

# Maternal sociodemographic factors are associated with methylphenidate initiation in children in the Netherlands: a population-based study

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## ABSTRACT

*Background and objectives:* Methylphenidate is widely used to treat children with attention deficit hyperactivity disorder (ADHD). Apart from the indication, multiple factors may contribute to the decision to initiate treatment such as maternal sociodemographic factors of which relatively little is known. Therefore, the objective was to investigate the association between these factors and child methylphenidate initiation.

*Methods:* The study population included 4,243 children with pharmacy dispensing records from the Generation R Study in the Netherlands. Maternal sociodemographic characteristics were tested as determinants of methylphenidate initiation through a time-dependent Cox regression analysis with date of first prescription as event date. Subsequently, we stratified by mother-reported clinically relevant ADHD symptoms.

*Results:* Methylphenidate was less likely to be prescribed to girls (adjusted hazard ratio (HR):0.34,95%CI:0.24-0.49) and to children born to a mother with a non-western ethnicity (adjusted HR:0.41,95%CI:0.28-0.60) compared to mothers of Dutch-Caucasian ethnicity, and more likely if mothers completed secondary education compared to a higher education (adjusted HR:1.52,95%CI:1.09-2.12). After stratification on ADHD symptoms, the associations remained similar, except for maternal education where no association was found in children with ADHD symptoms. Children without ADHD symptoms were more likely to receive methylphenidate when their mother completed a low (adjusted HR:2.29,95%CI:1.10-4.77) or secondary (adjusted HR:1.71,95%CI:1.16-2.54) education.

*Conclusion:* The current study showed that even when there are no reported ADHD symptoms, boys and children born to a mother of Dutch-Caucasian ethnicity or a low maternal education were more likely to receive methylphenidate treatment. Treatment initiation in children without ADHD symptoms should be further investigated.

## INTRODUCTION

Worldwide, 5% of children will develop or have symptoms of attention deficit hyperactivity disorder (ADHD) [83]. Stimulant medication is widely used for the treatment of ADHD of which methylphenidate is considered the first choice of pharmacological treatment [84]. However, not all children eligible for methylphenidate treatment receive the medication and conversely some children may receive methylphenidate when it is not needed [85]. Even though, there are clear guidelines with regard to ADHD treatment, symptom severity and functional impairment are not the sole determinants of treatment initiation. Numerous studies have explored other factors that might contribute to the use of stimulant medication in children diagnosed with ADHD [86, 87]. One of the factors known to be related to initiation with stimulant medication is the patient's sex. Stimulants are more often prescribed to boys than girls, which can partly be explained by the fact that ADHD is more often diagnosed in boys than in girls and this may reflect differences in ADHD symptoms between boys and girls [88-90]. Apart from child characteristics, the prescribing behavior of physicians as well as the availability of non-pharmacological treatment options to the family are important [91-93].

Not every child diagnosed with ADHD receives pharmacological treatment [94]. While symptom's severity as well as non-response to non-pharmacological interventions play an important role in the initiation of pharmacological treatment [94], there may be other factors contributing to a family's decision to visit a general practitioner or specialist, a child psychiatrist or to start medication [95]. Children often rely on caregivers for support and management of chronic conditions involving taking medications, where mothers are mostly considered as the primary caregiver [96]. However, the importance of the mothers, notably maternal characteristics in determining methylphenidate treatment initiation should be studied further [97-99]. Previous studies showed that the utilization of ADHD medication may be influenced by sociodemographic factors such as ethnicity and socioeconomic status [89, 100]. However, these studies do not address the presence or absence of any ADHD related symptoms in these children, which may also vary across the different sociodemographic groups [11, 101].

The objective of our study was to investigate the association between maternal sociodemographic and prenatal lifestyle factors in relation to child methylphenidate treatment initiation. Subsequently, we performed analyses stratified by the presence of maternal reports of clinically relevant ADHD symptoms in children using the determinants that were significantly associated with child methylphenidate prescription.

## METHODS

### *Design & study population*

The study was conducted within The Generation R Study, which is a large prospective population-based cohort study investigating children's health from fetal life onwards in Rotterdam, the Netherlands [17]. Pregnant women who were resident in Rotterdam and who had a delivery date between April 2002 and January 2006 were asked to participate in the study. In this cohort, detailed and extensive data collection has been conducted, which include questionnaires, interviews, and behavioral observations of children and their parents [17]. In addition, we retrieved pharmacy records from community pharmacies throughout Rotterdam, depending on where the child resided and collected their prescription-only drugs. In total, 9,778 mothers were enrolled in the study and gave birth to 9,749 live born children (Figure 1). Of this group, 7,896 children and their parents were invited to participate in the follow-up study (56 died; 1,086 withdrawn from study; 639 lost to follow-up). Children were excluded from the study if their parents chose to later withdraw from the study (n=74). They were also excluded if

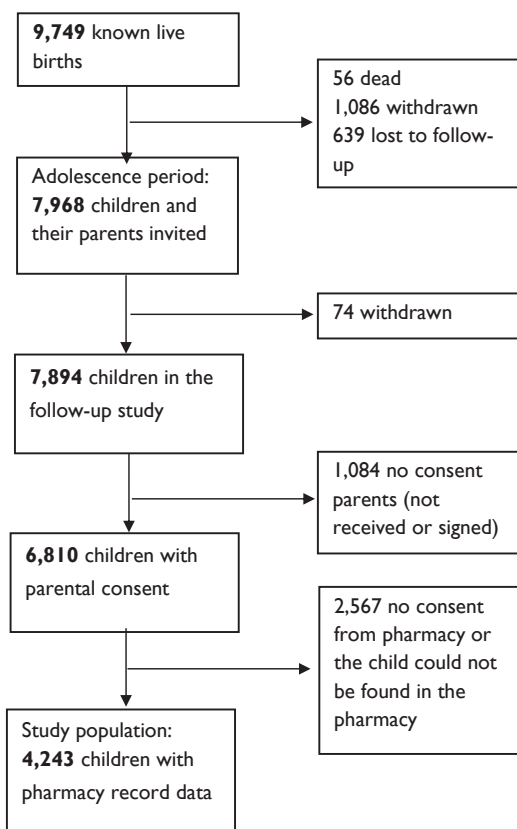


Figure 1. Selection of the study population

no consent by their parents was provided (n=1,084) or because no consent was given by the pharmacist or the child could not be found in the pharmacy (n=2,567). Pharmacy records could be obtained from 4,243 children. The Medical Ethics Committee of the Erasmus Medical Center approved all study procedures, and parents provided written informed consent.

### *Child Methylphenidate prescription*

Pharmacy records of Generation R participants were collected based on the living area of their mothers (northern, southern, western or eastern part of Rotterdam). This information was used to determine at which pharmacies they may collect their medication. Pharmacists were contacted and asked for consent to retrieve the pharmacy records. Children may collect their medication at more than one pharmacy and these pharmacy records were all linked to one particular child. Pharmacy records of children may not be available because either their pharmacy or their parents did not give consent to retrieve these records or because the child's pharmacy could not be found.

For 4,243 individuals in The Generation R Study, all prescriptions which were filled at their pharmacy during the entire study period were gathered starting at birth. For each prescription we had the product name, anatomical therapeutic chemical (ATC) code [102], date of filling, number of delivered tablets/capsules, and prescribed daily number of doses. All study participants were followed from date of birth until a first prescription of methylphenidate or end of the study period at 1 September 2017, whichever came first. Information about the use of ADHD medication (N06BA) was obtained from the collected pharmacy dispensing records. Furthermore, information about the type of prescriber of the first methylphenidate prescription (e.g. general practitioner, specialist or at the hospital) was available, which was retrieved from the electronic pharmacy records as well.

### *Child ADHD symptoms*

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 is a questionnaire that was filled out by mothers when children were 1.5, 3, 5 and 9 years of age. The CBCL/6-18 was only used at the 9 years assessment. The CBCL contains items on the child's behavioral and emotional problems during the preceding 2 months which were scored on a 3-point scale; 6 of the items make up the attention-deficit/hyperactivity problems scale. Children were classified as having ADHD symptoms in the borderline clinical range, when the cut-off score was above the 93<sup>rd</sup> percentile. 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 [103, 104]. For the statistical analysis, we used the last questionnaire that was filled out by the mother prior to date of first methylphenidate prescription. The average time between the completion of the last CBCL and first prescription of methylphenidate was 2.9 years (SD: 3.6).

### *Child and maternal characteristics*

The following maternal lifestyle and demographic characteristics were considered as potential determinants for starting treatment with methylphenidate: maternal age at intake, ethnicity (Dutch-Caucasian or other Western, non-western, defined according to the classification of Statistics Netherlands [105]), household income (<€1200, >€1200 and <2000, >€2000 per month), educational level (primary, secondary, higher), marital status (married, living together, no partner), alcohol use (yes/no), caffeine intake (yes/no) and smoking during pregnancy (yes/no) [106]. Maternal psychopathology in mid-pregnancy was assessed, using the Brief Symptom Inventory (BSI) which is a validated self-report questionnaire which includes a spectrum of psychiatric symptoms. A weighted sum score above 0.75 means that clinically relevant psychopathology symptoms were present [107, 108]. In addition, the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy (the most frequently used antidepressant in our study), which was obtained from pharmacy records and self-reported information [109]. This information from mothers was collected during pregnancy or at birth of their child. Finally, we also considered child's sex as a potential determinant.

### *Analysis*

Child and family characteristics were presented for all children with pharmacy records, which also included the type of prescriber, age of first methylphenidate prescription and the life style factors of the mothers. Second, we investigated which maternal lifestyle and demographic characteristics were related to methylphenidate initiation. For the main analyses, we calculated the hazard ratio (HR), with 95% confidence interval (CI) for each determinant associated with initiation of methylphenidate using a time-dependent Cox regression model, where non-methylphenidate users can serve as a control more than one time [110]. A time-dependent model was used, because the CBCL questionnaires were completed at different points in time (1.5, 3, 5 and 9 years). For this analysis, we considered the presence of clinically relevant ADHD symptoms based on the CBCL questionnaire data completed prior to the date of first methylphenidate prescription. As determinants of methylphenidate treatment initiation, we considered all above-mentioned maternal and child characteristics in the univariate analysis. Second, a multivariable Cox regression analysis was performed with the variables that were univariably associated. Separately, we tested the interaction between maternal education and ethnicity in the post-hoc analysis with an interaction term. Finally, we performed analyses stratified by clinically relevant ADHD symptoms (above 93<sup>rd</sup> percentile) using the factors that were associated with child methylphenidate prescription in the main analysis.

First, we performed complete-case analyses. In the non-response analysis, we explored differences between mothers and children of responders and non-responders. In the sensitivity analysis, we performed the same analysis using multiple imputation of the covariates (where less than 30% was missing) using the expectation maximization algorithm to deal with miss-

ing data. 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

### *Child methylphenidate prescription*

Pharmacy records were available for 4,243 children. A total of 295 children were prescribed an ADHD medication, where 291 (99%) received methylphenidate. Due to the small number of other ADHD medication (dexamphetamine  $n=3$  and atomoxetine  $n=1$ ) prescribed, we only analyzed data of children who started their treatment with methylphenidate. In total, 291 children received a methylphenidate prescription. The average age of receiving their first methylphenidate prescription was 9.4 years. Of the children who received methylphenidate, 207 children received their first methylphenidate prescription from a specialist (71%) and they were more often boys ( $n=221$ , 75.9%).

### *Demographic and lifestyle characteristics*

In Table 1, the characteristics of the study population are shown. Half of the children who were included in our study were girls ( $n=2,066$ , 48.7%). Of those children whose mother filled in the CBCL questionnaires ( $n=2,070$ ), 179 (8.6%) had ADHD symptoms above the cut off score. Furthermore, 1,621 (38.2%) mothers had a non-western background, 2,016 (47.5%) had a relatively high monthly household income ( $\text{€} > 2000$ ) and only a small percentage had a low educational level ( $n=361$ , 8.5%).

**Table 1.** Maternal and child characteristics of study population

Characteristic	N (%), $n=4,243$
Sex, girl	2,066 (48.7)
<i>ADHD symptoms present (CBCL by mother)<sup>o</sup></i>	
No	1,891 (44.6)
Yes	179 (4.2)
Age of first methylphenidate prescription, mean (SD)*	9.4 (2.2)
<i>Type prescriber *</i>	
No methylphenidate prescription	3,955 (93.2)
Specialist	209 (4.9)
General Practitioner	37 (0.9)
Hospital	10 (0.2)
Maternal age (at intake) in years, mean (SD)	30.6 (5.2)
<i>Parity</i>	
1	2,260 (53.3)
>1	1,983 (46.7)

**Table 1.** Maternal and child characteristics of study population (continued)

Characteristic	N (%), n=4,243
<i>Ethnicity mother</i>	
Dutch-Caucasian and other western	2,480 (58.4)
Non-western	1,621 (38.2)
<i>Household income</i>	
<€1200	570 (13.4)
€1200-2000	571 (13.5)
€>2000	2,016 (47.5)
<i>Maternal education level</i>	
No education/ primary education	361 (8.5)
Secondary education	1,708 (40.3)
Higher education	1,747 (41.2)
<i>Marital status</i>	
Married	1,921 (45.3)
Living together	1,418 (33.4)
No partner	484 (11.4)
<i>Smoking during pregnancy</i>	
No	3,056 (72.0)
Yes	596 (14.0)
<i>Alcohol use during pregnancy</i>	
No	1,991 (46.9)
Yes	1,322 (31.2)
<i>Caffeine intake during pregnancy</i>	
No	2,105 (49.6)
Yes	1,468 (34.6)
<i>Maternal psychopathology (BSI)</i>	
<0.76	2,770 (65.3)
0.76 and higher	485 (11.4)
<i>SSRI use during pregnancy</i>	
No	1,798 (42.4)
Yes	36 (0.8)

Numbers are given in numbers (percentages) unless stated otherwise. The numbers of the missing values are not shown in this table, but are as follows: type prescriber 22 (0.5%); reported ADHD symptoms 2,173 (51.2%); ethnicity 142 (3.3%); household income 1,086 (25.6%); maternal education 427 (10.1%); marital status 420 (9.9%); smoking during pregnancy 591 (14%); alcohol use during pregnancy 930 (21.9%); caffeine intake during pregnancy 670 (15.8%); maternal psychopathology 988 (23.3%) and SSRI use during pregnancy 2,409 (56.8%). \*The information about the type of prescriber was only provided of children who received methylphenidate (n=291). <sup>a</sup> Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93<sup>rd</sup> percentile. BSI indicates Brief Symptom Inventory; N, number of children; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors. All numbers are given in percentages or mean (SD).



### Determinants of methylphenidate treatment initiation

In the multivariable analysis (Table 2), we found that girls were less likely to be treated with methylphenidate than boys (adjusted HR: 0.34, 95%CI: 0.24-0.49). As expected, children were more likely to receive a methylphenidate prescription when mothers reported clinically relevant child ADHD symptoms (adjusted HR: 8.67, 95%CI: 6.25-12.02). We observed that children were more likely to start treatment with methylphenidate when mothers completed secondary school (adjusted HR: 1.52, 95%CI: 1.09-2.12) compared to mothers with a higher educational level. Furthermore, a non-western ethnicity of mothers was associated with a lower likelihood of methylphenidate treatment (adjusted HR: 0.41, 95%CI: 0.28-0.60) compared to a Dutch-Caucasian or other western background. Finally, the interaction between maternal education and maternal ethnicity was found to be significant ( $P: 0.001$ ). Children whose mother received a secondary education as compared to a higher education in the western group were more likely to receive methylphenidate (HR:1.93, 95%CI: 1.45-2.58). In the non-western group, no significant association was found (no/ primary education HR: 0.70, 95%CI: 0.36-1.38; secondary education HR: 0.71, 95%CI: 0.42-1.20).

**Table 2.** Maternal and child factors associated with methylphenidate treatment initiation

Characteristic	Cases, N (%) (n=291)	Crude HR, 95%CI	Adjusted HR, 95%CI (cases, n=180)
<i>Sex child</i>			
Boy	221 (75.9)	Ref	Ref
Girl	70 (24.1)	0.31 (0.24-0.41)	0.34 (0.24-0.49)
<i>ADHD symptoms present (CBCL by mother)<sup>a</sup></i>			
No	128 (44.0)	Ref	Ref
Yes	78 (26.8)	9.06 (6.71-12.23)	8.67 (6.25-12.02)
<i>Maternal age at baseline, years</i>			
<25	44 (15.1)	Ref	
25-30	85 (29.2)	0.87 (0.59-1.27)	
31-36	123 (42.3)	0.77 (0.54-1.10)	
>36	39 (13.4)	0.81 (0.52-1.27)	
<i>Parity</i>			
1	154 (52.9)	Ref	
>1	137 (47.1)	1.02 (0.80-1.29)	
<i>Ethnicity mother</i>			
Dutch-Caucasian and other western	201 (69.1)	Ref	Ref
Non-western	82 (28.2)	0.60 (0.46-0.79)	0.41 (0.28-0.60)

**Table 2.** Maternal and child factors associated with methylphenidate treatment initiation (continued)

Characteristic	Cases, N (%) (n=291)	Crude HR, 95%CI	Adjusted HR, 95%CI (cases, n=180)
<i>Household income</i>			
<€1200	29 (10.0)	0.67 (0.44-1.00)	
€1200-2000	38 (13.1)	0.89 (0.61-1.28)	
€>2000	150 (51.5)	Ref	
<i>Maternal educational level</i>			
No education/ primary	20 (6.9)	0.91 (0.56-1.49)	1.04 (0.52-2.06)
Secondary	138 (47.4)	1.37 (1.06-1.78)	1.52 (1.09-2.12)
Higher	106 (36.4)	Ref	ref
<i>Marital status</i>			
Married	113 (38.8)	Ref	
Living together	106 (36.4)	1.29 (0.98-1.70)	
No partner	40 (13.7)	1.44 (0.99-2.10)	
<i>Alcohol use during pregnancy</i>			
No	124 (42.6)	Ref	
Yes	100 (34.4)	1.23 (0.94-1.62)	
<i>Smoking during pregnancy</i>			
No	196 (67.4)	Ref	Ref
Yes	55 (18.9)	1.48 (1.09-2.03)	1.02 (0.70-1.48)
<i>Caffeine intake during pregnancy</i>			
No	143 (49.1)	Ref	
Yes	97 (33.3)	1.04 (0.80-1.35)	
<i>Maternal psychopathology (BSI)</i>			
<0.76	178 (61.2)	Ref	
0.76 and higher	33 (11.3)	1.06 (0.72-1.56)	
<i>SSRI use during pregnancy</i>			
No	132 (45.4)	Ref	
Yes	4 (1.4)	1.58 (0.55-4.53)	

A time-dependent model was used where the ADHD scores of the last completed CBCL questionnaire prior to methylphenidate prescription was considered. In the adjusted model we included all univariably associated determinants. The number of non-methylphenidate users are not presented in the table due to the time component of the model where non-methylphenidate users can serve as a control more than once.<sup>a</sup> Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93<sup>rd</sup> percentile ADHD indicates attention deficit hyperactivity disorders, BSI, Brief Symptom Inventory; CBCL, Child Behavior Checklist CI, confidence interval; HR, hazard ratio; N, number of children; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

### Stratification by ADHD symptoms

#### Absence of ADHD symptoms

Table 3 shows that girls without clinically relevant ADHD symptoms were less likely to receive a methylphenidate prescription than boys (adjusted HR: 0.25, 95%CI: 0.16-0.39). Children with

mothers of a non-western background were less likely to receive a methylphenidate prescription than those with a Dutch-Caucasian background (adjusted HR: 0.42, 95%CI: 0.26-0.68). Furthermore, we found that children were more likely to receive a methylphenidate prescription when mothers completed lower education than those who completed high education (no education/ primary education adjusted HR: 2.29, 95%CI: 1.10-4.77 and secondary education adjusted HR: 1.71, 95%CI: 1.16-2.54).

**Table 3:** Maternal and child factors associated with methylphenidate treatment initiation stratified by the presence and absence of clinically relevant ADHD symptoms

CBCL filled out by the mother	Characteristic	Cases, N	Crude HR, 95% CI	Adjusted HR, 95% CI <sup>b</sup>
ADHD symptoms absent	<i>Sex</i>			
	Boy	101	Ref	Ref
	Girl	27	0.26 (0.17-0.39)	0.25 (0.16-0.39)
	<i>Ethnicity</i>			
	Dutch Caucasian and other western	94	Ref	Ref
	Non-western	32	0.51 (0.33-0.77)	0.42 (0.26-0.68)
	<i>Maternal education</i>			
	No education/ primary	11	1.20 (0.61-2.35)	2.29 (1.10-4.77)
	Secondary	57	1.33 (0.90-1.95)	1.71 (1.16-2.54)
	Higher	48	Ref	Ref
ADHD symptoms present <sup>a</sup>	<i>Sex</i>			
	Boy	58	Ref	Ref
	Girl	20	0.54 (0.32-0.89)	0.53 (0.32-0.90)
	<i>Ethnicity</i>			
	Dutch Caucasian and other western	55	Ref	Ref
	Non-western	23	0.41 (0.25-0.68)	0.45 (0.26-0.77)
	<i>Maternal education</i>			
	No education/ primary	5	0.38 (0.14-1.03)	0.60 (0.21-1.70)
	Secondary	44	0.92 (0.55-1.54)	1.10 (0.65-1.86)
	Higher	26	Ref	Ref

A time-dependent model was used where the ADHD scores of the last completed CBCL questionnaire prior to methylphenidate prescription was considered. In the adjusted model we included all determinants. The number of non-methylphenidate users are not presented in the table due to the time component of the model where non-methylphenidate users can serve as a control more than one time.<sup>a</sup> Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93<sup>rd</sup> percentile. <sup>b</sup>Corrected for time between completion of CBCL and first methylphenidate prescription. ADHD indicates attention-deficit hyperactivity disorder; CBCL, child behavior checklist; CI, confidence interval; HR, hazard ratio; N, number of children.

### *Presence of ADHD symptoms*

When child ADHD symptoms above the cut-off were reported, we found that girls were less likely to receive a methylphenidate prescription than boys (adjusted HR: 0.53, 95%CI: 0.32-0.90) (Table 3). Children of non-western mothers were less likely to receive a methylphenidate prescription compared to those of mothers with a Dutch-Caucasian or other western background (adjusted HR: 0.45, 95%CI: 0.26-0.77).

### *Sensitivity analyses*

In the multivariable analysis with imputed data we found similar results: direction and size of the effect estimates overall did not change much. We found that girls were less likely to receive methylphenidate (adjusted HR: 0.31, 95%CI: 0.21-0.47) or when they had a mother with a non-western background (adjusted HR: 0.48, 95%CI: 0.31-0.75). Children were more likely to receive a methylphenidate prescription when they had ADHD symptoms above the cut-off reported by their mothers (adjusted HR: 10.12, 95%CI: 6.95-14.74). However, the association between methylphenidate initiation and a low maternal education was non-significant (no/primary education adjusted HR: 2.01, 95%CI: 0.94-4.28; secondary education adjusted HR: 1.37, 95%CI: 0.94-2.01).

### *Non-response analyses*

For the variables that were included in the analyses, less than 30% were missing, except for SSRI use during pregnancy (56.8%) and the reported clinically relevant ADHD symptoms (51.2%). The non-response analysis showed no significant differences between children with and without information for the maternal characteristics. However, we found that 2,173 women did not complete the CBCL questionnaires at all or did not complete the questionnaire prior to the first prescription of methylphenidate. A dropout analysis on this variable showed that the missing of the CBCL questionnaire was not significantly associated with sex, but it was associated with ethnicity ( $P < 0.001$ ), maternal education ( $P < 0.001$ ) and methylphenidate initiation ( $P < 0.001$ ).

The analysis in the group without information on ADHD symptoms (missing information) showed similar results for sex and ethnicity (girls adjusted HR 0.49, 95%CI: 0.30-0.83 and non-western background (adjusted HR 0.61, 95%CI 0.36-1.03). For maternal education, we found that a lower education was significantly associated with a decreased risk of methylphenidate use compared to higher education (no education/ primary HR 0.31, 95%CI 0.11-0.91).

Pharmacy records were not available for half of the cohort participants (results not shown in table). For children of whom no pharmacy records were available, we found that their mothers were significantly younger (maternal age 29.6 vs 30.6,  $P < 0.001$ ), had a lower household income (20.6%  $< 1200$  vs 18.1%,  $P < 0.02$ ), were lower educated (12.0% no education/primary education vs 9.5%,  $P < 0.001$ ), more often did not have a partner (15.6% no partner vs 12.7%,  $P < 0.001$ ), used less alcohol during pregnancy (35.4% vs 39.9%,  $P < 0.001$ ), smoked more during pregnancy (19.7% vs 16.3%,  $P < 0.001$ ) and used less caffeine during pregnancy (61.9% vs 58.9%).

## DISCUSSION

### *Main findings*

In the current study, we found that several child and maternal sociodemographic factors were related to methylphenidate treatment initiation. In our study we were able to study these determinants stratified by the presence and absence of clinically relevant ADHD symptoms. Our findings show that methylphenidate was more frequently prescribed to boys than girls. It also shows that children of mothers with a non-western background were less likely to receive methylphenidate treatment than those of mothers with a Dutch-Caucasian or other western background. These findings are both in line with results that have been shown in previous studies [89, 90, 111]. However, the previous studies as described above only addressed the association with sociodemographic factors in patients with an ADHD diagnosis. In our study, we found that even when no ADHD symptoms were reported by mothers, boys and children born to mothers with a western ethnic background were still more likely to receive methylphenidate. Furthermore, we found that a low and secondary maternal education was associated with methylphenidate prescription in children without reported symptoms. A previous study of Russel et al., found no significant association between maternal education and medication use in children in a UK population [88]. This could also be explained by the differences in the educational system of the Netherlands and the UK. It is also possible that they did not find the association as they only explored the sociodemographic factors of medication use among children with ADHD.

### *Explanations for these findings*

First, sex differences with regard to use of methylphenidate or other stimulants is probably related to the diagnosis of ADHD, which is more common in boys than girls [9]. Moreover, boys with clinically ADHD, present more outwardly signs of ADHD, such as hyperactive and impulsive behavior, while girls present more inwardly signs, such as inattentiveness and low self-esteem [112]. In addition, girls may express their difficulties differently; for example emotional problems are more common in girls with ADHD than in boys. Also, boys tend to show more hyperactivity, than girls [10, 113]. This may both lead to boys being diagnosed with ADHD more often as well as earlier initiation of pharmacological treatment as shown previously [88]. However, in our study we observed that girls are still less likely to be treated with methylphenidate irrespective of the presence of ADHD symptoms. It is possible that girls may be less qualified as their symptoms are not considered severe enough [114]. However, it could also imply that girls with ADHD symptoms are undertreated while on the other hand boys without ADHD may be overtreated [115]. Parents may find it more difficult to cope with the hyperactive and impulsive behavior which is more prevalent in boys and this could also be the reason why boys are more likely to be treated with medication.

Second, we showed that children without clinically relevant ADHD symptoms with mothers who only had limited education (no education, primary and secondary education) were more likely to receive a methylphenidate prescription. On the other hand, no significant association with maternal education was observed in children with ADHD symptoms. This finding might be interpreted that as long as the child has ADHD, there is no problem with inequity. When it comes to children without a diagnosis, there is inequity in treatment. Nevertheless, a previously published study showed that a low maternal education was associated with less involvement in the decision-making of medication initiation in children. Parents may not have sufficient knowledge about ADHD and feel that it is necessary to initiate methylphenidate when this is not thoroughly discussed with them [116]. Furthermore, we found that children whose mother had a western ethnic background who received a lower education, were more likely to receive methylphenidate than children whose mother received a high education. It may seem that only mothers with a western ethnic background with a low education are less likely to be involved. This association was not found in the non-western group. This may suggest that mothers with a non-western background, irrespective of educational level, are treated differently than mothers with a western ethnic background.

Third, children with ADHD problems and their parents from ethnic minority groups may have less access to healthcare or less communication with healthcare professionals due to a language barrier [101, 117-121]. They may also receive less appropriate diagnoses or treatments as the symptoms observed for these disorders may differ across ethnic groups, and may differ from what clinicians are trained to expect [122, 123]. ADHD problems are also often recognized by teachers when children are more hyperactive than others. However, not all parents may consider hyperactivity as a behavioral problem as some parents may have a positive attitude towards a child with high energy [124]. This view and recognition of ADHD related problems may vary across different ethnic groups. Furthermore, ethnic minority families may also be less likely to recommend medication and may prefer behavioral therapy over stimulant medication as found in previous studies [125, 126]. The findings of the current study may reflect cultural differences, knowledge and perceptions about ADHD and its pharmacological treatment.

### *Strengths and limitations*

Strengths of our study are the relatively large population-based cohort, its prospective design, independent registration of dispensed medicines, and the multi-ethnic nature of the sample which limit the chance of selection and information bias. Treatment initiation was based on pharmacy dispensing records, which is more accurate in terms of dispensation date than information on prescription medication from medical records or questionnaires as medication can be prescribed but not collected at pharmacies. However, our study also has some limitations. One of the limitations is that we had to rely on questionnaires filled out by mothers to assess the presence of ADHD symptoms. These mother reports are considered valuable as they provide more insight into the perspective of the mothers with regard to their child's behavior

as ADHD symptoms are not always recognized as such across different demographic groups. However, not all mothers completed the CBCL questionnaire, which is also considered as an important limitation as we were not able to assess the presence of ADHD symptoms in these groups. Information bias may have occurred if the association between maternal characteristics or sociodemographic factors and treatment initiation is different for responders and non-responders, but this is difficult to ascertain. Nevertheless, the stratified analysis in the group without information on ADHD symptoms showed similar results for sex and ethnicity, except for maternal education. Another limitation is that pharmacy records were not available for half of the participants of The Generation R study as not all pharmacists provided consent to obtain the dispensing records from their pharmacies. As shown in the results, we found that mothers of children without pharmacy records differed on several aspects. Despite this selection bias, we observed similar results in our study compared to the available literature showing an association between initiation of methylphenidate and ethnicity, maternal educational level and smoking during pregnancy [116, 127]. Furthermore, no information about other treatment (e.g. behavioral therapy) was available. Therefore, we were not able to assess if specific demographic groups were not receiving therapy or were treated with behavioral therapy. Finally, information about maternal characteristics were not available for each child, but the non-response analysis showed no significant differences between both groups.

## Conclusion

In conclusion, the current study showed that even when there are no reported ADHD symptoms, boys and children born to a mother of Dutch-Caucasian ethnicity or a low maternal education were more likely to receive methylphenidate treatment. This may suggest overtreatment. Considering these findings, it is important for healthcare professionals to be aware of these differences and take these into account when deciding on initiating treatment with methylphenidate. Reasons for treatment initiation in children without ADHD symptoms should be further investigated.