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ORIGINAL RESEARCH ARTICLE

Dosing and Discontinuation of Methylphenidate Medication in Relation to Weight Status in Children and Adolescents

Julia Izsak[1,2] · Elin E. Kimland[3,4] · Jari Martikainen[5] · Elin Dahlén[4,6] · Linda Halldner[7] · Jenny M. Kindblom[1,2]

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Abstract

Background and Objective Evidence and clinical guidelines on methylphenidate dosing in different weight status groups are limited. This study aimed to evaluate real-world methylphenidate dosing practices and treatment discontinuation rates in children and adolescents in relation to weight status.

Method We used data from the BMI Epidemiology Study Gothenburg cohort, which includes weight and height measurements linked to national registers. Exposures included body weight, standardised body mass index (zBMI), and body mass index (BMI) status. The main outcome was the dose and weight-adjusted dose of methylphenidate for the baseline and follow-up prescriptions. We used a logistic regression model to evaluate treatment discontinuation in relation to weight status, sex, and age.

Results The study included 1741 children and adolescents who initiated methylphenidate treatment and had BMI available. Among them, 612 had a follow-up prescription with BMI available. Children and adolescents with overweight and obesity received slightly higher absolute doses of methylphenidate at baseline prescriptions, but lower weight-adjusted doses. Children and adolescents with underweight received higher weight-adjusted doses. Absolute dose increases between treatment initiation and follow-up were highest in children and adolescents with obesity and lowest in children and adolescents with underweight. Girls received higher absolute and weight-adjusted doses than boys at follow-up, while children over 12 years of age received higher absolute but lower weight-adjusted doses than children under 12 years. A significantly higher proportion of children and adolescents with baseline underweight discontinued treatment during the first year, compared with the normal weight group. Beside lower baseline zBMI, female sex and higher age were also significantly associated with treatment discontinuation during the first year.

Conclusion Our findings suggest that weight status, sex, and age are significantly associated with differential methylphenidate dosing and treatment discontinuation in children and adolescents.

✉ Julia Izsak
julia.izsak@gu.se

1 Unit of Clinical Pharmacology, Department of Pharmaceuticals, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden

2 Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

3 Swedish Medical Products Agency, Uppsala, Sweden

4 Department of Pharmacy, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden

5 Bioinformatics and Data Centre, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

6 The NEPI foundation-Network for Pharmacoepidemiology, Stockholm, Sweden

7 Department of Clinical Sciences, Child and Adolescent Psychiatry, Umeå University, Umeå, Sweden

Key Points

Real-world methylphenidate dosing and treatment discontinuation vary significantly by weight status in children and adolescents.

Dose increases of methylphenidate over time were highest in children and adolescents with obesity and lowest in children and adolescents with underweight.

Children and adolescents with underweight were more likely to discontinue methylphenidate treatment within the first year.

These findings highlight the need for further research on how dosing influences the effectiveness and safety of methylphenidate in children and adolescents with underweight, overweight, and obesity.

1 Introduction

The number of children with attention-deficit/hyperactivity disorder (ADHD) diagnoses has shown a pronounced increase over the past decades [1]. In parallel with the rise in ADHD diagnoses, the prescription of central stimulant medications has also increased, with methylphenidate being the most frequently used central stimulant among children and adolescents in Scandinavia [2]. In Sweden, available methylphenidate formulations include osmotic-release oral system (OROS) methylphenidate, extended-release capsules, and immediate-release tablets. They became available in the early to mid-2000s, with generics introduced later [3].

ADHD affects individuals across all weight status groups; however, a growing body of research suggests a frequent co-occurrence with obesity [4–6]. Given the rising prevalence of obesity among children and adolescents [7], it is important to understand how stimulant medication impacts this population, as overweight and obesity can influence drug disposition by altering pharmacokinetic parameters such as volume of distribution and clearance [8]. At the same time, children and adolescents with underweight also remain underrepresented in clinical research, despite potential differences in pharmacokinetics and treatment response that may impact dosing and efficacy [9]. Although methylphenidate is widely used, specific dosage guidelines for children and adolescents with underweight, overweight, or obesity are lacking [10–12], primarily due to the limited literature in this area.

Dosing of methylphenidate is typically individualised through titration based on therapeutic effect and tolerability. The recommended dosage ranges between 0.5 and 2 mg/kg/day [10, 12], with a suggested maximal absolute dose ranging between 54 and 60 mg for children and 72 and 80 mg for adults [11]. Research on dosing of medications in children and adolescents with obesity is scarce but has indicated substantial interindividual variability in dosing regimens. One study reported that methylphenidate dosing ($n = 109$) was calculated per total body weight in 57%, and using fixed dose by age in 39%, of children with overweight or obesity [13]. This variability raises concerns, as high stimulant doses may increase the risk for side effects [14, 15], while lower doses may potentially lead to undertreatment. Additionally, a meta-analysis suggests that the maximum dose limits of methylphenidate are not supported by evidence, further complicating dosing decisions, particularly for individuals with elevated weight [16].

Given the inconsistencies in dosing across weight status groups, it is important to explore whether these variations influence treatment discontinuation. Since ADHD treatment is primarily symptomatic, treatment is titrated to effective symptom management. It has been shown that the reasons for discontinuation of stimulant medication include lack of symptom control, adverse effects, dosing inconvenience, social stigma, or patient attitudes to treatment [17]. However, treatment discontinuation in relation to weight status, and the potential importance of low or high weight on continuation rates is not well understood. Identifying factors contributing to discontinuation and understanding how continuation rates vary across weight status groups could provide valuable insights for treatment optimising strategies.

This study aims to examine real-world dosing practices for methylphenidate in relation to weight status in children and adolescents in a Swedish cohort. Additionally, we aim to evaluate treatment discontinuation patterns across weight status groups.

2 Methods

The BMI Epidemiology Study Gothenburg cohort has developmental height and weight measurements available from school health care and child health care, as well as information on diagnoses and prescribed medications from linkage to the National Prescribed Drug Register and the National Patient Register [18]. The National Prescribed Drug Register is held by the National Board of Health and Welfare in Sweden and was initiated in 2005. Linkage to registers was performed using each individual's Personal Identity Number. Individuals in the BMI Epidemiology Study Gothenburg cohort were eligible for the present study if they had at least one prescription of methylphenidate dispensed before 18 years of age in the National Prescribed Drug Register before January 31st, 2021 and, in addition, had a weight and height measurement available within 1 year before dispensing. If several measurements were available, the measurement closest to the prescription date was used. To ascertain inclusion of methylphenidate naïve users, we required at least 1 year free of methylphenidate prescription before inclusion.

The data included in the present study required that the drug prescriptions were dispensed by the pharmacy. For simplicity, the term "prescription" is used throughout the article. Methylphenidate was defined using the Anatomical Therapeutic Chemical (ATC) code N06BA04 [19].

2.1 Exposure and Background Factors

The exposures in the present study were body weight, standardised body mass index (zBMI), and body mass index (BMI) status. We calculated BMI as weight in kilograms divided by height in metres squared (kg/m^2) and categorised the values according to the International Obesity Task Force's age- and sex-specific cutoffs for underweight, overweight, and obesity [20, 21]. According to these cutoffs, underweight was defined as having a BMI below the values

corresponding to an adult BMI < 18.5, overweight as BMI ≥ 25, and obesity as BMI ≥ 30. Children and adolescents not meeting these criteria were classified as normal weight. *Z*-scores for BMI were calculated based on the least mean squares method [20, 21]. To assess psychiatric comorbidity, we used information on psychiatric diagnoses from the Swedish National Patient Register and data on prescribed psychotropic medications from the National Prescribed Drug Register. We defined the presence of psychiatric disorders using the International Classification of Diseases (ICD) system as F00-F99, before the baseline methylphenidate prescription. Psychotropic medications were defined using the following ATC codes: N05A (antipsychotics), N05B, R06AD (anxiolytics), N06A (antidepressants), and N05C (sedatives). These medications were considered if dispensed within 6 months before or after the baseline dispensing date of methylphenidate.

2.2 Outcomes

The main outcome of the present study was the dose of methylphenidate (mg) and weight-adjusted dose (mg/kg) for the first eligible prescription (baseline prescription) for the entire cohort ($n = 1741$), and dose of methylphenidate (mg) and weight-adjusted dose (mg/kg) for the 1-year follow-up prescription using a subgroup ($n = 612$). The 1-year follow-up prescription was extracted between 6 and 12 months after the baseline prescription for children who also had an available weight and height measurement at follow-up.

To determine the dose, we used tablet strength and prescription details recorded as free text in the National Prescribed Drug Register. Prescriptions dispensed on the same date were counted as one prescription. Total daily dose was calculated by summing the number of tablets per day either prescribed in one prescription or from multiple prescriptions. For a few prescriptions with unclear dosing instructions, the dose was determined through consensus between two authors (JI, LH). The term "dose" refers to the total daily dose throughout the manuscript.

To assess medication continuation, we evaluated the number of dispensings during the first and second year after the baseline prescription. Treatment discontinuation was defined as fewer than three dispensings of methylphenidate in 12 months, considering that in Sweden, a prescription can cover a maximum of a 3-month medication supply and continuous treatment is prescribed in amounts suitable for four dispensings per year. For the analysis of treatment discontinuation, we used the total number of drug dispensings per year, 1 and 2 years after baseline. These analyses did not require height and weight measurement at follow-up and were therefore performed in the entire cohort ($n = 1741$).

2.3 Statistical Analyses

The study did not include a pre-specified statistical analysis plan, and all analyses were conducted post hoc. Descriptive statistics for continuous variables are presented using mean and standard deviation (SD) and categorical variables using number and percentage, if not stated otherwise. We used a two-sided Welch´s test or two-sided Wilcoxon rank-sum test to compare differences between groups and Chi-square test to analyse proportions. Analyses focused on clinically relevant comparisons, comparing underweight, overweight, and obesity groups with the normal-weight reference group. No correction for multiple comparisons was applied, as these comparisons constituted our primary hypotheses. Analyses stratified by sex and age were considered exploratory. A logistic regression model was fitted to evaluate the odds for treatment discontinuation according to weight status, sex, and age groups. Logistic regression analyses and Kaplan–Meier survival analyses were done using SPSS and R, with the survival package used for survival analysis in R. p values < 0.05 were considered statistically significant and are presented as $^{***}p < 0.001$, $^{**}p < 0.01$, and $^{*}p < 0.05$. SPSS version 29.0 and R version 4.2.0 (2022-04-22) were used.

3 Results

We used the population-based BMI Epidemiology Study Gothenburg cohort to evaluate dosing practices and treatment discontinuation of methylphenidate in relation to weight status in children and adolescents. In total 1741 children and adolescents below 18 years of age were initiating methylphenidate treatment during the study period and had a weight and height measurement available within 1 year before dispensing. The mean age at treatment start was 11.3 years, with 59% of children aged below 12 years and 72% being male (Table 1). Methylphenidate treatment was prescribed at an average dose of 15.9 mg and 0.40 mg/kg at baseline (Table 1). Among children and adolescents initiating methylphenidate, we further selected the subgroup who had a follow-up prescription 6–12 months after treatment initiation and had an available follow-up weight and height measurement. The cohort characteristics of the included 1741 children and adolescents, and the subgroup of 612 individuals, are presented in Table 1.

3.1 Dosing of Methylphenidate at Start of Treatment

At treatment start ($n = 1741$), children and adolescents with baseline overweight or obesity received significantly higher doses than children and adolescents with normal

weight. There was no significant difference in dose for children and adolescents with underweight, compared to normal weight. However, children and adolescents with overweight and obesity received lower weight-adjusted doses (i.e. dose per kilogram body weight), and children and adolescents with underweight received higher weight-adjusted doses, compared to children and adolescents with normal weight (Table 2; Supplementary Fig. 1 in the electronic supplementary material). There was no difference in age between the weight status groups. Girls received significantly higher doses, but similar weight-adjusted doses compared with boys. Girls were older than boys. Children aged 12 or older received higher doses but significantly lower weight-adjusted doses than children below 12 years of age (Table 2).

3.2 Dosing of Methylphenidate in Children and Adolescents with Follow-Up Data

In the subgroup including 612 children and adolescents who had a dispensed baseline and follow-up prescription, in combination with an available weight and height at both time points, we analysed both the overall dose change (i.e. the difference between the baseline and follow-up dose) and

Table 1 Characteristics and descriptive statistics of the included cohort of children and adolescents initiating methylphenidate ($n = 1741$) and of a subgroup with 1 year follow-up ($n = 612$)

	Children and adolescents starting methylphenidate who had an available weight and height ($n = 1741$)		Children and adolescents with a dispensed baseline and follow-up prescription with an available weight and height ($n = 612$)	
	Mean (SD) or *n* (%)	Range	Mean (SD) or *n* (%)	Range
Cohort descriptives				
Age at prescription (years)	11.3 (3.2)	3.9–17.99	10.5 (2.9)	4.7–17.9
Height (cm)	146.3 (18.8)	97.0–190.0	142.7 (17.7)	97.0–189.8
Weight (kg)	42.9 (17.7)	14.5–138.0	40.1 (16.7)	14.5–106.3
BMI (kg/m^2)	19.2 (4.1)	12.5–44.1	18.9 (3.9)	12.6–34.1
BMI *z*-score (SD)	0.65 (1.16)	−3.80 to 3.75	0.70 (1.18)	−2.69 to 3.46
Patient subgroups, *n* (%)				
Males	1254 (72.0)		462 (75.5)	
Age < 12	1032 (59.3)		428 (69.9)	
Underweight	127 (7.3)		42 (6.9)	
Overweight	352 (20.2)		136 (22.2)	
Obesity	163 (9.4)		64 (10.5)	
Psychiatric diagnosis before prescription	1417 (81.4)		497 (81.2)	
Treatment with sedatives	432 (24.8)		124 (20.3)	
Treatment with anxiolytics	155 (8.9)		34 (5.6)	
Treatment with antidepressants	138 (7.9)		33 (5.4)	
Treatment with antipsychotics	81 (4.7)		23 (3.8)	
Prescription descriptives				
Baseline prescription				
Dose (mg)	15.9 (6.9)	2.5–60.0	15.8 (6.8)	5–54.0
Dose per kg (mg/kg)	0.40 (0.19)	0.05–1.49	0.43 (0.19)	0.05–1.18
Follow-up prescription				
Dose (mg)	NA	NA	30.0 (12.2)	5–72.0
Dose per kg (mg/kg)	NA	NA	0.74 (0.32)	0.14–2.36

Characteristics of the included children and adolescents ($n = 1741$) from the BMI Epidemiology Study Gothenburg, below 18 years of age with at least one dispensing of methylphenidate, and with height and weight available within 1 year before the baseline dispensing. Among the 1741 children and adolescents initiating methylphenidate, we further selected individuals ($n = 612$) who also had a dispensed follow-up prescription within 6–12 months after the baseline prescription and had an available weight and height measurement. Underweight, overweight, and obesity were defined according to the international cutoffs from the International Obesity Task Force [20, 21]. Registered psychiatric diagnoses (F00-F99) were considered before the baseline prescription of methylphenidate. Treatment with sedatives (N05C), anxiolytics (N05B, R06AD), antidepressants (N06A), and antipsychotics (N05A) was considered in the interval 6 months before to 6 months after the dispensing of methylphenidate. Data are presented as means (SD) and range for continuous variables and as number (%) for categorical variables

BMI body mass index, *NA* not applicable, *SD* standard deviation

the final dose at follow-up, in relation to weight status, age, and sex at baseline.

Children and adolescents with overweight and obesity at baseline received significantly higher absolute doses at both baseline prescriptions and follow-up prescriptions, and children and adolescents with underweight at baseline received significantly lower doses compared to children with normal weight (Table 2). However, the weight-adjusted doses were significantly higher for children and adolescents with underweight and lower for children and adolescents with overweight or obesity, compared to children with normal weight at baseline prescription. For follow-up prescriptions, children and adolescents with overweight at baseline continued to receive significantly lower weight-adjusted doses (Table 2). Age at prescription did not differ between children and adolescents in the different weight status groups.

We further calculated dose changes between baseline and follow-up prescriptions by subtracting the dose at baseline prescription from the dose at follow-up prescription. Children and adolescents with obesity at baseline had significantly higher absolute dose increases from baseline to follow-up prescription, whereas children and adolescents with underweight had significantly smaller dose increases compared to children with normal weight. A linear regression model showed a significant association between baseline zBMI and absolute dose change ($p < 0.001$), indicating larger increases in dose with higher

Table 2 Methylphenidate dosing in relation to weight status, sex, and age in children and adolescents

Variable	Weight status at baseline				Sex		Age group	
	UW	NW	OW	OB	Boys	Girls	Age < 12	Age ≥ 12
Baseline prescription in all ($n = 1741$)	$n = 127$	$n = 1099$	$n = 352$	$n = 163$	$n = 1254$	$n = 487$	$n = 1032$	$n = 709$
Dose; mg, mean (SD)	14.7 (6.5)	15.5 (6.7)	16.8 (7.4)*	17.6 (7.3)***	15.4 (6.6)	17.1 (7.5)***	14.0 (6.2)	18.6 (7.1)***
Dose per kg; mg/kg, mean (SD)	0.50 (0.23)***	0.42 (0.18)	0.35 (0.17)***	0.32 (0.16)***	0.40 (0.19)	0.40 (0.18)	0.45 (0.19)	0.34 (0.15)***
Age at prescription; years, mean (SD)	11.7 (3.4)	11.2 (3.2)	11.5 (3.3)	10.8 (3.0)	10.9 (3.1)	12.3 (3.4)***	9.0 (1.8)	14.6 (1.6)***
Baseline prescription in the subgroup with available follow-up data ($n = 612$)	$n = 42$	$n = 370$	$n = 136$	$n = 64$	$n = 462$	$n = 150$	$n = 428$	$n = 184$
Dose; mg, mean (SD)	14.4 (6.5)*	15.1 (6.1)	17.4 (8.1)*	17.4 (7.4)*	15.6 (6.7)	16.4 (7.1)	14.6 (6.4)	18.6 (7.0)***
Dose per kg; mg/kg, mean (SD)	0.55 (0.27)*	0.45 (0.18)	0.38 (0.20)***	0.34 (0.17)***	0.43 (0.19)	0.44 (0.20)	0.47 (0.20)	0.34 (0.14)***
Age at prescription; years, mean (SD)	10.3 (2.9)	10.5 (2.8)	10.9 (2.9)	10.2 (2.7)	10.4 (2.8)	10.9 (2.9)	9.0 (1.8)	14.1 (1.3)***
1-year follow-up prescription ($n = 612$)								
Dose; mg, mean (SD)	23.8 (11.2)**	28.6 (11.5)	31.7 (12.0)**	38.7 (12.8)***	29.2 (11.9)	32.6 (12.9)**	27.0 (10.8)	36.9 (12.5)***
Dose per kg; mg/kg, mean (SD)	0.81 (0.35)	0.78 (0.32)	0.64 (0.28)***	0.70 (0.28)	0.72 (0.31)	0.81 (0.34)**	0.79 (0.33)	0.63 (0.24)***
Dose adjustments ($n = 612$)								
Delta dose; mg, mean (SD)	9.4 (9.2)*	13.5 (11.1)	14.3 (12.3)	21.3 (13.6)***	13.6 (11.4)	16.2 (13.0)*	12.4 (10.6)	18.3 (13.4)***
Delta dose/kg; mg/kg, mean (SD)	0.25 (0.27)	0.33 (0.32)	0.26 (0.30)*	0.37 (0.29)	0.29 (0.30)	0.36 (0.34)*	0.32 (0.34)	0.29 (0.25)

Doses and doses per kilogram of body weight are presented for 1741 children and adolescents from the BMI Epidemiology Study Gothenburg, below 18 years of age with at least one dispensing of methylphenidate, and height and weight available within 1 year before the dispensing, as well as for the subgroup of 612 children and adolescents below 18 years of age with a dispensed follow-up prescription with an available weight and height. Follow-up prescriptions were considered within 6–12 months after the baseline prescription for children and adolescents with available BMI. Weight status groups were defined according to baseline BMI, using cutoffs from the International Obesity Task Force [20, 21]. Dose adjustments (delta doses) were calculated by subtracting the baseline prescription dose from the follow-up prescription dose. Values are presented as mean (SD). Statistical comparisons of dosing were performed using two-sided Wilcoxon rank-sum test, comparing each weight status group with the NW group as well as sex and age groups with each other. Age at prescription was analysed using two-sided Welch's test, with comparisons made between each weight status group and the NW group, as well as between sex and age groups, respectively. Statistically significant results are indicated as ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$

BMI body mass index, *NW* normal weight, *OB* obesity, *OW* overweight, *SD* standard deviation, *UW* underweight

baseline BMI. There was no significant association between baseline zBMI and dose adjustments normalised per body weight ($p > 0.05$). Dose distributions for baseline and follow-up prescriptions as well as for dose adjustments are visualised in Supplementary Fig. 2 (see the electronic supplementary material).

We further evaluated weight adjusted doses by reclassifying children and adolescents based on their actual weight status at follow-up prescription. This reclassification revealed that children and adolescents who were underweight at 1-year follow-up received significantly higher weight-adjusted doses compared to those with normal weight at follow-up prescription. Children and adolescents categorised as overweight or having obesity at follow-up received significantly lower weight-adjusted doses compared to those with normal weight (Supplementary Table 1 in the electronic supplementary material).

In the subgroup of 612 children and adolescents who retrieved a baseline and follow-up prescription and had a recorded weight and height measurement, girls were initially prescribed similar doses of methylphenidate to boys. However, girls received significantly greater dose increases, leading to higher absolute and weight-adjusted doses at follow-up prescription (Table 2). In the subgroup with follow-up data, no significant age difference was seen between girls and boys (Table 2).

Adolescents (≥ 12 years) received higher absolute doses, but lower weight-adjusted doses compared to children under 12 years at baseline. Additionally, the absolute dose increase was significantly higher in adolescents, whereas weight-normalised dose adjustments did not differ between age groups (Table 2).

3.3 Treatment Discontinuation

We further assessed treatment discontinuation (fewer than three dispensings within 12 months) among the included children and adolescents ($n = 1741$) at 1 and 2 years of follow-up. Overall, 27% of children and adolescents discontinued methylphenidate during the first year and an additional 24% during the second year. A significantly higher proportion of children and adolescents with baseline underweight, and a significantly lower proportion of children and adolescents with baseline obesity, discontinued methylphenidate treatment during the first year, compared with children and adolescents with normal weight (Table 3). A significantly higher proportion of girls and adolescents had treatment discontinuation, compared with boys and children under 12 years, respectively, during the first year (Table 3). During the second year, no significant differences were observed in treatment discontinuation based on baseline weight status or sex. However, adolescents (≥ 12 years) discontinued treatment at a significantly higher rate than children under 12 during the second year of treatment (Table 3).

We used a logistic regression model to further evaluate the association between baseline zBMI, sex, age, and treatment discontinuation. We included treatment discontinuation during the first or second year as the outcome, and zBMI, sex, and age as covariates, in the logistic regression model. Higher age was significantly associated with increased odds of treatment discontinuation in both the first and second year after treatment start with methylphenidate (year 1: odds ratio [OR] = 1.04, 95% confidence interval [CI] 1.01–1.08, $p = 0.018$; year 2: OR = 1.15, 95% CI 1.10–1.19, $p < 0.001$). Sex was also significantly associated with discontinuation, with girls having higher odds of treatment discontinuation compared to boys, but only during the first year of treatment (year 1: OR = 1.27, 95% CI 1.00–1.61, $p = 0.047$; year 2: OR = 1.05, 95% CI 0.80–1.38, $p = 0.7$). Additionally, a higher baseline zBMI was associated with a lower risk of treatment discontinuation in the first year (year 1: OR = 0.81 per SD increase in BMI, 95% CI 0.73–0.88, $p < 0.001$), but this association was attenuated and not significant in the second year after treatment start with methylphenidate (year 2: OR = 0.93 per SD increase in BMI, 95% CI 0.84–1.04, $p = 0.2$). Kaplan–Meier survival analysis and pairwise log-rank test demonstrated significant associations between higher discontinuation rates over the first 2 years and being underweight, female, or ≥ 12 years of age. Discontinuation was more common among individuals who were underweight, female, or aged ≥ 12 years during the first 2 years after starting methylphenidate (Fig. 1).

Children and adolescents with underweight who discontinued methylphenidate treatment during the first year of treatment had a lower zBMI at baseline prescription compared to children with underweight who continued treatment (Table 4). No significant difference in baseline zBMI within the different baseline weight status groups of normal weight, overweight, and obesity, respectively, was seen between children who continued treatment compared to those who discontinued. Doses and weight-adjusted doses at baseline prescription did not differ between children with or without treatment continuation (Table 4).

4 Discussion

There is a lack of evidence and clinical recommendations to support dosing of methylphenidate in different weight status groups. In the present study, we used the BMI Epidemiology Study Gothenburg cohort with data on height and weight linked to information on prescriptions from high-quality Swedish registers. In this real-world setting, we evaluated dosing according to weight and weight status in 1741 children and adolescents who started methylphenidate treatment

Table 3 Treatment continuation and discontinuation during the first 2 years of treatment in 1741 children and adolescents initiating methylphenidate

Variable	Baseline category	Year 1		Year 2	
		Treatment continuation *n* (%)	Treatment discontinuation *n* (%)	Treatment continuation *n* (%)	Treatment discontinuation *n* (%)
Weight status	UW ($n = 127$)	72 (56.7)	55 (43.3)***	41 (32.3)	31 (24.4)
	NW ($n = 1099$)	793 (72.2)	306 (27.8)	532 (48.4)	261 (23.7)
	OW ($n = 352$)	268 (76.1)	84 (23.9)	179 (50.9)	89 (25.3)
	OB ($n = 163$)	133 (81.6)	30 (18.4)*	88 (54.0)	45 (27.6)
Sex	Male ($n = 1254$)	934 (74.5)	320 (25.5)**	633 (50.5)	301 (24.0)
	Female ($n = 487$)	332 (68.2)	155 (31.8)	207 (42.5)	125 (25.7)
Age	Age < 12 ($n = 1032$)	783 (75.9)	249 (24.1)***	580 (56.2)	203 (19.7)***
	Age ≥ 12 ($n = 709$)	483 (68.1)	226 (31.9)	260 (36.7)	223 (31.5)

Treatment continuation and discontinuation in 1741 children and adolescents from the BMI Epidemiology Study Gothenburg, below 18 years of age with at least one dispensing of methylphenidate, and height and weight available within 1 year before the dispensing. Children and adolescents who retrieved their methylphenidate prescriptions at least three times during a year of treatment were classified as treatment continuation, while those who retrieved their prescriptions fewer than three times per year were classified as treatment discontinuation. Weight status groups were defined according to baseline BMI, using cutoffs from the International Obesity Task Force [20, 21]. Number and percentage of baseline categories for weight status groups, males, females, and children < 12 and ≥ 12 years, respectively of children and adolescents with treatment continuation and treatment discontinuation for the first and second year of treatment with methylphenidate are shown. Statistical comparisons were performed using Chi-square test comparing each weight status group with the NW group as well as sex and age groups with each other. Statistically significant results are indicated as ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$

BMI body mass index, *NW* normal weight, *OB* obesity, *OW* overweight, *UW* underweight

between 2006 and 2021 and in a subgroup of 612 children and adolescents with follow-up data. In addition, we evaluated discontinuation rates in relation to weight status. We found that children and adolescents with overweight and obesity received slightly higher absolute doses of methylphenidate at baseline prescription, but lower weight-adjusted doses. Children and adolescents with underweight received higher weight-adjusted doses. Absolute dose increases between treatment initiation and follow-up were highest in children and adolescents with obesity and lowest in children and adolescents with underweight. In addition, discontinuation within the follow-up period was more common among children and adolescents with underweight compared with those with higher weight.

The evidence regarding dosing of methylphenidate according to weight status is inconsistent and scarce. Some prior studies have reported no significant association between body mass and dosing or treatment outcomes. For instance, dose-response studies of methylphenidate in children and adolescents with ADHD found no significant association between body weight and effective dose [22, 23], although one of the studies found that weight-adjusted dosing was slightly more sensitive for predicting potential adverse effects [23]. Observational studies examining the predictors of methylphenidate response in children with ADHD found no substantial effect of weight or BMI on treatment outcomes [24, 25]. Some other studies suggest that body weight may influence dose-response to methylphenidate. The Multimodal Treatment Study of Children with ADHD (MTA study) found that children between the age of 7 and 9 years with weight below 25 kg showed steeper dose-response curves compared to children above 25 kg [26]. According to growth charts from the US Centers for Disease Control and Prevention, the weight of 25 kg reflects an average weight for this age span. A recent randomised dose-response trial also reported a steeper dose-response among children with lower body weight [27]. Notably, the sample sizes in some of these studies were relatively small [22, 27], and only one used age-adjusted body weight in its analysis [22]—methodological limitations that may influence the observed relationship between weight and dosing. Additionally, none of the studies evaluated the effect of methylphenidate according to weight status. Thus, treatment effect and dose selection of methylphenidate in children and adolescents with underweight, normal weight, overweight, and obesity is not well understood. Nevertheless, the finding of a steeper dose-response in children with low body weight indicates that body weight is of importance for the therapeutic window and has a potential to guide dose selection. Our real-world data on dosing practices of methylphenidate in children and adolescents support and extend this perspective. We observed a significant linear association between baseline zBMI and methylphenidate dose increases, with children and adolescents who had higher zBMI at baseline

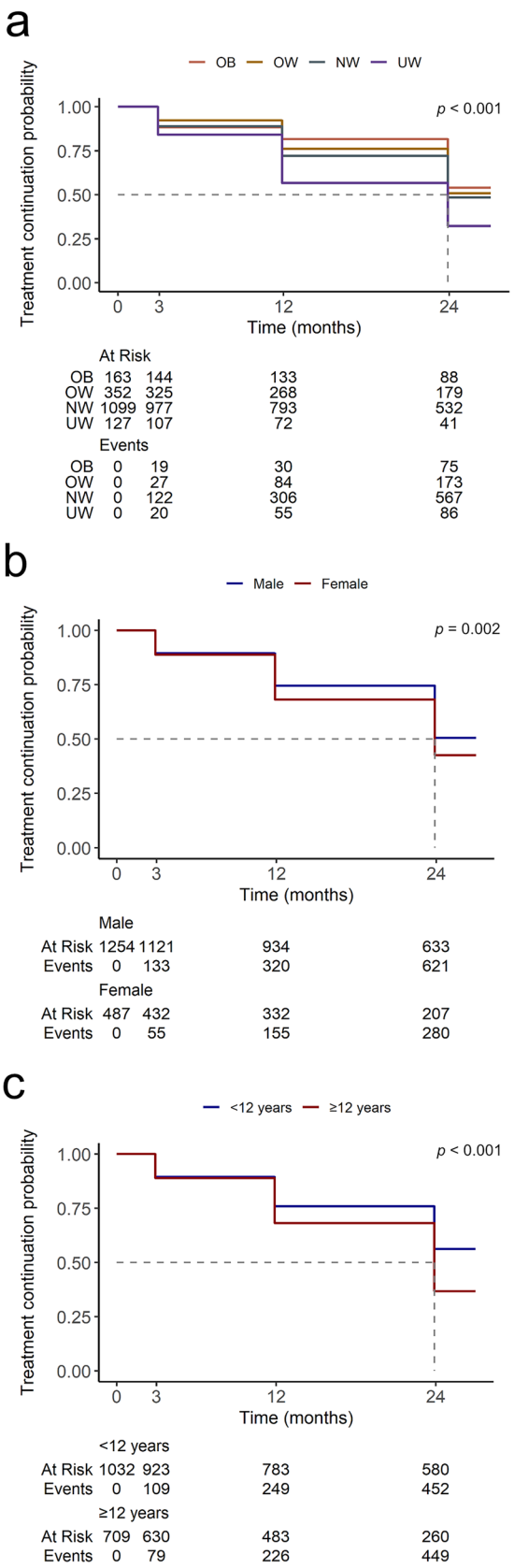

Fig. 1 Kaplan–Meier curves for methylphenidate treatment continuation by weight status, sex, and age at 3, 12, and 24 months after the baseline prescription. Panels **a**–**c** display treatment continuation probabilities by weight status (**a**), sex (**b**), and age group (**c**) in 1741 children and adolescents from the BMI Epidemiology Study Gothenburg, below 18 years of age with at least one dispensing of methylphenidate, and height and weight available within 1 year before the dispensing. Children and adolescents who retrieved only their baseline prescription were classified as discontinuing after 3 months, and children and adolescents who retrieved their prescriptions fewer than three times per year were classified as not continuing methylphenidate during the respective year. Weight status groups were defined according to baseline BMI, using cutoffs from the International Obesity Task Force [20, 21]. The *p* values for the log-rank tests are indicated, with $p < 0.05$ considered statistically significant. Risk tables show the number of children and adolescents remaining on treatment after each time point (at risk) as well as the number of children and adolescents who discontinued over time (events). *BMI* body mass index, *NW* normal weight, *OB* obesity, *OW* overweight, *UW* underweight

being prescribed greater absolute dose increases in real-world practice. Our results suggest that clinicians may be adjusting doses of methylphenidate based on body weight, even in the absence of formal guidelines recommending such practices. This may reflect attempts to account for varying pharmacological needs, as lighter children often respond to smaller dose increases [26, 27], whereas those with higher body weight may require larger dose increases to achieve a comparable effect. Additionally, dose decisions are likely influenced by safety concerns, particularly appetite loss, which may make clinicians, parents, or patients more cautious with dose increases in thinner children and less restrictive in heavier children.

In our study, weight-adjusted doses at treatment initiation were highest in children and adolescents with underweight and lowest in those with obesity. At follow-up, the weight-adjusted doses did not differ significantly between children and adolescents with baseline underweight or obesity and those with normal weight. However, after reclassifying children and adolescents based on their weight status at follow-up, we found that children and adolescents who had underweight at follow-up received significantly higher doses per kilogram of body weight, while those with overweight or obesity received significantly lower weight-adjusted doses compared to their normal-weight peers. One may speculate that these findings may in part reflect weight changes during the first year of treatment, potentially related to adverse drug reaction, leading some children to shift between weight categories; however, in the absence of such data, this remains hypothetical.

Interestingly, the pattern of weight status-based variation in methylphenidate dosing differs from previous findings with selective serotonin reuptake inhibitors (SSRIs) and melatonin, where absolute doses were similar across weight status groups, and only weight-adjusted doses varied

Table 4 Baseline BMI *z*-score and prescribed starting doses of methylphenidate among children and adolescents continuing and discontinuing treatment during the first year ($n = 1741$)

Variable	Baseline category	Treatment continuation Mean (SD)	Treatment discontinuation Mean (SD)
BMI *z*-score	UW ($n = 72/55$)	− 1.35 (0.33)	− 1.62 (0.67) **
	NW ($n = 793/306$)	0.25 (0.62)	0.22 (0.59)
	OW ($n = 268/84$)	1.75 (0.28)	1.77 (0.29)
	OB ($n = 133/30$)	2.68 (0.36)	2.71 (0.32)
Dose (mg)	– ($n = 1266/475$)	15.9 (6.8)	16.0 (7.4)
Dose (mg/kg)	– ($n = 1266/475$)	0.40 (0.19)	0.41 (0.19)

We included 1741 children and adolescents from the BMI Epidemiology Study Gothenburg, under 18 years of age with at least one dispensing of methylphenidate, and height and weight available within 1 year before the dispensing. Children and adolescents who retrieved their methylphenidate prescriptions at least three times during the first year of treatment were classified as treatment continuation, while those who retrieved their prescriptions fewer than three times were classified as treatment discontinuation. Weight status groups were defined according to baseline BMI, using cutoffs from the International Obesity Task Force [20, 21]. Baseline BMI *z*-scores for the different weight status groups as well as doses and weight adjusted doses of baseline prescriptions of methylphenidate are shown for children and adolescents with and without treatment continuation. The number of children and adolescents per baseline category is indicated in parenthesis, with the first number referring to children and adolescents continuing treatment and the second number to children and adolescents discontinuing treatment during the first year. Values are shown as mean (SD). Comparisons were performed using two-sided Welch's test comparing those with treatment continuation and treatment discontinuation. A statistically significant result is indicated as $^{**}p < 0.01$

BMI body mass index, *NW* normal weight, *OB* obesity, *OW* overweight, *SD* standard deviation, *UW* underweight

[28, 29]. The contrast further supports the interpretation that body weight might be associated with methylphenidate dosing decisions in clinical practice.

In addition to weight, we also observed sex-based differences in dosing. Girls in our cohort were prescribed higher absolute doses and higher weight-adjusted doses compared to boys at follow-up prescriptions. It is unlikely that these findings are explained by differences in drug metabolism, as a population pharmacokinetic study in children with ADHD found similar methylphenidate pharmacokinetics in boys and girls [30]. However, sex-related variations in clinical response may offer a potential explanation. One study reported that although girls experienced better therapeutic response in the first 3 h after methylphenidate administration, the effect declined more rapidly than in boys, with a decline after 7.5 h [31]. This pattern of a steeper but shorter duration of response in girls may lead clinicians to prescribe higher doses or additional afternoon doses, potentially explaining the higher total daily doses in girls observed in our cohort. Other factors such as symptoms and severity that might show sex-related differences may also contribute to the observed higher doses prescribed to girls in our study [32].

When it comes to dosing in different age groups, previous studies have noted that children with younger age respond to lower doses of methylphenidate [23, 26, 27], and older children benefited from lower weight-adjusted doses [33]. Our findings support this trend, with adolescents being prescribed higher doses and lower weight-adjusted doses in the real-world setting. This difference may be due to several factors, including body weight, developmental changes in drug metabolism, and variations in pharmacodynamics as the brain matures. Additionally, differences in ADHD symptoms between age groups may also contribute to dosing differences [34].

Age, sex, BMI, symptom severity, and symptom type may interact with one another and collectively influence the dosing patterns observed in our study. For example, a longitudinal study on ADHD and obesity found that higher ADHD symptom levels significantly predicted higher BMI *z*-scores at later ages in both boys and girls, with age-related differences between the sexes [6]. This suggests that variations in symptom type and severity, in interaction with age, sex, and BMI, may have contributed to the dosing patterns identified in our real-world analysis of dosing practices.

In addition to differences in dosing practice across BMI, sex, and age groups, we observed differential patterns in drug discontinuation across BMI groups. A significantly higher proportion of children and adolescents with baseline underweight discontinued methylphenidate treatment during the first year, and a higher baseline zBMI was associated with a lower risk of treatment discontinuation. One may speculate that this is related to the known appetite-suppressive effect of methylphenidate, which often leads to reduction in BMI [35, 36]. Indeed, children and adolescents with underweight who did not continue treatment during the first year had a significantly lower zBMI at treatment start, compared to children and adolescents in the same weight status group who continued treatment. It is plausible that children and adolescents who discontinued treatment represent a group who had little room for further weight loss. In contrast, children and adolescents with obesity may

have been more likely to continue treatment, as the weight-reducing side effect could be perceived as beneficial. Interestingly, by the second year, weight status no longer was associated with treatment discontinuation, further suggesting that weight-related side effects may have influenced early dropout. Nevertheless, we cannot exclude that side effects other than those related to weight may have contributed to the early discontinuation of children and adolescents with underweight who received higher weight-adjusted methylphenidate doses.

We further found that girls had higher odds of discontinuing methylphenidate during the first year of treatment compared to boys. This contrasts the findings of Brikell et al., which did not show any sex-related differences in discontinuation rates [37]. Other studies, however, have reported higher medication discontinuation in females [38–40]. The higher discontinuation rates in girls may be linked to several factors, including symptom severity, higher prescribed doses, differential effectiveness, and a higher incidence of side effects. In fact, research has found more frequent adverse drug reactions in females over 12 years than in males [41], which could, at least partly, explain the increased dropout rates in girls compared to boys during the first year of treatment with methylphenidate observed in our study. The absence of sex-related differences in treatment discontinuation by the second year further suggests that poorer medication tolerance may have contributed to the higher early dropout rates observed in girls. Additionally, the older age of girls at treatment start might have contributed to the higher discontinuation rate, as age itself has been identified as a risk factor, in line with our results [37]. Moreover, although the literature is mixed, differences in methylphenidate effectiveness between girls and boys cannot be ruled out as a contributing factor to higher discontinuation rates in girls, which may be more relevant in older girls where hormonal influences could play a role [32, 42].

The lower discontinuation rate among children under 12 years may, in part, reflect their limited ability to express adverse effects, as well as their limited control over treatment decisions. The higher discontinuation rate in children over 12 years old may be further influenced by the previously noted peak in discontinuation at age of 18 [37].

This study is not without limitations. First, we did not have data on disease severity, comorbidities, treatment effects, and side effects of methylphenidate, limiting the interpretation of the results. Although, both the relatively low rates of psychiatric co-medication in our cohort and the existing literature [26, 43] suggest that comorbidities are unlikely to explain the subgroup differences in dosing observed in our study, residual confounding cannot be excluded. Second, even though we applied a 1-year washout period by excluding the data from the first year of the drug register, we cannot exclude that some children were reinitiating the medication and were not treatment-naïve for methylphenidate. Third, the observational design is subject to inherent bias, and residual confounding cannot be excluded. This aspect could be addressed in randomised clinical trials. Moreover, our analyses were based on a Swedish cohort, and the generalisability of the findings to other populations may be limited.

Future studies are warranted to further investigate how the differential dosing strategies observed in our real-world data influence the effectiveness and safety of methylphenidate treatment in children and adolescents. Such studies should also incorporate detailed clinical information, such as ADHD symptoms and severity, comorbidities, and treatment response, to further clarify the roles of age, sex, and BMI in dosing practices and determine whether adjusting prescriptions based on these factors can improve treatment effectiveness and safety. Clinical trials should consider assessing effect and safety according to underweight, overweight, and obesity to evaluate potential weight status-related differences.

5 Conclusion

These findings highlight the complexity of dosing decisions in paediatric ADHD treatment and suggest that factors like weight status, sex, and age may be associated with how clinicians adjust dosing of methylphenidate to meet the specific needs of each patient. Additionally, these factors also appear to be associated with treatment discontinuation.

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Declarations

Conflict of interest None of the authors has any conflict of interest. EEK is employed by the Swedish Medical Products Agency. The views expressed in this study are the personal views of the authors and not necessarily the view of the government agency.

Ethics approval The BMI Epidemiology Study Gothenburg has been approved by the ethics committee of the University of Gothenburg, Sweden (D-nr 013-10, date of approval 28 January 2010).

Consent to participate The need for informed consent was waived by the ethics committee of the University of Gothenburg.

Consent for publication Not applicable.

Availability of data and materials The data are not publicly available due to privacy and ethical reasons. Anonymised data can be made available upon reasonable request to the corresponding author and with approval from the University of Gothenburg, in accordance with national law.

Code availability The code for data extraction and analysis in this study can be provided by the corresponding author upon reasonable request.

Author contributions JI contributed to the conceptualisation of the study, analysed the data, and drafted the manuscript. EEK, ED, and LH contributed to the interpretation of the data. JM contributed to statistical analysis. JMK conceptualised the study and supervised the project and manuscript preparation. All authors reviewed and critically revised the manuscript and approved the final version.

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