DANISH MEDICAL JOURNAL

Original Article

Geographic variation of recorded neurodevelopmental disorders in children and adults

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Dan Med J 2024;71(12):A02240144. doi: 10.61409/A02240144

ABSTRACT

INTRODUCTION. While diagnosis rates of autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) vary within countries at a large-scale municipal level, small neighbourhood geographic variation remains understudied. In this nationwide study, we describe the rates of ASD and ADHD diagnoses in children and adults by geographical data zones of approximately 2,500 residents across Denmark.

METHODS. We included a population of children born from 1993 through 2020 and an adult population born from 1977 through 2003. We followed children from their first birthday and adults from their 18th birthday to either diagnosis, death, emigration or 31 December 2021, whichever came first. Data were analysed using multilevel log-linear Poisson regression adjusting for age and sex. Data zones, a data-driven approach to define small geographical neighbourhoods, were used as the unit for spatial analyses. We present incidence rates in data zones and median incidence rate ratios (MRRs) as estimates of the variation in rates of the disorders between data zones.

RESULTS. ASD and ADHD diagnoses among children showed considerable variations between data zones (ASD: MRR = 1.44; 95% confidence interval (CI): 1.42-1.47, ADHD: MRR = 1.38; 95% CI: 1.36-1.40), suggesting that the incidence can be 44% and 38% higher in high incidence zones than in others. Similar variations were observed for diagnoses among adults (ASD: MRR = 1.44; 95% CI: 1.40-1.48, ADHD: MRR = 1.44; 95% CI: 1.41-1.46).

CONCLUSIONS. The large variations might reflect differential treatment seeking, referral practice and diagnostic procedures across Denmark.

FUNDING. This study received funding from BERTHA – the Danish Big Data Centre for Environment and Health, and the Novo Nordisk Foundation Challenge Programme (grant NNF17OC0027864).

TRIAL REGISTRATION. Not relevant.

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders, with estimated cumulative incidences before age 18 years at 3% for girls and almost 6% for boys for ADHD, and about 2% for girls and 4% for boys for ASD [1]. Although the disorders are often recognised in childhood, ASD and ADHD are persistent and may affect individuals across their lifespan [2, 3]. This awareness has resulted in increasing numbers of individuals being diagnosed in adulthood [3].

As with other psychiatric disorders, prevalence rates of neurodevelopmental disorder diagnoses vary across countries, which is often explained by differences in applied diagnostic criteria, welfare systems and availability of diagnostic services [4]. However, within-country variation has also been described in several studies despite using uniform diagnostic standards, and Denmark is no exception [5-8]. Despite the centrally organised welfare system and free access to healthcare services in Denmark, we have previously shown a high degree of geographical variation in incidence proportions of ADHD diagnoses in children [9]. Similarly, a recent Norwegian study using nationwide survey and register data found considerable municipal variations in ADHD diagnoses that were not explained by corresponding ADHD symptom variation [6].

However, using municipal borders to describe geographical units may challenge the interpretation of the results because these delineations reflect administrative boundaries that vary considerably in population size and over time [10]. These challenges may bias geospatial analyses. Therefore, we have developed a data-driven approach to defining neighbourhoods based on the spatial distributions of the home addresses. These new geographical units, hereafter referred to as data zones, are homogeneous in population size [10].

Finally, while much of the existing research in geographical variation focuses on children with ADHD, the literature is scarce for ASD and negligible for ADHD and ASD in adult populations. This study aimed to describe the geographical variations in rates of ADHD and ASD diagnoses in children and adults in Denmark on a small-area neighbourhood level using data zones. We aimed to contribute to the academic understanding of geographic variation in individuals diagnosed with neurodevelopmental disorders while providing practical insights for policymakers, healthcare providers and caregivers.

Methods

Design and study populations

This nationwide cohort study comprises two populations identified through the Danish Civil Registration System [11]: 1) *Children*: All individuals born in Denmark between 1 January 1993 and 31 December 2020 who were alive and resided in Denmark at their first birthday 2) *Adults*: All individuals born in Denmark between 1 January 1977 and 31 December 2003 who were alive and resided in Denmark at their 18th birthday.

Recorded diagnoses of ADHD and ASD

Individuals were followed for ADHD or ASD discharge diagnoses recorded in the Danish Psychiatric Central Research Registry [12] and medication prescriptions recorded in the Danish National Prescription Registry [13]. In Denmark, ADHD medication is available by prescription only. We identified all incident ADHD diagnoses (International Classification of Diseases, 8th edition (ICD-8): 308.01, International Classification of Diseases, version 10th edition (ICD-10): F90, F98.8) and/or prescriptions of ADHD medications (ATC: N06BA01 “amphetamine”, N06BA02 “dexamphetamine”, N06BA04 “methylphenidate”, N06BA07 “modafinil”, N06BA09 “atomoxetine”, N06BA12 “lisdexamfetamine”, C02AC02 “guanfacine”) and all incident ASD diagnoses (ICD-8: 299.00, 299.03, ICD-10: F84.x, excl. F84.2-F84.4) during follow-up. We considered ADHD medication prescriptions as proxies for ADHD diagnoses received in private psychiatric services not recorded in the Danish Psychiatric Central Research Registry.

Data zones

Across Denmark, a zoning algorithm generated 1,885 small-area geographic neighbourhoods, *data zones*, that were homogenised in population density and size, aiming at a mean data zone size of 2,500 individuals [10]. These data zones were nested within the 98 Danish municipalities and created based on the geographic coordinates of residential addresses for all Danish residents.

Statistical analysis

We followed children from their first birthday and adults from their 18th birthday until diagnosis or medication, death, emigration from Denmark, age 18 (for children only) or end of study (31 December 2021), whichever came first.

Data were analysed using multilevel log-linear Poisson regression, allowing for the clustering of individuals within data zones. All statistical analyses were conducted using R, version 4.0.4. The models were fitted using Markov Chain Monte Carlo using the Bayesian Regression Models *(brm)* function in the *brms* package (version 2.14.4). We used five chains with 2,500 iterations, each with a burn-in of 500 iterations, leaving 10,000 iterations for estimation. We defined data zones at the start of follow-up and calculated the

general contextual effect (degree of clustering) of data zones using the median incidence rate ratio (MRR) with 95% confidence intervals (CIs) based on the formula used by Austin et al. [14]. A 95% CI means that there is a 95% probability that the parameter lies within this interval, given the observed data and prior beliefs. The MRR provides a metric of the degree of variation in incidence rates between data zones and quantifies the median relative change in the incidence rate of the disorder when comparing identical individuals from two randomly selected different zones ordered by incidence rate. Incidence rates (septiles) in the data zones across Denmark are presented in maps. All analyses were adjusted for age, sex and their interaction. Also, we conducted separate analyses for males and females.

Results

The child population consisted of 1,789,463 children, of whom 40,307 were diagnosed in public psychiatric services with ASD and 53,828 with ADHD (65,955 when including prescriptions) before the age of 18 years. Crude incidence rates were 19.51 and 26.13 (32.12) per 10,000 person-years at risk for ASD and ADHD, respectively. The adult population consisted of 1,752,417 adults, of whom 8,844 were diagnosed with ASD and 24,775 with ADHD (52,916 when including prescriptions), yielding crude incidence rates of 4.33 and 12.22 (26.40) per 10,000 person-years at risk, respectively.

Figure 1 shows the incidence rates of ASD diagnoses in children (Figure 1 A) and adults (Figure 1 B). For children, clustering of low incidence was found in the Southern Region, especially on Funen, whereas the highest incidence was found in the Zealand Region. For the adult population, ASD diagnoses were more evenly scattered around the country, with the highest incidence rates in Northern Denmark. We found an unexplained variation in ASD incidence for both children (MRR = 1.44; 95% CI: 1.42-1.47) and adults (MRR = 1.44; 95% CI: 1.40-1.48), suggesting that on average across data zones, the incidence was approximately 44% higher in certain data zones than in others (**Table 1**). This geographical variation in incidence rates was slightly higher for girls (MRR = 1.48; 95% CI: 1.44-1.52) than boys (MRR = 1.41; 95% CI: 1.38-1.43), but the overall pattern did not differ between the sexes (Table 1).

FIGURE 1 Maps of Denmark showing data zone-specific incidence rates in septiles for autism spectrum disorder (ASD) in children (**A**), ASD in adults (**B**), ADHD in children diagnosed in public psychiatric services (**C**), ADHD in adults diagnosed in public psychiatric services (**D**), ADHD in children diagnosed in public psychiatric services or through private psychiatric services (p+p) (**E**) and ADHD in adults (p+p) (**F**).

TABLE 1 Heterogeneity in autism spectrum disorder (ASD) and ADHD across data zones expressed as the median incidence rate ratio (MRR) with 95% confidence intervals (CI) adjusted for age, sex, and their interaction and for age in sex-stratified analyses.

	MRR (95% CI)
ASD, children	1.44 (1.42-1.47)
Boys	1.41 (1.38-1.43)
Girls	1.48 (1.44-1.52)
ASD, adults	1.44 (1.40-1.48)
Men	1.42 (1.36-1.48)
Women	1.48 (1.41-1.56)
ADHD, children	1.38 (1.36-1.40)
Boys	1.40 (1.37-1.42)
Girls	1.35 (1.33-1.38)
ADHD, adults	1.44 (1.41-1.46)
Men	1.45 (1.41-1.49)
Women	1.43 (1.39-1.47)
ADHD (p+p)[a], children	1.33 (1.31-1.35)
Boys	1.33 (1.31-1.35)
Girls	1.33 (1.31-1.36)
ADHD (p+p)[a], adults	1.27 (1.26-1.29)
Men	1.25 (1.23-1.27)
Women	1.31 (1.29-1.34)

a) Diagnoses from both public and private psychiatric services.

Figure 1 shows incidence rates of ADHD diagnoses (and/or filled ADHD medication prescriptions) in children (Figure 1 C and E) and adults (Figure 1 D and F). We observed unexplained variation in ADHD diagnoses across data zones for both children (MRR = 1.38; 95% CI: 1.36-1.40) and adults (MRR = 1.44; 95% CI: 1.41-1.46) (Table 1). These estimates were attenuated but remained significant when including filled ADHD medication prescriptions (children: MRR = 1.33; 95% CI: 1.31-1.35, adults: MRR = 1.27; 95% CI: 1.26-1.29) (Table 1). For the child population (Figure 1 C and E), clustering of low incidence rates of ADHD

diagnoses received either through public or both public and private services were similarly located in the Region of Southern Denmark, especially on Funen, and the southern part of Zealand. For the adult population, clustering of low incidence was present in the Region of Southern Denmark, including diagnoses from private psychiatric services. Still, it disappeared when only diagnoses from public services were considered.

The geographical variation was slightly higher for women (MRR = 1.31; 95% CI: 1.29-1.34) than men (MRR = 1.25; 95% CI: 1.23-1.27) diagnosed with ADHD in either public or private psychiatric services, but the overall geographical pattern was seemingly not different.

Discussion

Using the population-based Danish registries with complete residential address information for all Danish residents, we showed clear variation in both ASD and ADHD incidence between neighbourhoods for both children and adults. Using the homogenous data zones enabled us to examine the detailed variation of ASD and ADHD incidence across Denmark for an extensive period. However, although we present small-area neighbourhood level incidence, the variation seems to occur mainly between regions, which is most clearly shown in relation to ASD in children, where clustering of data zones with high incidence levels was present in Region Zealand, while clustering of data zones with low incidence was present in the Region of Southern Denmark, especially on Funen.

One might contend that the significant discrepancies in ASD and ADHD incidence rates across the regions mirror different thresholds for receiving a diagnosis, attributable to divergent diagnostic practices [15]. While diagnoses largely rely on subjective assessments of behaviour and are defined categorically for clinical purposes, it is argued that ASD and ADHD should be seen as continuously distributed traits in the population, which makes the distinction between normal and abnormal somewhat arbitrary. However, referral practice and treatment-seeking behaviour may also vary in the five Danish regions as the frequency of referrals to psychiatric services differs widely according to statistics from Danish Regions. For example, despite the similarity of demographical and population size, the number of referrals to child and adolescent psychiatric services in Southern Denmark was only half of that in the Central Denmark Region in 2020-2021, and referral rejection rates were similar in the two regions. Moreover, in the Region of Southern Denmark, most referrals come from general practice, whereas in the Central Denmark Region, a higher proportion of referrals come through the municipality. For adults, the geographical differences when also using prescription data (Figure 1 F) might reflect differences in the capacity of practising psychiatrists, with a lower capacity in the Region of Southern Denmark and the North Denmark Region than in Region Zealand.

The process of identifying and referring children with ADHD involves input from teachers, school psychologists and parents. Variations in knowledge and values among these stakeholders can significantly impact the recognition of ADHD [16]. A study from the US suggests that differences in the regional prescribing of ADHD medication may, in part, be attributed to variations in teachers' likelihood of suggesting an ADHD diagnosis, which indicates that schoolteachers play a crucial role in identifying children with ADHD [17]. A recent study investigating barriers to accessing services for their child's mental health problems in the North Denmark Region found that more than half of parents experienced that professionals such as school teachers and educational psychologists were reluctant to initiate interventions

or provide a referral to other services. Among others, this included teachers not wanting to refer the child to school educational psychologists, disagreement about who should refer the child to mental health services and professionals opposing referral [18].

Similarly, cultural influences linked to the location of a family's residence may affect treatment-seeking behaviour, which has been observed for ASD. The hypothesis posits that in areas with a high prevalence of ASD, increased information sharing among parents leads to greater community awareness of ASD signs and symptoms. Consequently, children residing near a child previously diagnosed with ASD are more likely to receive an ASD diagnosis themselves. In contrast, children living in areas with none or few diagnosed children are less likely to be diagnosed [19]. These mechanisms are probably complex and involve an interplay between the individual family, the community, healthcare professionals and more structural factors such as access to mental health services.

Limitations

Our analyses may not reflect true variation in the incidence of ASD diagnoses in adults because due to the long waiting time for referral in public psychiatric services, some adults may have been diagnosed in private services which are not obliged to report diagnoses. While we can use medication prescriptions as proxies for diagnoses for ADHD, this is not possible for ASD as no medication is indicated for this condition. Nevertheless, variation of ADHD between neighbourhoods was still evident when information from private mental health services was added, although with a smaller effect size. Finally, our results show the basic variation between neighbourhoods since our estimates are only adjusted for age and sex (and their interaction). Although some of the variation could be explained by known (or unknown) risk factors, we are unaware of potential confounders adhering to the regional boundaries in Denmark.

Although we initially aimed to study the detailed geographical pattern of ASD and ADHD to inform on yet-to-be-explored environmental risk factors [20], we found a pattern that largely follows regional boundaries. Hence, our results likely identify differential treatment-seeking, referral practice and diagnostic procedures across Denmark, which may have important implications for service planning.

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Accepted 12 September 2024

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2024;71(12):A02240144

doi 10.61409/A02240144

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