed in most cases (98%). That only 2% of our study population used medication other than methylphenidate (atomoxetine) may indicate a conservative approach to the European guidelines in Norwegian CAMHS (National Institute for Health and Care Excellence 2018).

The percentage of children on medication is higher than reported from a large population-based study, where 52% of the children with ADHD received drug treatment (>90% used methylphenidate) (Garbe et al. 2012), and several clinical studies where ~50%–65% of the children were medicated for ADHD (Anderson 2018; Falissard et al. 2010; Winterstein et al. 2008). This discrepancy in the use of medication could result from established clinical practices in our country, where medication is offered as a treatment option.

Mean age at start of treatment was 9 years, in line with the age range 5–9 years often reported for initiation of methylphenidate (Miller et al. 2004; Winterstein et al. 2008; Romano et al. 2009). In accordance with the large clinical ADHD Observational Research in Europe (ADORE) study (Novik et al. 2006), this study found no significant gender difference in the use of medication (77% in both boys and girls), although we replicated the well-known male preponderance of ADHD diagnoses (Thapar and Cooper 2016). The similar use in boys and girls is contrary to several previous findings where male gender was a significant predictor of medication use (Garbe et al. 2012; Galera et al. 2014; Courtabessis et al. 2018).

Diagnostic characteristics

By comparing children who were medicated and unmedicated for ADHD, we found the ADHD diagnostic subtype hyperactive conduct disorder (F90.1) to be associated with use of medication, while children with the inattentive subtype (F98.8) used medication less frequently (Table 1). Our finding is in line with the ADORE study (Falissard et al. 2010), a longitudinal population-based cohort study (Scholle et al. 2020), and the clinical study of factors related to the decision of recommending methylphenidate for children with ADHD (Courtabessis et al. 2018). It is reasonable that for parents and teachers, children with the inattentive subtype of ADHD may be perceived as less impaired and their behavior less problematic compared to children with disruptive behavioral problems. However, support has also been found for the clinical utility of medication for the inattentive subtype (Solanto et al. 2009), suggesting a possible undertreatment of this subtype.

In line with two recent studies (Courtabessis et al. 2018; Scholle et al. 2020), this study did not find that comorbid emotional disorders (axis I) were more frequent in those who used medication. However, the medicated children were considered to be more globally impaired (axis VI, CGAS). This finding suggests that clinicians in the CAMHS have followed the clinical guidelines, where severity

as a criterion for treatment with medication has been underlined (National Institute for Health and Care Excellence 2018).

In accordance with a twin registry study (Mowlem et al. 2019), comorbid learning disorders (axis II) were not significantly associated with medication use in this study (Table 1). Our finding stands in contrast to the ADORE study (Falissard et al. 2010), where poor academic achievement was associated with medication use, and findings in two later studies, where presence of comorbid learning disorders and/or developmental coordination disorder (Courtabessis et al. 2018) and specific developmental disorders (Scholle et al. 2020) predicted use of medication. The different associations mentioned above might partly be due to the degree of relevance of learning disorders for both referral and medication for ADHD in different countries. The lack of more learning disorders among the medicated children is in agreement with a recent review underlining a limited size of medication effect on academic performance (with qualitative changes solely in mathematics) (Kortekaas-Rijlaarsdam et al. 2019).

Preschool characteristics

In line with our hypotheses, we found that disruptive symptoms rated at child age 3 years had some impact on later use of medication, although the effect size was low (Table 2). The multivariable logistic regression model, after backward elimination, confirmed this result as three predictors contributed to medication use ($p < 0.20$), and only disruptive symptoms significantly. Contrary to our hypotheses, and findings from other studies (Courtabessis et al. 2018; Efron et al. 2019; Galera et al. 2014), preschool ADHD symptoms did not predict medication use, only a trend was noticed ($p = 0.07$) in the group as a whole. However, those who started medication between ages 5–8 years had significantly higher ADHD and disruptive symptoms than children who were medicated at ≥9 years. This may suggest that the clinicians are aware of the change in ADHD symptomatology during development, with hyperactive-impulsive symptoms being more prominent in young children (Lahey et al. 2005), and/or indicate that clinicians have a higher threshold for medicating young children.

Disruptive symptoms are not an indication for treatment with medication in the clinical ADHD guidelines. Yet this study found parent-rated disruptive behavior significantly more frequently among the medicated children compared to the unmedicated children. Support of disruptive symptoms affecting parental openness to ADHD medication has been found in a preschool study ($n = 151$) of medication-naive children (Hart et al. 2018). That study found that children of parents who were open to medication tended to have higher levels of parent-reported oppositional behavior and aggression compared to the children of parents who were not open to medication. Interestingly, there was no significant difference on parental openness to medication associated with child gender, ADHD symptom severity, or socioeconomic status in the family (Hart et al., 2018). A review study has also concluded with high-quality evidence for psychostimulants having a moderate-to-large effect on disruptive behavior in children with ADHD (Pringsheim et al. 2015). The amelioration of disruptive symptoms by medication is probably also a clinical experience in CAMHS, and this might increase the recommendation of medication to children with comorbid behavior problems to ADHD.

Although we found equal medication rates in boys and girls, we could not replicate findings in a twin registry study, where girls, more than boy,s were significantly more prone to medication use if comorbid disruptive symptoms were present (Mowlem et al. 2019). One reason for this divergence may be the difference in time, as our disruptive symptom measure was from preschool years, not concurrent symptoms. However, this finding from the preschool years was strengthened by the lack of a significant difference between medicated and unmedicated girls concerning the frequency of the registered ADHD subtype hyperkinetic conduct disorder (F90.1). One reason for the lack of gender differences in medication rates may be that medication use is closely tied to the diagnosis of ADHD in this sample, as we may assume that the most severe cases are referred to CAMHS, in line with European guidelines. Another reason could be that the boy/girl ratio of medication use for ADHD has been reduced in more recent years, as prescribing has increased for girls (Sayal et al. 2018).

In this study, parental characteristics in the form of social variables, life and relationship satisfaction, and psychiatric symptoms were not associated with medication use in children with ADHD (Table 2).

Contrary to our findings, a community study concluded that beyond ADHD symptoms, the likelihood of receiving ADHD medication was predicted by social variables (Galera et al. 2014). However, the authors only adjusted for parent-reported child ADHD symptoms, possibly with limited effect on their statistical model for at least two reasons. First, as acknowledged by the authors, this adjustment did not include impairment, central to clinical ADHD diagnoses (American Psychiatric Association (APA) 2013). Second, a registry study reported that among children who fulfilled DSM-5 ADHD symptom criteria using a parent-reported questionnaire, only 19% of boys and 12% of girls were registered with ADHD diagnoses (Mowlem et al. 2019). Thus, in line with a commentary on large studies of medication effects, this suggests that ex postfacto statistical analyses have limitations (Sonuga-Barke 2016), a limitation that was avoided in this study by directly comparing medicated and unmedicated children. Also, there are no longer unambiguous findings on the association between medication use and social variables. Investigation of prescription fills by poverty status and insurance coverage for children 5–17 years of age was reported for 2014–2015 in the United States. Children from upper income households were more likely to use medication than children from poor and medium income households, and filled prescriptions were lower in families with no insurance (36%) versus private (57%) or public (52%) insurance (Anderson 2018). Another study found that low area-level socioeconomic status at age 7 was associated with medication use at age 7 years ($p = 0.04$), but not at age 10 in cross-sectional ($p = 0.40$) or prospective ($p = 0.06$) adjusted analyses (Efron et al. 2019). Different organization of health care services between countries probably explains these differences. In our study, we did not find that parental education was different between medicated and unmedicated children, a finding that might be due to a public and free-of-charge health care.

Strengths and limitations

A strength of this study is the use of a national prescription registry, which includes all patients treated with psychostimulants in Norway. As such, it provides valuable information about real-life treatment of ADHD in the cohort study and may be considered representative of clinical practice.

Our study had several limitations. First, our results may be influenced by selection bias due to attrition in the MoBa (Magnus et al. 2006). The proportion of children medicated for ADHD in

MoBa was 1.2%. As expected, the proportion was somewhat larger in the general child population (1.8%) (personal communication, Kari Furu). Although this was a significant difference, the effect size was low ($p < 0.0001$, $d = 0.24$). However, two studies comparing MoBa participants with the rest of the population found that, although the prevalence rates for some predictor variables differ from the total population (higher maternal education and age, and lower rates of smoking), the bivariate associations between variables were not biased (Nilsen et al. 2009; Oerbeck et al. 2017a). Second, although we have valid data on dispensed medication for ADHD, and thus, primary nonadherence is not an issue, we have no knowledge of whether the child actually took the medication. Third, our study did not include data on antipsychotics. However, they are not indicated for treatment of ADHD in Norway, although we cannot rule out that some have used it, as a study of Nordic children showed that 5%–7% of children medicated with psychostimulants were co-medicated with antipsychotics (Furu et al. 2017). Fourth, our data are from 2008 to 2013. In the following years (2014–2018), there were no substantial change in number of ADHD diagnoses among children and adolescents in the annual reports (in Norwegian) from our NPR, and the same diagnostic system (ICD-10) has been used during the last decade. Concerning medication, a relatively stable use (an annual increase of 0.08%) of treatment with ADHD medication was found in Norway during years 2004–2013 (Raman et al. 2018). Similarly, data extracted from the NorPD website show relative stability in the prescribed ADHD medications for children and adolescents during the following years (2014–2018). Fifth, the NPR only report data in the form of consultation dates for received care, not the content of the care. Thus, whether participants have received a behavioral treatment for ADHD, as also recommended in the clinical guidelines, is unknown. Furthermore, the NPR does not provide information on the training to use multiaxial classification in the clinics. Sixth, there is a limitation to our analysis of the importance of preschool anxiety due to low internal consistency of our anxiety scale, where few mothers reported anxiety symptoms to be present. We therefore also dichotomized the scoring to yes/no on each anxiety item, with no significant differences between medicated and unmedicated children. Finally, we did not include paternal ADHD symptoms in our analyses due to low N, as the first waves of MoBa questionnaires did not contain fathers' ADHD symptoms.

Conclusions

In this large birth cohort study, where a great majority of children with ADHD used medication, only child disruptive symptoms were significantly associated with the use of medication. We could not replicate previous findings suggesting that ''environmental factors,'' such as parental education and psychopathology, drive medication use. The small differences between medicated and unmedicated children in our study might be due to strong established clinical practices, where medication is offered as a treatment option in a public health care service free of charge. These findings from an egalitarian high-income society do not necessarily apply to general U.S. samples, where a greater variability of health care and educational availability is found. However, our findings underline the importance of controlling for ADHD diagnosis (where there is a significant male preponderance) when investigating predictors for ADHD medication. Future studies of predictors of medication should account for whether investigated predictors pertain to ADHD diagnosis or medication.

Clinical Significance

Concern has been raised that factors other than child symptom load have been found to influence the use of medication in children with ADHD. The findings from this cohort study, where a majority used medication, do not support that.

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Disclosures

No competing financial interests exist.

Supplementary Material

Supplementary Table S1

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