Persistence and adherence to methylphenidate in children in the Netherlands

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ABSTRACT

Background and objectives: Several studies have examined factors that may contribute to adherence and/or persistence to methylphenidate, but these were mainly conducted in adults and not in children. In children, determinants of adherence and are probably different from adults. However, information about the family and child characteristics in relation to adherence and persistence to methylphenidate treatment in children is limited. Therefore, the objective was to study determinants of adherence to and persistence of methylphenidate in children.

Methods: The study population included a subset of 307 children, from the population-based Generation R Study in the Netherlands, who all had at least one dispensing record of methylphenidate from birth up to the age of 16 years. Adherence was defined as a medication possession ratio (MPR) ≥ 0.80. Persistence was defined as duration of methylphenidate use until a discontinuation period ≥ 6 months. Family and child characteristics were tested as determinants of adherence with multivariable logistic regression analysis. Persistence was evaluated using a Kaplan Meier analysis.

Results: Children of a nulliparous mother (adjusted OR: 2.31, 95%CI: 1.17-4.54) or a mother with an average household income (compared to high) were more likely to be adherent (adjusted OR: 3.45, 95%CI: 1.43-8.31). Girls were more often non-persistent than boys (adjusted HR: 1.44, 95%CI:1.07-1.95) and children who started treatment at age 12-16 were more often non-persistent than children who started before 12 years of age (adjusted HR: 3.55, 95%CI:2.54-4.98).

Conclusion: In conclusion, the results of our study showed that both child and family characteristics may play a role in methylphenidate treatment adherence. Furthermore, sex and age at start of the treatment was found to be associated with non-persistence. These findings may be important for healthcare professionals when initiating methylphenidate treatment in children.

INTRODUCTION

Methylphenidate is the first line pharmacological treatment option for attention deficit hyperactivity disorder (ADHD) as it is considered an effective pharmacological treatment in children[84]. However, for medication to be effective, compliance to treatment is crucial. Two important aspects of compliance are reflected by adherence and persistence. Adherence refers to the extent to which patients take medications as prescribed and persistence refers to continuing treatment for the prescribed duration . Various studies have shown that adherence and persistence to stimulant medication in children and adolescents is only 40 to 50% [128, 129]. Many studies investigating adherence and persistence to methylphenidate were performed in adolescents and adults, whereas limited information is available in children [130, 131]. A previous study in adults, examined different sociodemographic factors that may contribute to adherence and persistence to methylphenidate treatment, and showed that male gender and a lower educational level were associated with discontinuation [132]. To investigate treatment adherence and persistence in children, it is important to consider also parental involvement as there are many parental factors that may contribute, such as socio-economic status and ethnicity [133]. A previous study that followed children with attention deficit hyperactivity disorder (ADHD) for 3 years, showed that pharmacological treatment was not accepted by all families [134], which may influence adherence and persistence to methylphenidate as parents are supposed to encourage children to continue to take their medication. However, the number of patients included in that study was small [134] and family or patient characteristics were not investigated. For example, the age at treatment initiation may play a role as adolescents usually manage their own medication intake and could be more likely to forget or abstain from medication [135]. For school-aged children, parents usually make treatment decisions and have a greater influence on adherence and persistence to medication. Studies also showed that medication adherence was greater when both children and parents felt that symptoms improved with treatment. The adherence and persistence may also be dependent on the dosage and the number of pills they have to take on a daily basis [130, 133, 136]. Finally, many studies have assessed adherence and persistence separately [135, 137-139]. However, it is important to assess adherence together with persistence, as they both are important aspects of adequate pharmacotherapy. For this reason, the objective of our study was to determine adherence to and persistence of methylphenidate treatment in children and to study potential determinants that were associated with these outcomes.

METHODS

Study population

This study was conducted within the Generation R Study, a large population-based cohort study investigating children's health from fetal life onwards in Rotterdam, the Netherlands [17]. All pregnant women from Rotterdam with a delivery date between April 2002 and January 2006 were asked to participate in the study. Detailed and extensive data have been collected over the years which included interviews, questionnaires and behavioral observations of children and their parents [17]. In addition, pharmacy records of the children from community pharmacies from Rotterdam were retrieved. In the current study, all children (n=7,986) and their parents were invited to participate in the follow-up. Children were excluded if parents withdrew from the study (n=74), if no consent by parents was provided (n=1,084) or if the pharmacy did not consent to retrieve the pharmacy records, or because no pharmacy records were available in the pharmacy database (which may include non-users) (n=1,742). For 5,068 individuals in The Generation R Study, all prescriptions which were filled at their pharmacy during the entire study period were gathered. Of these, 6% (n=307) of children received at least one methylphenidate prescription and formed the study population (Figure 1 for flowchart). All methylphenidate-using individuals were followed as of their first prescription until a) the end of the study period at 30 October 2018, b) loss to follow-up or c) end date of the last methylphenidate prescription, whichever came first.

Pharmacy records

Linkage between pharmacy records and Generation R participants was done at the community pharmacies in Rotterdam, but the information on methylphenidate use was extracted from automated pharmacy records, which was provided by the Dutch Foundation for Pharmaceutical Statistics [18]. For each dispensation, we collected the product name, Anatomical Therapeutic Chemical (ATC) code [102], date of filling, number of delivered tablets/capsules, and prescribed daily number. A methylphenidate dispensation was selected based on the ATC code N06BA04.

Methylphenidate use

Adherence was measured by the Medication Possession Ratio (MPR). The MPR measures the percentage of time a patient has access to medication and was calculated when children received at least 2 prescriptions of methylphenidate. The MPR is the sum of days' supply of methylphenidate during the follow-up period divided by the number of days in the that time period, i.e. between the first and end of the last prescription. According to international literature, a good adherence is set at an MPR of 0.80 or higher [129, 140]. Persistence of methylphenidate was calculated for all children who received at least one prescription of methylphenidate. Currently, there is no clear definition of non-persistence of methylphenidate treatment. In general, as previous studies used a gap period of 15 to 180 days as non-persistence [138, 139].

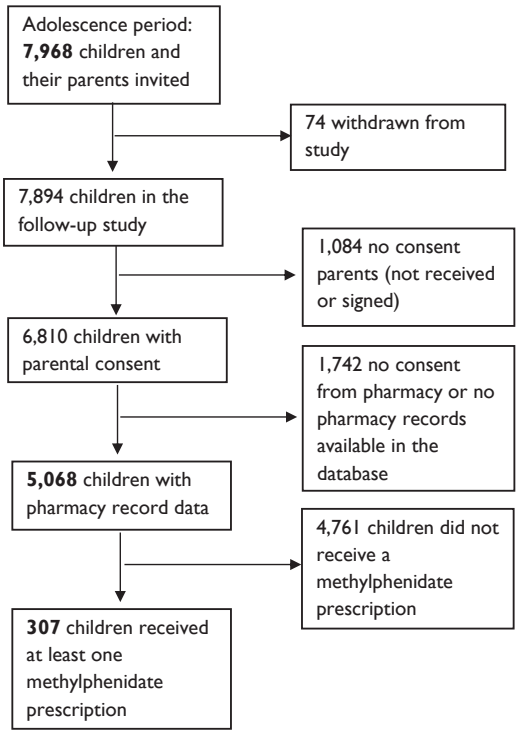

***Figure 1**. Selection of study the population*

Prescriptions for methylphenidate in the Netherlands are generally filled for 3 months. To ensure that no methylphenidate was dispensed after that, a gap period of 6 months (without prescription) was chosen for non-persistence. Non-persistence was calculated starting from the calculated end date of the last prescription. Additionally, we collected information on the type of methylphenidate prescriber (specialist, general practitioner), as well as prescriptions of other psychotropic medication prior to the first methylphenidate dispensation, including anti-epileptics, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants or other ADHD medications (ATC code N06BA). We included the number of times the prescription was switched from short-acting methylphenidate to long-acting methylphenidate or vice versa and the number of prescriptions of short- or long-acting methylphenidate (number of long-acting prescriptions greater than short-acting or number of short-acting greater than long-acting).

Child characteristics and other determinants

Child characteristics that were considered as determinants of adherence, include age at first methylphenidate prescription (5-11 and 12-16 years), sex, ethnicity (Dutch , non-Dutch western, and non-Dutch non-western) [105], and the presence of ADHD symptoms and other emotional and behavioral problems as reported by mothers using the Child Behavior Checklist

[103]. The Child Behavior Checklist (CBCL/1.5-5 and CBCL/6-18) was used to obtain information about behavioral and emotional problems in children [103]. The CBCL questionnaire has been filled out by the mother when the child was 3, 5 and 9 years old. The CBCL/6-18 was only used at the 9-years of age assessment. For the analyses, we used the most recently completed questionnaire prior to the first methylphenidate prescription. The CBCL contains items on the child's behavioral and emotional problems which are scored on a three-point scale (0=not true, 1=somewhat or sometimes true, 2=very or often true) during the preceding 2 months. There are five Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales: affective problems, anxiety problems, pervasive developmental problems, ADHD and oppositional defiant problems. It has been reported that these DSM-oriented scales provide accurate and supplementary information on clinical diagnosis with a good reliability and validity for the CBCL [104, 123]. We also measured the level of ADHD symptoms using the revised Conner's' Parent Rating Scales, (CPRS-R), which was filled out by primary caregiver at the age of 7-8 years. The CPRS-R consisted of 27 items that yielded several subscales: ADHD combined, ADHD Inattentive, ADHD Hyperactive-impulsive and Oppositional Defiant Disorder Scale [141]. The score ranges from 0-18 for the ADHD inattentive, hyperactive-impulsive and oppositional defiant disorder and a possible score between 0-36 for the ADHD combined. Higher scores indicate more problems. Autistic traits were assessed using the Social Responsiveness Scale (SRS) short form [142]. Each item is rated from 0 to 3 (never true to almost always true), covering social, language, and repetitive behaviors. We used a cut-off defined as the upper 15% for the presence of autistic traits.

Family characteristics

We considered several family characteristics as potential determinants for adherence in children: parity (1, >1), marital status (married, living together, no partner), maternal education (no/primary, secondary and high) and household income (low: ≤€2000, moderate: €2100-4000, high: €>4000). The demographic data was obtained using self-reports.

Analysis

Baseline characteristics were presented for all methylphenidate users with regular summary statistics.

First, determinants for methylphenidate adherence (MPR ≥0.80) at 2 years of follow-up (after receiving their first prescription) were assessed using logistic regression analyses to calculate odds ratios (OR) and their 95% confidence interval (CI). For all determinants, we tested their independent association with adherence. Then, a multivariable logistic regression model was performed with all relevant determinants and confounders based on the literature (age, sex, ethnicity, type of prescriber, other psychotropic medication, number of short-acting and long-acting methylphenidate, number of switching, parity, marital status, maternal education

and household income) [136, 138, 143] to assess the association with the 2-years adherence. The MPR was only calculated for children who received at least 2 prescriptions.

Second, to evaluate the extent of medication non-persistence between a low (MPR lower than 0.50), moderate (MPR between 0.50 and 0.79) and a high MPR (MPR of 0.80 and higher), we used unadjusted Kaplan-Meier curves. Statistically significant differences in methylphenidate persistence among children with a MPR<0.50, a MPR 0.50-0.80 and a MPR≥0.80 were identified using Wilcoxon tests. An extended Cox proportional hazards model was used to assess the risk of non-persistence adjusting for determinants.

Missing data of the determinants (ethnicity, type of prescriber, parity, marital status and household income) were imputed using multiple imputation (n=5)[144]. Missing data were only imputed if less than 30% of the specific variable was missing. Data of the child's behavioral characteristics (CBCL, SRS and CPRS-R) were not imputed. Results were considered statistically significant at p<0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline

The characteristics of the study population and information about the dispensed medications are shown in Table 1. The mean age of first methylphenidate prescription was 9.7 years and the majority of children receiving methylphenidate were boys (74.6%). Children were more often

Table 1. *Baseline child and family characteristics of children who have received a methylphenidate (MPH) prescription (n=307)*

Child characteristic	
Age at first methylphenidate prescription (years), mean (SD)	9.7 (2.4)
Sex	
Boy	229 (74.6)
Girl	78 (25.4)
Ethnicity	
Dutch and other western	226 (73.6)
Non-western	81 (26.4)
Type of prescriber of first methylphenidate prescription	
Specialist	274 (89.3)
General practitioner	33 (10.7)
Other psychotropic medication prior to the first methylphenidate dispensation[a]	
No	276 (89.9)
Yes	31 (10.1)

Table 1. *Baseline child and family characteristics of children who have received a methylphenidate (MPH) prescription (n=307)* (*continued*)

Child characteristic	
Short- and long-acting MPH	
Number of short-acting MPH per child, mean (SD)	9.7 (21.1)
Number of long-acting MPH per child, mean (SD)	14.0 (22.7)
Number of times of switching between long- and short-acting stimulants	
0	174 (56.7)
1	60 (19.5)
2 or more	73 (23.8)
Affective problems (CBCL)[b] , mean (SD)	3.6 (4.4)
Anxiety problems (CBCL) [b], mean (SD)	2.0 (3.7)
Pervasive developmental problems (CBCL) [b], mean (SD)	2.1 (4.0)
Attention deficit/ hyperactivity problems (CBCL) [b], mean (SD)	2.5 (4.3)
Oppositional defiant problems (CBCL) [b], mean (SD)	2.1 (3.7)
Presence of autistic traits (SRS)[c]	
No	149 (48.5)
Yes	58 (18.9)
Attention deficit hyperactivity disorder (CPRS)[d], mean (SD)	15.6 (8.2)
Cognitive problems/ inattention (CPRS)[d], mean (SD)	7.5 (4.7)
Oppositional defiant disorder (CPRS)[d], mean (SD)	5.1 (3.6)
Hyperactivity (CPRS)[d], mean (SD)	5.0 (4.1)
Family characteristics	
Parity	
1	169 (55.0)
>1	138 (45.0)
Marital status	
Married, living together	249 (81.1)
No partner	58 (18.9)
Maternal education	
No/ primary education	11 (3.6)
Secondary education	145 (47.2)
Higher education	151 (49.2)
Household income	
Low	61 (19.9)
Moderate	125 (40.7)
High	78 (25.4)

*Values are given in numbers (%), unless stated otherwise. *Number of missing values are not shown. [a]anti-epileptics, anti-depressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. [b]CBCL indicates Child Behaviour Checklist (CBCL/1.5-5 and CBCL/6-18) [c]SRS indicates Social Responsiveness Scale short form. [d] CPRS indicates Conner's Parent Rating Scale. Abbreviations: MPH indicates methylphenidate; N, number; SD, standard deviation.*

Dutch or had a western ethnic background (73.6%) compared to non-wester and the majority of our children received their first methylphenidate prescription from a specialist (89.3%). 10.1% of the children received other psychotropic medications prior to their first methylphenidate prescription. Finally, 18.9% of the children had autistic traits above the cut-off score.

Determinants of adherence

Table 2 shows determinants that were associated with adherence (MPR ≥0.80) to methylphenidate treatment. Of the 264 children with more than one prescription, 63 were adherent 2 years after treatment initiation. In the univariable analyses, we found that children more likely to be adherent when they mainly received long-acting methylphenidate during the follow-up

Table 2. *Determinants associated with adherence (MPR ≥0.80) to methylphenidate treatment at 2 years after treatment initiation (n=264)**

Characteristics	Adherent at 2 years (n=63), n (%)**	Univariable, OR (95% CI)	Multivariable, OR (95%CI)
Child characteristics			
Age at first methylphenidate prescription, years			
5-11	50 (79.4)	Ref	Ref
12-16	13 (20.6)	0.66 (0.33-1.30)	0.75 (0.34-1.64)
Sex			
Boy	52 (82.5)	Ref	Ref
Girl	11 (17.5)	0.58 (0.28-1.19)	0.54 (0.24-1.21)
Ethnicity			
Dutch and other western	54 (85.7)	Ref	Ref
Non-western	9 (14.3)	*0.39 (0.18-0.85)*	0.50 (0.21-1.21)
Type of prescriber of first MPH prescription			
Specialist	60 (95.2)	Ref	Ref
General practitioner	3 (4.8)	0.39 (0.11-1.34)	0.38 (0.10-1.49)
Other medication before first MPH prescription[a]			
No	54 (85.7)	Ref	Ref
Yes	9 (14.3)	1.80 (0.76-4.28)	1.78 (0.66-4.81)
Short-acting and long-acting MPH			
Mainly short-acting	20 (31.7)	ref	ref
Mainly long-acting	43 (68.3)	*2.50 (1.37-4.54)*	*2.01 (0.99-4.11)*
Number of switching between long- and short-acting MPH			
0	23 (36.5)	Ref	ref
1	11 (17.5)	1.12 (0.51-2.48)	1.15 (0.46-2.88)
2 or more	29 (46.0)	*3.15 (1.65-6.03)*	*2.35 (1.08-5.09)*

Table 2. *Determinants associated with adherence (MPR ≥0.80) to methylphenidate treatment at 2 years after treatment initiation (n=264)** (*continued*)

Characteristics	Adherent at 2 years (n=63), n (%)**	Univariable, OR (95% CI)	Multivariable, OR (95%CI)
Affective problems (CBCL)[b]	45 (71.4)	0.96 (0.89-1.04)	
Anxiety problems (CBCL) [b]	58 (92.1)	0.92 (0.80-1.05)	
Pervasive developmental problems (CBCL) [b]	58 (92.1)	1.05 (0.95-1.15)	
Attention deficit/ hyperactivity problems (CBCL) [b]	57 (90.5)	1.00 (0.93-1.08)	
Oppositional defiant problems (CBCL) [b]	58 (92.1)	1.03 (0.93-1.14)	
Presence of autistic traits (SRS)[c]			
No	31 (49.2)	Ref	
Yes	18 (28.6)	1.74 (0.86-3.51)	
Attention deficit hyperactivity disorder (CPRS)[d]	42 (66.7)	1.01 (0.96-1.05)	
Cognitive problems/ inattention (CPRS)[d]	42 (66.7)	1.00 (0.93-1.08)	
Oppositional defiant disorder (CPRS)[d]	42 (66.7)	1.02 (0.92-1.12)	
Hyperactivity (CPRS)[d]	42 (66.7)	1.07 (0.99-1.16)	
Family characteristics			
Parity			
1	42 (66.7)	*2.00 (1.10-3.66)*	*2.31 (1.17-4.54)*
>1	21 (33.3)	Ref	Ref
Marital status			
Married, living together	59 (93.7)	Ref	Ref
No partner	4 (6.3)	*0.26 (0.09-0.77)*	0.26 (0.06-1.07)
Maternal education			
No/ primary education	2 (3.2)	1.04 (0.19-5.59)	1.83 (0.24-13.77)
Secondary education	29 (46.0)	0.95 (0.50-1.81)	0.91 (0.42-1.97)
Higher education	32 (50.8)	Ref	Ref
Household income			
Low	8 (12.7)	0.79 (0.28-2.23)	2.25 (0.46-11.05)
Moderate	42 (66.7)	*2.49 (1.20-5.17)*	*3.45 (1.43-8.31)*
High	13 (20.6)	Ref	Ref

*Values are given in numbers (%), unless stated otherwise. * The MPR was only calculated when more than 2 prescriptions was received. **Number of missing values are not shown. ***The multivariable model included all variables except for the behavioural characteristics. Determinants were selected based on the literature. [a]anticonvulsants, antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. [b]CBCL indicates Child Behaviour Checklist (CBCL/1.5-5 and CBCL6-18). We corrected for the time between the date the questionnaire was completed and the date of first prescription [c]SRS indicates Social Responsiveness Scale short form. [d] CPRS indicates Conner's Parent Rating Scale. Abbreviations: CI indicates confidence interval; N, number; OR, odds ratio; SD, standard deviation.*

period (OR: 2.50, 95%CI: 1.37-4.54). However, this association did not remain present in the multivariable analysis (adjusted OR: 2.01, 95%CI: 0.99-4.11). Also, children who switched their medication multiple times from short-acting to long-acting (and vice versa) were more likely to be adherent than those who did not switch (adjusted OR: 2.35, 95%CI: 1.08-5.09).

Further, children of nulliparous mothers (adjusted OR: 2.31, 95%CI: 1.17-4.54) were more likely to be adherent. Compared to those with a high household income, we observed an association between a moderate household income and methylphenidate treatment adherence (adjusted OR: 3.45, 95%CI: 1.43-8.31). For the remaining determinants, including age of first treatment, sex, type of prescriber of first prescription, dispensation of other medications prior to the first methylphenidate prescription, maternal education and behavioral characteristics, no significant associations were found in the univariate or multivariate analysis.

Persistence

In total, 264 children were included in the survival analyses as they received more than one prescription for which the MPR could be calculated (43 children only received one prescription). In the study population, 67 children had an MPR below 0.50 (25.4%), 125 children had an MPR between 0.50 and 0.79 (47.3%) and 74 children had an MPR of 0.80 or above (28.0%). The overall mean treatment duration until discontinuation was 2.7 years (SE: 0.14). In patients with an MPR <0.50, the mean treatment duration was 2.6 years (SE: 0.24), the mean treatment duration in patients with a MPR between 0.50 and 0.79 was 5.6 years (SE: 0.17), and the mean treatment duration in patients with a good adherence (MPR≥0.80) was 3.1 years (SE: 0.33).

Figure 2 shows the survival curves of persistence in children with a low, (MPR <0.50), intermediate (MPR 0.50-0.70) and a high adherence (MPR≥0.80). We found that children with a low or intermediate MPR had a higher persistence in the first 2.7 years of methylphenidate treatment (P<0.001). After 2.7 years, persistence was higher in children with a good adherence (P<0.001). Differences in survival curves between the three MPR groups were observed (p= 0.03).

Table 3 shows the risk of non-persistence in children who started methylphenidate treatment. Only 4 children (1.3%) were persistent during the entire follow-up period. Girls were more likely to discontinue treatment than boys (adjusted HR: 1.44, 95%CI: 1.07-1.95). The risk of non-persistence increased with age (adjusted HR: 3.55, 95%CI: 2.54-4.98). Children who were more often prescribed short-acting methylphenidate than long-acting methylphenidate were more likely to be non-persistent (number of short-acting higher than long-acting, adjusted HR: 1.49, 95%CI: 1.13-1.96).

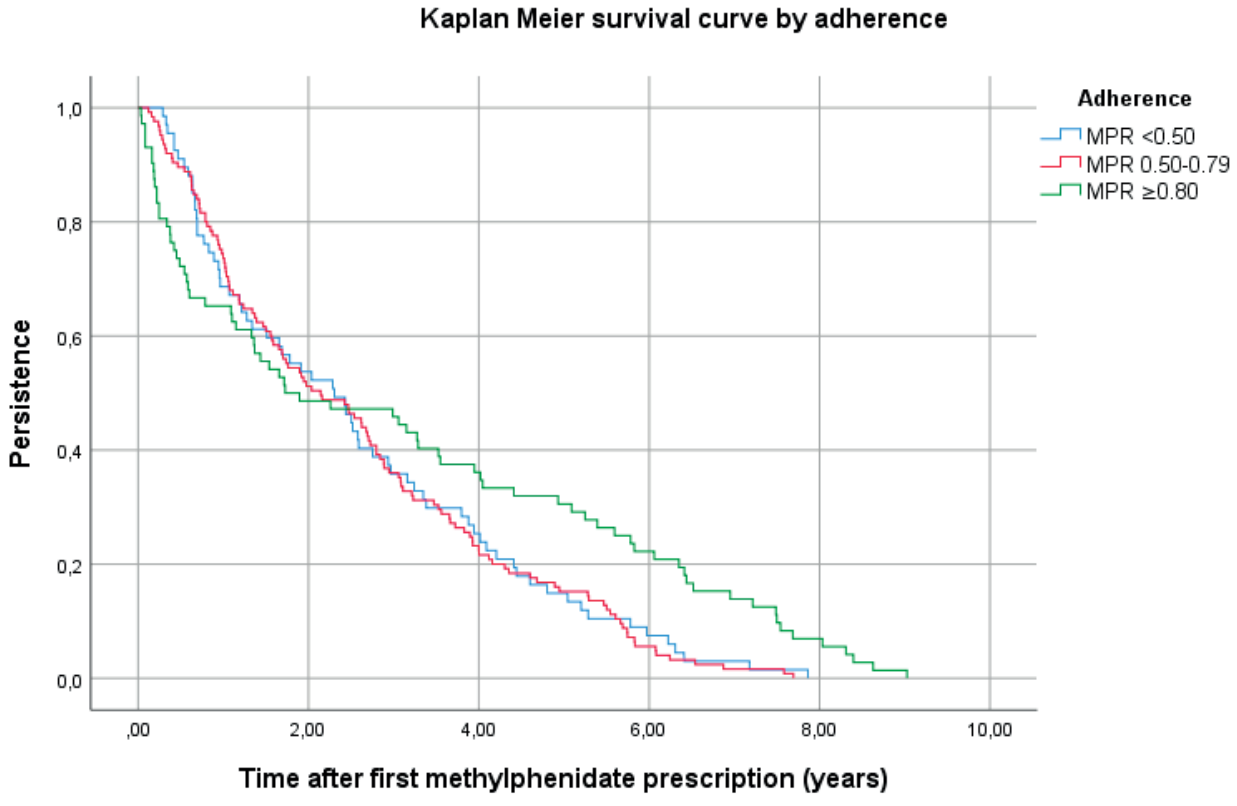

Figure 2. *Kaplan Meier curve for persistence by adherence (n=264)*

The Kaplan Meier curve was presented for persistence where children were censored when having a gap period without prescriptions for 6 months or more (non-persistence). This curve shows the probability of persistence of methylphenidate treatment in three adherence groups (low, intermediate and high) over a time interval with a maximum of 9 years after the first methylphenidate prescription. Abbreviations: MPR indicates medication possession ratio; n, number.

Table 3. *Risk factors for medication discontinuation (non-persistence) (n=307)*

Variable	Adjusted HR (95% CI)
MPR	
<0.50	ref
0.50-0.79	1.01 (0.74-1.38)
≥0.80	0.82 (0.56-1.19)
Sex	
Boy	ref
Girl	*1.44 (1.07-1.95)*
Age of first prescription	
5-11 years	ref
12-16 years	*3.55 (2.54-4.98)*
Ethnicity	
Dutch and other western	ref
Non-western	1.13 (0.83-1.53)
Type of prescriber of first MPH prescription	
Specialist	ref
General practitioner	1.26 (0.82-1.92)
Other medication before first MPH prescription[a]	
No	ref
Yes	0.91 (0.60-1.40)
Short-acting and long-acting MPH	
Mainly short-acting	*1.49 (1.13-1.96)*
Mainly long-acting	ref
Number of switches between long- and short-acting MPH	
0	ref
1	1.05 (0.75-1.47)
2 or more	*0.77 (0.56-1.06)*

**Adjusted for MPR, Sex, age of first prescription, ethnicity, type of prescriber, other medications prior to the first MPH prescription, number of short-acting and long-acting methyphenidate and the number of switches between long-acting and short-acting. [a]anticonvulsants, antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. Abbreviations: CI indicates confidence interval; MPH, methylphenidate, N, number; OR, odds ratio; SD, standard deviation.*

DISCUSSION

Main findings

This study aimed to investigate the adherence and persistence of methylphenidate treatment and their associated determinants. The current findings show that children who switched their medication multiple times from short-acting to long-acting (and vice versa) were more likely to be adherent than those who did not switch. Also, a number of family characteristics played a

role in the treatment adherence of children. We found that children whose mother had given birth to more than one child had a lower adherence and children from families with a moderate household income were more adherent than those with a high household income.

We found that girls were more likely to discontinue treatment than boys and that the risk of discontinuation increases with age. Furthermore, we found that children who were mainly using long-acting methylphenidate, were less likely to discontinue.

Explanation of these findings

First of all, it is important to emphasize that adherence in children is, unlike adolescents and adults, not only based on child determinants but also on parental factors. Parents play an important role in the medication adherence of children as they usually depend on them. We found that children whose mother gave birth to more than one child, were less likely to be adherent. As these children are mostly reliant on their parents, it is possible that mothers who have more than one child may find it difficult to make sure that their child follows the prescribed treatment regimen due to an overload of responsibilities and tasks (as they have to take care of more than one child) [145]. Furthermore, we found that children from families with an average household income were more likely to have a good adherence than those from families with a higher household income. Whether this is due to a higher household income where both parents are working and therefore have less time to monitor medication use in children, could not be studied. Further research is needed to investigate this observation. It is also possible that mothers with a higher household income are more ambivalent towards this type of pharmacotherapy [146].

Second, we found that after the 2.7 years, the persistence was higher in children with a good adherence compared to the lower ones. Children may stop using their medication due to adverse effects (e.g. problems with sleep or loss of appetite) or contra-indications and only take it when needed, resulting in discontinuity of treatment and thus a lower adherence [147]. They may also stop taking methylphenidate if they feel that the treatment does not work. Children who do not take their medication as prescribed (non-adherence) may eventually discontinue treatment as shown previously [137].

However, the question of whether patients are non-persistent or non-adherent may also be influenced by the fact that children are advised to have a medication-break (of one to two weeks) at least once a year. The Dutch Guidelines for General Practitioners describes that these breaks should be initiated to determine whether or not the pharmacological treatment should be continued, preferably during a representative period. However, in some cases it may only be possible to have these breaks during vacations and weekends [8].

Third, the results of our study show that girls were more likely to be non-persistent than boys, which was previously reported [138]. One of the possible reasons is that the effectiveness of methylphenidate is easier to measure in boys in terms of symptoms improvement than girls, because boys more often show hyperactivity while girls more often have concentration

problems. When these symptoms improve, parents will probably encourage their children to take their medication according to prescribed treatment regimen [10, 113]. It is important to conduct further research to investigate the differences in non-persistence to methylphenidate treatment among boys and girls.

Finally, we found that children who started methylphenidate treatment at an older age were more likely to be non-persistent than those who started at a young age. This is in line with a previously published study where a younger age (0-8 years vs 10-19 years) was associated with greater persistence [138]. A possible explanation is that they may have used methylphenidate (often short-term) for other reasons than treating ADHD symptoms, such as increasing school performance and are therefore less persistent [148]. However, the number of prescriptions of short-acting stimulants in the young and older children was not significantly different. Another possible reason is that methylphenidate was prescribed for other indications such as oppositional defiant disorder (ODD), where methylphenidate may be less effective.

When considering long- and short-acting methylphenidate, our finding shows a greater persistence in children who mainly received long-acting methylphenidate, which is in line with a previous study [149]. Also, children who switched medication multiple times from long-acting to short-acting and vice versa, were more likely to be adherent than those who did not switch at all. It may be possible that they switch based on the severity of the disorder, but also the symptom improvement and adverse events may have played a role. This group may be more willing to try and find the best possible treatment and therefore are more likely to be adherent to treatment [150].

Strengths and limitations

One of the strengths of this study is the population-based cohort of young children with up to 16 years of follow-up and the multi-ethnic nature of this population. This long follow-up duration enabled us to investigate potential factors associated with adherence at 2 years (rather than 6 months as in previous studies)[135, 136]. Pediatric patients who started with methylphenidate may stop and restart again. Therefore, it is important to examine adherence at least 1 year after treatment initiation. Also, extensive information about the children and parents was collected prospectively since birth, which made it possible to assess numerous factors that are associated with a good treatment adherence. Furthermore, adherence and persistence were calculated based on dispensing records which is more accurate in terms of dispensation dates than information on prescription records as these medications may have been prescribed but not collected from pharmacies.

However, our study also has several limitations. We did not have information on clinical diagnoses and relied on maternal reported questionnaire data on emotional or behavioral problems in the child. Furthermore, we did not have information about other treatment such as behavioral therapy, which may have also influenced the persistence and adherence to methylphenidate. Also, the number of children in the older age groups is lower as for most children

in our study, they were followed until the age of 16 years. Therefore, the follow-up after treatment initiation in the older children was shorter. However, persistence was only calculated in children when at least 7 months of follow-up was available after starting treatment to ensure a gap-period of 6 months (which is needed to measure non-persistence). Finally, we did not have sufficient power to assess the association between several determinants, such as child ethnicity and marital status with adherence as the numbers were too low. Further research in a larger population is needed to assess if and how ethnicity or marital status would affect adherence to methylphenidate in children.

Conclusion

In conclusion, the results of our study showed that both child and family characteristics may play a role in treatment adherence. Furthermore, child sex and start of treatment was found to be associated with persistence. Considering these findings, it is important for healthcare professionals to take these into account when initiating methylphenidate treatment.