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ORIGINAL CONTRIBUTION

# Melatonin use among children, adolescents, and young adults: a Danish nationwide drug utilization study

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## Abstract

We aimed to provide a detailed description of the use of melatonin in Danish children, adolescents, and young adults during 2012–2019. We identified melatonin users 0–24 years of age ($n = 43{,}652$; median age 16 years) via the Danish nationwide health registers. Melatonin is a prescription drug in Denmark. The incidence of melatonin use increased from 2.4 to 3.9/1000 person-years during 2012 to 2019. Among 6,557 incident users in 2019, 53% filled only a single prescription within the first 6 months. Long-term use was most common among the younger age groups, with 17% of 5–9-year-olds and 14% of 10–13-year-olds being in continued treatment (no treatment breaks) 12 months after their first melatonin prescription. Disregarding treatment breaks, 3 in 10 were using melatonin 12 months after their first melatonin prescription and this proportion was also highest among 5–9-year-olds (63%) and 10–13-year-olds (51%). Psychopathology was common among melatonin users with 75% registered with either a psychiatric disorder diagnosis (54%), a filled prescription for another psychotropic (58%), or a contact to a private practice psychiatrist (15%) within ± 12 months of treatment initiation. General practitioners authorized melatonin prescriptions to almost half of all new users (48%), while psychiatric specialists authorized 37% of first prescriptions. In conclusion, the incidence of melatonin use increased in Denmark from 2012 to 2019. A substantial proportion of users had concurrent psychopathology most likely explaining their use of melatonin. Long-term melatonin use was more common among the youngest age groups, which should be a focus of interest due to limited safety data.

**Keywords** Melatonin · Drug utilization study · Child · Adolescent · Register-based cohort study

## Introduction

Sleep problems are common in childhood and adolescence affecting 20–40% of the general population [1] and the frequency is even higher in children with psychiatric and neurodevelopmental disorders [2]. Poor sleep may be caused by psychiatric morbidity [3] but can in itself lead to emotional and behavioural problems, reduced educational performance, and impaired quality of life that may affect the entire family [4–6].

Therefore, the motivation to intervene towards childhood sleep problems is high and relevant approaches include both non-pharmacological and pharmacological treatment. Melatonin is one of the most commonly used drugs for treatment of insomnia in children and adolescents [7]. It is an equivalent to the naturally occurring hormone involved in regulation of the sleep cycle [8]. Although the literature is sparse [9], exogenous melatonin treatment seems to reduce sleep onset latency and may enhance sleep efficiency in children

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and adolescents with neurodevelopmental disorders, whereas the effect seems limited in neurotypical children [10].

Melatonin use among Scandinavian children and adolescents has increased over the last decades [11], but melatonin was only formally approved in the European Union in 2018, specifically for treatment of insomnia in children and adolescents with autism spectrum disorder or Smith–Magenis syndrome [12]. It was approved for treatment of insomnia in children and adolescents with ADHD in 2020 [13]. Meanwhile, the potential long-term consequences of melatonin use remain largely unknown [14].

A detailed description of melatonin utilization patterns and time trends is needed to guide our understanding of the increase in melatonin use among Danish youths. We therefore aimed to describe melatonin use in children, adolescents and young adults in Denmark during 2012–2019 by looking at the incidence and prevalence of use, quantity of use, treatment duration, user psychopathology, and specialty of prescribers over time.

## Methods

Using the nationwide health registers, we identified all Danish individuals aged ≤ 24 years with at least one filled prescription of melatonin during 2012–2019. For each individual, we extracted data on filled prescriptions of melatonin and other psychotropic drugs, hospital contacts and assigned diagnoses, and contacts to private practicing psychiatrists.

### Data sources and study population

A unique personal identification number is assigned at birth or first registered immigration for all Danish inhabitants, enabling linkage between national registers of individual-level data [15]. Three registers were used for the purpose of this study: The Danish National Prescription Registry, the Danish National Patient Registry and the Danish National Health Insurance Service Registry. The Danish National Prescription Registry has documented high completeness and validity and contains data on all filled prescriptions from Danish outpatient pharmacies since 1995 [16]. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification system [17], and the registry provided information on quantity of drug use [defined daily dose (DDD)], date of filling, and specialty of the prescriber. The Danish National Patient Registry holds data on all inpatient and outpatient hospital contacts from 1995 onwards [18], and provided information on date of admission and assigned diagnoses classified by the International Classification of Diseases, version 10 (ICD-10) [19]. The Danish National Health Insurance Service Registry provided information on contacts to private practicing psychiatrists serving under the tax funded public healthcare system [20], although containing no clinical information. To be noted, virtually all primary health care services are free of charge in Denmark [20]. We obtained population statistics from Statistics Denmark that collects and maintains electronic records for statistical and scientific purposes [21].

The study population was identified using the Danish National Prescription Registry, where we included individuals ≤ 24 years of age, who filled at least one prescription of melatonin (ATC code N05CH01) from January 1, 2012 to December 31, 2019. The study population did not include individuals from 2020 to have 365 days follow-up for analyses.

### Analyses

We performed the following seven analyses overall and stratified by sex and age groups (0–4, 5–9, 10–13, 14–17, 18–24 years). Age group intervals were unevenly distributed, separating 18+ years from younger individuals, due to the age limits of clinical guidelines for melatonin use in children and adolescents (0–17 years) [22, 23].

First, we calculated the incidence rate of melatonin use per 1000 individuals by dividing the number of new users (*first ever* filled prescription) by the total population ≤ 24 years of age on January 1 in the given year. Due to a negligible number of new users compared to the total population count, we did not remove patients that were no longer at risk from the denominator. We tested for difference between sexes using Poisson regression analysis. To control for time trends, we included a natural cubic spline with three knots to allow for potential non-linear time trends in the analysis. A $p$ value < 0.05 was considered statistically significant.

Second, we calculated the annual prevalence of use, i.e. the total number of current users per 1000 individuals aged 0–24 years per year divided by the total population. As a sensitivity analysis, we required the filling of two or more melatonin prescriptions within a given year to be considered a prevalent user.

Third, we calculated the annual average quantity of melatonin use in milligrams (mg) per user by summing the DDD for melatonin for each year.

Fourth, we estimated the proportion of early discontinuation of melatonin use. This was defined as the number of users who did not fill a second melatonin prescription within the first 6 months after treatment initiation divided by the number of initiators within the same time frame.

Fifth, we estimated treatment duration and persistence using two different analyses. A Kaplan–Meier survival analysis was used to estimate duration of the first treatment episode for each individual, i.e. time from treatment onset to first treatment gap (reflecting continuous treatment), and the

Proportion of Patients Covered (PPC) method [24] was used to estimate the proportion of individuals covered by treatment at any given day after treatment initiation disregarding treatment breaks (reflecting current treatment). In these analyses, users were censored upon migration, death or end of study period. We estimated the duration of a single prescription based on the assumption of the consumption of one tablet per day and added a grace period of 25% to account for non-compliance and irregular refill patterns.

Sixth, we described potential psychopathology indicators of melatonin users by calculating the proportion of users who within ± 12 months of their first filled prescription had either: (1) received a psychiatric disorder diagnosis (ICD-10 F00-99) at an inpatient or outpatient hospital admission, (2) filled a prescription for a psychotropic drug (ATC code N05 or N06: antipsychotic, anxiolytic, hypnotic (excl. melatonin), sedative, antidepressant, or stimulant, or (3) had a contact to a private child/adolescent or adult psychiatrist. Hospital diagnoses of psychiatric disorders were divided into the following subgroups: (a) mood disorders (ICD-10 F32-39), (b) anxiety disorders (ICD-10 F40-48 + F93), (c) personality disorders (ICD-10 60–69), (d) autism spectrum disorders (ASD) (ICD-10 F84), (e) Attention Deficit Hyperactivity Disorder (ADHD) (ICD-10 F90.0 + F98.8C), (f) tic disorders (ICD-10 F95), or (g) psychiatric disorder diagnoses not included in the former categories. Individuals could be included in more than one category. The proportion of melatonin users with any psychopathology (any of the three categories above) was plotted across the 2-year time window in relation to the day of the first prescription filling. Data from the National Patient Registry were updated to December 31, 2018 and results are presented for 2017 to have complete follow-up on diagnoses.

Finally, we identified the specialty of the physician prescribing the first and subsequent melatonin prescriptions. Prescribers were divided into: (1) general practitioners, (2) child/adolescent or adult psychiatrists (from hospitals or private practice), (3) other private practicing specialists (i.e. excluding psychiatrists), (4) hospital paediatricians, or (5) other hospital specialists.

All statistical analyses were performed using STATA Release 16.0 (StataCorp, College Station, TX, USA).

## Results

### Trends in use of melatonin

We identified 43,652 users of melatonin aged 0–24 years between 2012 and 2019. The median age at first prescription was 16 years (interquartile range (IQR) 12–20 years) with females initiating use at a median age of 17 years (IQR 14–20 years) and males at a median age of 15 years (IQR 10–19 years). In the study period, the incidence of melatonin use increased from 2.4 to 3.9 per 1000 person-years. This increase was mainly driven by 14–24-year-olds females where the incidence rate almost doubled (from 3.5–3.7 to 7.2). Incidence rates were relatively stable under the age of 14 years for girls and under the age of 10 years for boys (Fig. 1A and B). Females were more likely to initiate melatonin treatment than males ($p$ value < 0.05).

From 2012 to 2019, the prevalence of melatonin use increased from 4.6 to 10.3 per 1000 individuals mainly due to an increase among the older age groups in both sexes (Fig. 1C and D). The annual prevalence was lowered to 6.1 per 1000 in 2019, when we limited the analyses to users, who filled at least two prescriptions of melatonin within the first year. In total, the prevalence of melatonin use was slightly higher for males than females throughout the study period ($p < 0.05$). When we examined prevalent melatonin use in accordance to sex and age in 2019, we found a sex by age interaction with more male users compared to females until age 15 years, and after that a preponderance of female users (Fig. 2B). This apparent sex difference among older age groups was not seen in 2012 (Fig. 2A). A similar sex by age interaction was seen in 2019 regarding incident use of melatonin with a majority of males among new users before age 16 years and a majority of females after (Supplementary Figure S1).

Overall, the annual median quantity of melatonin use increased from 360 to 600 mg/user/year from 2012 to 2019. In 2019, the median quantity of use varied widely between age groups ranging from 300 mg/user/year corresponding to ~ 0.8 mg/user/day among 18–24-year-olds to 936 mg/user/year corresponding to ~ 2.6 mg/user/day among 5–9-year-olds.

### Duration of melatonin treatment

In 2019, more than half (53%) of melatonin users discontinued use early and did not fill a second prescription within six months after treatment initiation. Early discontinuation was most pronounced for 18–24-year-olds (67%) as opposed to the 5–9-year-olds (24%). In general, the younger age groups experienced more long-term continuous use, and after 1 year, 17% of 5–9-year-olds and 14% of 10–13-year-olds were still in treatment (Fig. 3A). We also looked at melatonin exposure 1 year after treatment initiation disregarding treatment breaks, and found that approximately one third (29%) of incident users were in treatment at that point. Like for continuous use, we found that a higher proportion of the younger age groups were exposed to melatonin after 1 year (63% of 5–9-year-olds and 51% of 10–13-year-olds) compared to the older age groups (29% of 14–17-year-olds and 11% of 18–24-year-olds) (Fig. 3B). The analyses were

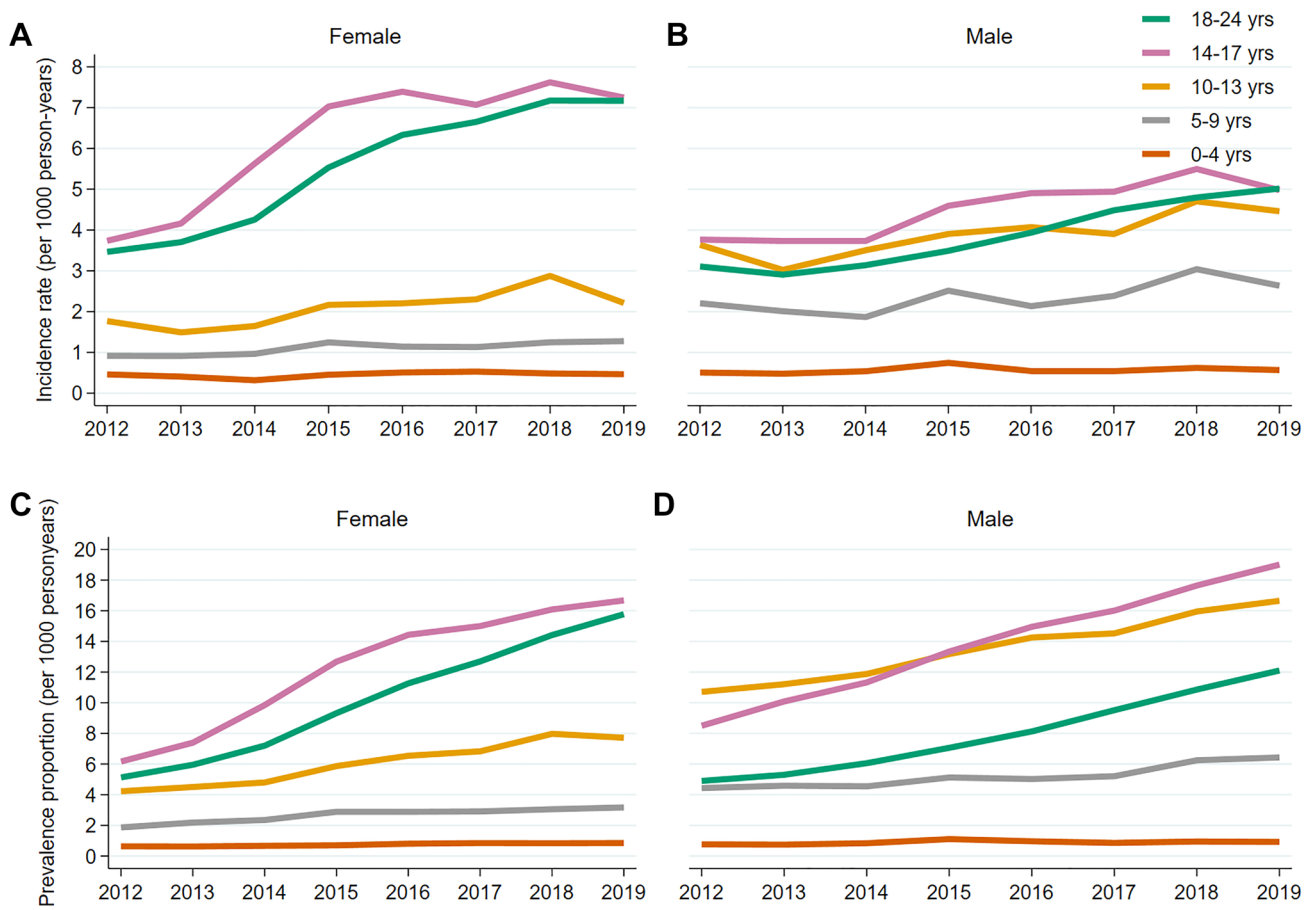


**Fig. 1** Incidence and prevalence per 1000 person-years of melatonin use stratified by sex and age in children, adolescents, and young adults, 2012–2019. **A** Incidence in females. **B** Incidence in males. **C** Prevalence in females. **D** Prevalence in males

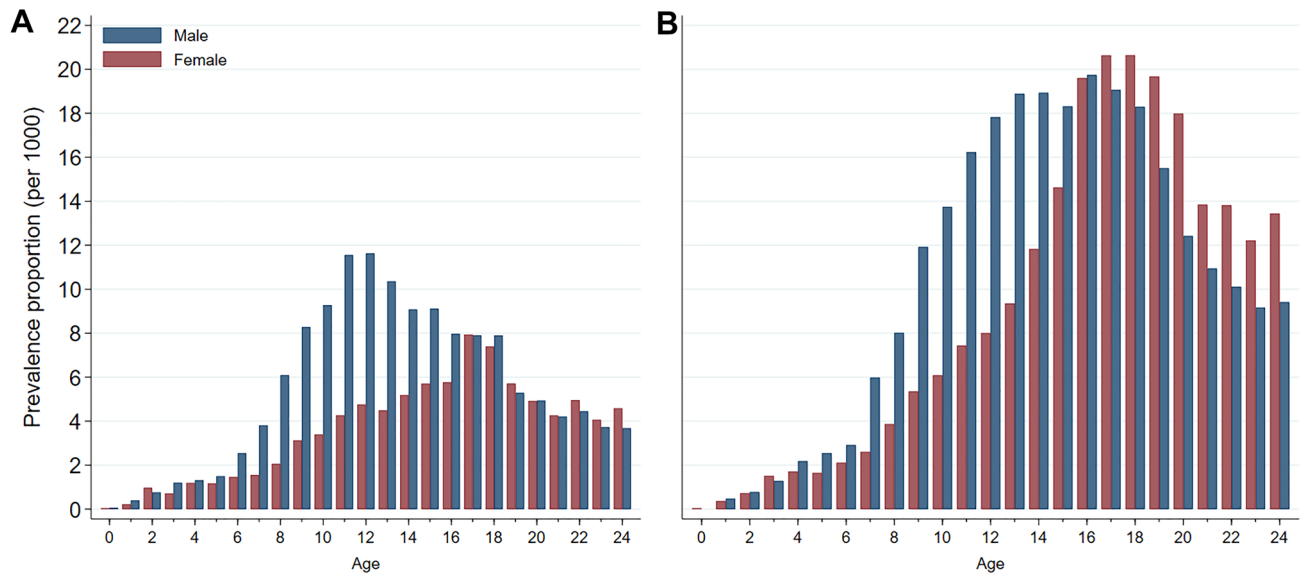


**Fig. 2** One-year prevalence proportion of melatonin use in children, adolescents, and young adults stratified by age and sex. **A** 2012, **B** 2019

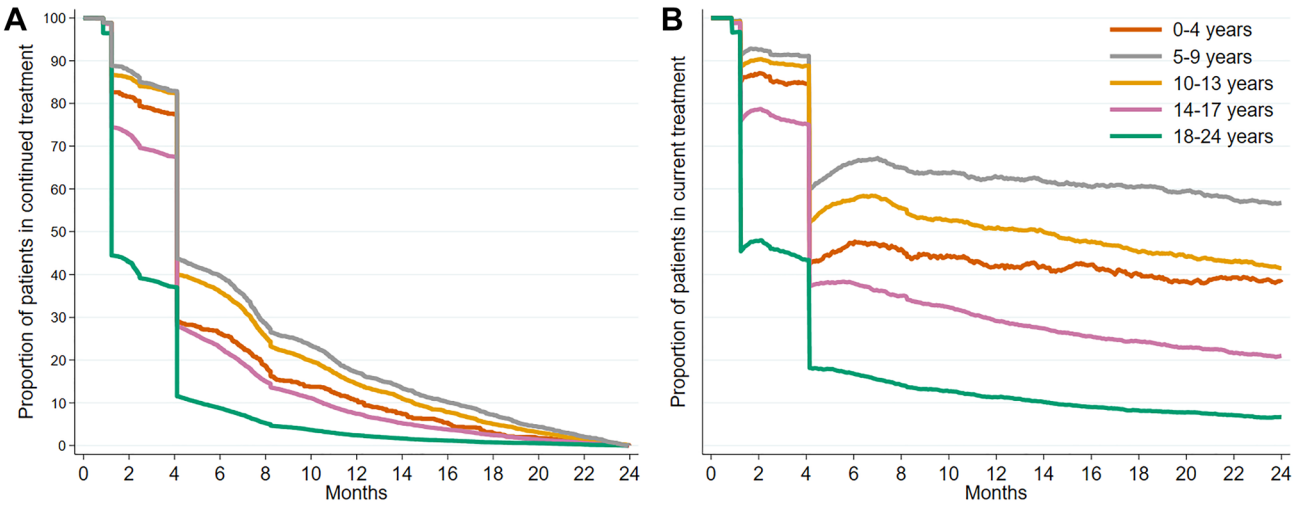


**Fig. 3** Treatment duration and persistence of melatonin use among children, adolescents, and young adults in Denmark in 2019. **A** Kaplan–Meier plot, stratified by age groups. **B** Proportion of patients covered (PPC) curve stratified by age groups. The first flat line on the curves illustrates the estimated minimum duration of the first prescription (based on pack size and including grace period). Sudden drops on the curves illustrate the failing of individuals to fill additional prescriptions

also stratified by sex, but there were no major differences between males and females (Supplementary Figure S2).

## Psychopathology among melatonin users

A substantial proportion (75%) of incident melatonin users had indicators of psychopathology during the 2-year time window surrounding their first filled melatonin prescription in 2017 (Table 1). This was a slight drop from 79% in 2012, but the proportion of users with a psychiatric diagnosis increased from 50 to 54% in the same time period. Overall, there were no marked sex differences between indicators of psychopathology. In regard to age groups, the proportion of melatonin users with any indicators of psychopathology throughout the study period was stable for 10–17-year-olds but decreased for the two youngest age groups and the oldest. In 2017, 47% of 0–4-year-olds had any indicators of psychopathology (56% in 2012), the equivalent proportion was 70% among 18–24-year-olds (77.2% in 2012). Approximately four out of five melatonin users aged 5–9 (79%) and 10–13 (84%) years had at least one indicator of psychopathology. Among all age groups (except from 0–4 year-olds), there was a shift of psychopathology indicators from psychotropic prescriptions towards psychiatric diagnoses; for example 57% of 14–17-year-olds had a psychiatric disorder diagnosis in 2012 compared to 66% in 2017 and conversely 70% filled a psychotropic prescription in 2012 compared to 58% in 2017. The same pattern was observed when all age groups were stratified by sex (Supplementary Table 1). Among incident users, 53% had indicators of psychopathology 1 year prior to initiation of melatonin use (Supplementary Figure S3). Psychiatric disorder diagnoses were assigned for approximately half of melatonin users within ± 12 months of the first prescription and the frequency varied substantially between age groups and sex. As an example, 29% of 5–9-year-old girls who filled a prescription for melatonin were diagnosed with ADHD, whereas the equivalent frequency was 42% for 5–9-year-old boys (Supplementary Figure S4). The most common psychiatric disorder among 14–17-year-old melatonin users was anxiety for both girls (51%) and boys (28%). Overall, the most frequent psychiatric diagnosis was anxiety disorder (25%), followed by ADHD (14%) and autism spectrum disorders (13%).

## Specialty of prescribing physician

General practitioners were in charge of most melatonin prescriptions for young individuals in 2019, both in regard to first (48%) and subsequent (51%) prescriptions (Fig. 4). Psychiatric specialists, irrespective of affiliation to hospital or private practice, accounted for 37% and 35% of first and subsequent melatonin prescriptions in 2019. The proportion of melatonin prescriptions carried out by general practitioners was lowest for 0–4-year-olds (5% of first and 20% of subsequent prescriptions) and increased with increasing age, reaching 61% of the first and 66% of the subsequent prescriptions for 18–24-year-olds. In children aged 5–9 and 10–13 years, 20 and 27%, respectively, had their first prescription authorized by a general practitioner.

**Table 1** Proportion of melatonin users ≤ 24 years who had any indicators of psychopathology by either (1) a psychiatric disorder diagnosis (ICD-10 F00-99) at an inpatient or outpatient hospital admission, (2) a filled prescription for a psychotropic drug (ATC code N05 or N06: antipsychotic, anxiolytic, hypnotic (excl. melatonin), sedative, antidepressant, or stimulant), or (3) had a contact to a private child/adolescent or adult psychiatrist) within ± 365 days of incident prescription in Denmark in 2012 and 2017

| | Any indicator (%) | Diagnosis (%) | Prescription (%) | Contact (%) | Multiple (%) |
|---|---|---|---|---|---|
| 2012 | | | | | |
| Total | 79.4 | 50.1 | 69.6 | 15.5 | 50.8 |
| By age group (years) | | | | | |
| 0–4 | 56.1 | 41.9 | 25.2 | 2.6 | 12.9 |
| 5–9 | 83.4 | 59.8 | 68.7 | 8.3 | 52.2 |
| 10–13 | 83.5 | 56.4 | 72.5 | 10.2 | 53.3 |
| 14–17 | 81.2 | 56.5 | 70.0 | 14.3 | 54.3 |
| 18–24 | 77.2 | 40.7 | 72.6 | 22.4 | 50.6 |
| By sex | | | | | |
| Male | 80.2 | 49.5 | 70.4 | 15.0 | 50.4 |
| Female | 78.3 | 50.9 | 68.6 | 16.3 | 51.4 |
| 2017 | | | | | |
| Total | 75.2 | 54.2 | 58.0 | 14.5 | 46.4 |
| By age group (years) | | | | | |
| 0–4 | 46.9 | 36.9 | 20.0 | 0.0 | 10.0 |
| 5–9 | 79.4 | 64.0 | 56.3 | 7.0 | 46.5 |
| 10–13 | 83.9 | 61.5 | 63.4 | 10.4 | 50.1 |
| 14–17 | 80.8 | 66.2 | 57.5 | 10.3 | 49.3 |
| 18–24 | 70.4 | 44.4 | 59.1 | 20.3 | 45.8 |
| By sex | | | | | |
| Male | 75.0 | 51.9 | 58.6 | 13.0 | 44.9 |
| Female | 75.4 | 56.2 | 57.5 | 15.9 | 47.8 |

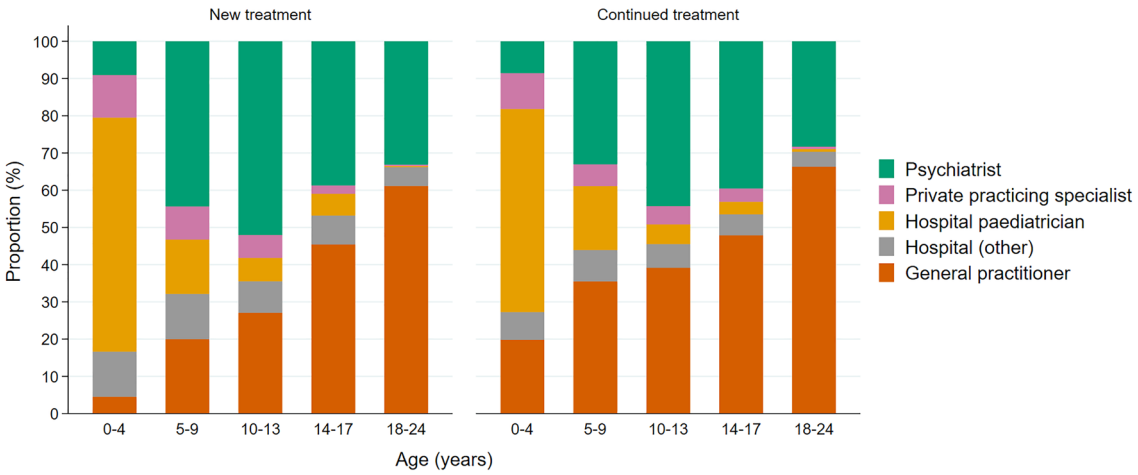


**Fig. 4** Specialties of physicians prescribing melatonin in Denmark in 2019 (%). 'New treatment' and 'Continued treatment' represent incident and prevalent prescriptions, respectively. The category 'Psychiatrist' covers child, adolescent or adult psychiatrist (hospital and private practicing). The category 'Private practicing specialist' excludes psychiatrists

## Discussion

This study showed an increase in melatonin use from 2012–2019 among Danish children, adolescents and young adults, driven mainly by increased use among young females. We observed a sex by age interaction, with males being more likely than females to use melatonin before age 15 years, which reversed after this point. This can be explained by different ages of onset in underlying psychopathology causing sleep problems such as anxiety disorders, ADHD and ASD. The majority of adolescents and

young adults discontinued melatonin treatment early, but long-term melatonin use was somewhat common among the youngest age groups, which should be a future focus of interest as consequences hereof are largely unknown. Melatonin prescribed by general practitioners was common and increasingly so with higher age of users.

The major strength of this study is the use of a nationwide cohort including all young melatonin users minimizing the risk of selection bias. Melatonin is only available by prescription in Denmark and the risk of undetected use is small. Melatonin can be purchased online from abroad, yet we expect that online purchase is limited in Denmark. The findings of our study were based on filled melatonin prescriptions as proxies for use. Filled prescriptions are, however, more indicative of use than prescriptions alone [25] and are considered superior to information collected from medical records or questionnaires [26]. A limitation to our study is the lack of data on indications for melatonin use. However, we collected information on psychopathology in relation to incident prescriptions to approximate the indication. However we cannot disentangle if the use of melatonin is rational use.

During the last 7 years, the overall use of melatonin increased steadily. These findings align with the trends in use previously described in Denmark [11, 27, 28] and other Scandinavian countries [11, 29–31] although considerable variation between countries exists. Females were more likely to start melatonin treatment in adolescence compared to males, which is in line with Norwegian and Swedish findings [29, 30]. It also aligns with an observed increase in self-reported sleep problems among Danish youths, particularly females and adolescents [32]. This could partly explain our finding of a shift towards a female preponderance of both incident and prevalent melatonin use among Danish adolescents from 2012 to 2019. Approximately half of all new melatonin users had a psychiatric disorder diagnosis within ± 12 months of the first melatonin prescription, but the proportion with a psychiatric disorder increased more among females than males throughout the study period. Hence, melatonin prescribed for sleep problems associated with psychiatric disorders, like anxiety disorders and depression, which are common among adolescent females [33], could also contribute to the rise in melatonin use among this group. Anxiety disorders and depressive disorders are more common among adolescent females than males [33, 34], whereas ADHD is more common among males until age 14 years [33, 35]. Hence, the observed conversion towards higher melatonin use among adolescent females could rely on concurrent changes in the incidence rates of clinical psychiatric disorders or the severity of comorbid sleep problems.

During the study period 2012–2019, the only formal approval of melatonin was provided in 2018 for insomnia in children and adolescents diagnosed with autism spectrum disorders or Smith–Magenis syndrome [12]. In 2020, however, melatonin use was approved for treatment of sleep problems caused by ADHD in Danish children aged 6–18 years, if sleep hygiene initiatives were insufficient [13]. This guideline became effective in 2020 and thus after our study period ended. In our study, three out of four incident melatonin users had underlying psychopathology, but only 13% were assigned with autism spectrum disorders and 14% with ADHD. This indicates that a substantial proportion of melatonin prescriptions were provided off-label in relation to existing guidelines, but likely with the indication to treat sleep problems due to psychopathology or based on a diagnosis provided by private practicing specialist. However, general practitioners were responsible for half of all initial melatonin prescriptions contrary to clinical guidelines that recommend these to be authorized by paediatricians or child and adolescent psychiatrists under the age of 18 years. This large proportion may raise concern, because it questions whether melatonin was prescribed based on proper indications like severe sleep problems due to psychopathology, and whether sufficient testing of other non-pharmacologic sleep strategies was conducted prior to treatment. The prescriptions authorized by general practitioners could arise due to waiting time for specialist treatment, but we consider this to be a minor issue since all Danish individuals are entitled to psychiatric specialist evaluation and potentially treatment within 30 days after referral by law since 2015 [36].

The majority of young adults filled only one melatonin prescription within the first 6months, suggesting either a transient need of melatonin, limited effect, a weak indication for use (i.e. no underlying psychopathology), or intended short-term treatment while initiating other sleep strategies. It could, however, also rely on the approval of Z-drugs from age 18 years leading to a higher use among young adults compared to younger age groups [11]. Younger melatonin users, on the other hand, had the highest quantity of use and more long-term, continued treatment. More than half of all 5–13-year-old melatonin users were still in treatment after 1 year, which is in accordance with both Norwegian [29] and Swedish [30] studies.

A fairly large proportion within this age group had no clear indicator of psychopathology (16–21%) and for equally many, the first melatonin prescription was authorized by a general practitioner (20–27%). These results are concerning given the conflict with clinical guidelines [22]and the limited knowledge on long-term use, especially in very young individuals [14]. Only half of 0–4-year-old melatonin users had any indicator of psychopathology. This probably reflects that melatonin use in this age group is initiated in pediatric units due to severe developmental or neuropediatric indications, which is supported by the rather low number of first prescriptions (< 5%) authorized by general practitioners.

## Conclusion

During the last 7 years, melatonin use among youths has increased in Denmark, particularly for females aged 15–24 years. Most adolescents and young adults fill only one prescription or use melatonin for less than 6 months and are characterized by psychopathology, which constitutes a likely explanation for their sleep problems. However, a large proportion of particularly younger children aged 5–13 are covered by melatonin prescriptions for more than 1 year after initiation. In addition, approximately one out of five 5–13-year-old melatonin users have no clear indication of psychopathology and equally many have their first melatonin prescription authorized by a general practitioner. Given the unknown long-term consequences of melatonin use, this should be a focus of interest. Danish clinical guidelines recommend that first melatonin use for children and adolescents is prescribed by specialists in paediatrics or child and adolescent psychiatry only, and after non-pharmacological interventions prove insufficient [22, 23]. We find that general practitioners authorize half of all first time melatonin prescriptions for children and adolescents, suggesting that the rationale for melatonin treatment in this particular group needs further attention.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00787-022-02035-1.

**Author contributions** MB, AP, and RW conceived and designed the study. HCKJ, LR, and RW contributed to conceptualization and writing. ME performed the statistical analyses. PJJ and SHM was consulted in regard to conceptualization and critically revised the manuscript. All authors reviewed and commented on the final product.

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**Code availability** Due to Danish legislation, individual-level data are not available. Coding scripts are available upon request.

## Declarations

**Conflict of interest** Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. All other authors declare no conflict of interests.

**Ethical approval** The study was registered on the repository at the University of Southern Denmark (10.080). According to Danish legislation, approval from an ethics committee is not required for registry-based studies.

**Informed consent** Not applicable.

**Consent for publication** Not applicable.

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