

Original article

Spatiotemporal distribution of autism spectrum disorder prevalence among birth cohorts during 2000–2011 in Israel



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ABSTRACT

Purpose: Studies indicate an apparent sharp increasing trend in autism spectrum disorder (ASD) incidence and prevalence worldwide. This nationwide study aims at depicting ASD prevalence distribution in Israel in both space and time.

Methods: Based on data from Israel National Insurance Institute, the study population included all children born in Israel 2000–2011 ($n = 1,786,194$), of whom 11,699 (0.655%) were subsequently diagnosed with ASD (until December 31, 2016). Prevalence was calculated and mapped by dividing the number of ASD cases within each year of birth by the number of births during that year, for each spatial unit, and similarly for several spatiotemporal levels of aggregation.

Results: ASD prevalence varies substantially across different geographic areas in Israel, with considerably higher prevalence concentrated in central Israel. Strong associations were found between locality-level socioeconomic index, ethnicity, and peripherality and ASD prevalence, and even after adjustment for them, excess prevalence for ASD still persisted in certain localities. No spatial dependence of prevalence, with and without adjustment for the locality-level variables, was found (Moran's $I = -0.000546, -0.00335$, respectively).

Conclusions: Our findings provide important insights regarding health disparities affecting ASD diagnosis, directing further health policy intervention and further research.

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Introduction

Over the last 2 decades, there has been a trend of sharp increases in the reported incidence and prevalence of autism spectrum disorder (ASD) worldwide [1]. In the United States, for

example, estimates of ASD prevalence per 1000 children at age 8 increased from 6.7 in 2000 to 18.5 in 2016 [2]. Existing evidence cannot rule out the possibility that some of the increase may represent a real increase in incidence [3,4].

Research on spatial distribution of ASD has been sparse, especially at the state or country level, for which the current literature mainly includes total population studies examining time trends of ASD prevalence [5–10]. Studies exploring spatial patterns of ASD detected clusters of heightened risk in certain areas in California [11–13], North Carolina [14,15], and Utah [16]. Those studies implemented advanced spatial analyses, but the generalizability of their results may be limited to the areas surveyed only. In a recent study that examined ASD spatial distribution across the United States, high spatial variability was found with children born in New England being 1.5 times more likely to be diagnosed with ASD compared with children born elsewhere in the United States [17].

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Higher prevalence of ASD in the Northeast of the United States (in comparison with other parts across the United States: Midwest, South, and West) was also shown in another recent study [18]. Limitations of these two recent studies include being based on a small number of cases ($n = 486$, $n = 711$, respectively) and on active consent and participation. Outside the United States, a recent study of children residing in Catalonia, Spain ($n = 1,326,666$ children, of whom 15,466 cases were found) detected considerable temporal variability and some geographic variability across health care areas in the region of Catalonia [19]. In Israel, no study has examined ASD spatial distribution so far, but some publications described and analyzed time trends of ASD in the country [20–25].

We examined spatial and spatiotemporal distribution of ASD, addressing the two key questions: ‘where’ and ‘when’, which are of high importance in descriptive epidemiology, as a preliminary step in exploring diseases. Our study aimed to describe spatial and spatiotemporal variations in ASD prevalence across Israel within 12 consecutive birth cohorts of the entire Israeli population. The study also aimed to examine possible associations between certain locality-level characteristics related to ASD prevalence and evaluate the spatial dependence (spatial autocorrelation) of prevalence rates with and without adjustment for those locality characteristics.

Methods

Case ascertainment

Israel has national health coverage that permits access to child development diagnostic services. The Israeli National Insurance Institute (NII) is a social security governmental institution that provides any Israeli family whose child has a confirmed ASD diagnosis, a child disability benefit for ASD. This NII benefit is independent of eligibility for or actual use of services and is provided regardless of income or other socioeconomic characteristics. Data on ASD diagnoses were extracted from computerized deidentified individual-level records of the NII, referring to all Israeli children (of whom the mother or father is an Israeli resident) born during 2000–2011 in Israel, with a follow-up from birth until December 31, 2016. ASD prevalence case status is based on NII claim confirmations of child disability benefit for ASD. To receive NII benefits, strict criteria must be met to verify an ASD diagnosis, which are based on Diagnostic and Statistical Manual of Mental Disorders criteria (DSM)—the fourth edition revised (DSM-IV-TR) for diagnoses conducted during most of the follow-up period (2000–2013, during which 85% of all diagnoses were made), and the fifth edition gradually accepted into the practice with diagnoses made toward the end of that period (2014–2016). ASD case status in the NII database has been described and validated in previous publications [24,26]. In brief, assessment and diagnosis of ASD typically start by the primary pediatrician referring a child to a certified child development center, where the diagnosis is made by a multidisciplinary team (based on the DSM criteria). Once a child is diagnosed with ASD, the parents may submit a claim to NII, which will then be inspected by an NII professional committee. The inspection is based on the medical information from the diagnosing health professionals.

Spatial and sociodemographic data

Census affiliation of each locality to its subdistrict and socioeconomic status (SES), ethnicity, and peripherality variables on the locality level were extracted from the Israel Central Bureau of Statistics (CBS). SES was defined as the CBS socioeconomic index (z-scores) attributed to the locality's population [27], categorized into ascending quartiles (the first quartile being the lowest SES). Ethnicity was defined as the locality's ethnic composition, as categorized in the census data: Jews, Arabs, or mixed. Peripherality was defined as the distance, by

shortest roads (in kilometers, categorized into ascending quartiles), between the locality and the boundary of the Tel Aviv subdistrict, which is the country's economic (and geographic) center. The CBS data also contain geographic information system (GIS) continuous polygon data layers of localities and subdistricts, which were used as the geographic units for which prevalence rates were mapped. For more details, see [Online Supplement 1](#).

Prevalence mapping

The year of birth and maternal address at birth for each child were obtained from NII, based on official data transferred from the Ministry of Interior. ASD prevalence was calculated for the study population by dividing the number of children diagnosed with ASD (“cases”) within each year of birth by the population (the number of live births) of that year, for each spatial unit. Prevalence was calculated similarly for different levels of aggregation in terms of space (locality and subdistrict) and time (combined for four separate annual 3-year birth cohorts). To generate reliable choropleth maps (i.e. mapping stable estimates) aimed at visually representing the spatial or spatiotemporal distribution of ASD prevalence, we set inclusion criteria for mapping, so that only spatiotemporal units with stable prevalence rates were mapped, as follows:

First, the statistical error of the prevalence rate for each unit was calculated by the standard confidence interval (CI)/margin of error formula for a population proportion, as

$$e = z * \sqrt{(p(1 - p)/N)}$$

where e = error for prevalence; p = actual prevalence (proportion) in the population within the unit; N = number of births within the unit; and $z = 1.96$ (representing 95% confidence interval).

Second, the relative error for each unit was calculated as

$$\text{relative error} = e/p$$

where e = the error and p = actual ASD prevalence rate in the population.

Finally, the inclusion criterion for a reliable mapping of a unit's prevalence was defined as having a relative error <40%. All spatiotemporal units that did not meet this inclusion criterion were aggregated to larger units until reaching a relative error <40%.

In addition to the choropleth mapping, we calculated the local Moran's I , a local indicator of spatial association [28,29], to detect clusters (hotspots or coldspots) of ASD prevalence. Units for which indices of local Moran's I were statistically significant (P -value < .05) were mapped.

Mapping was conducted using QGIS version, 2.18.21, [30] and R statistical software, version 3.5.0/3.6.1 [31], which was also used for all other data processing and analyses.

Locality characteristics and deviations from predicted prevalence

To evaluate possible associations between locality-level characteristics and ASD prevalence, a binomial generalized linear regression model was fitted, predicting prevalence for each locality. The model used prevalence in the locality as the dependent variable and SES, ethnicity, and peripherality as independent variables. Associations between each independent variable and the predicted prevalence (coefficients) were estimated in the model and expressed in PRR: prevalence rate ratio ($PRR = \exp(\text{model's coefficients})$). Taking into account a potential spatial autocorrelation (i.e., a tendency of nearby localities to have similar ASD prevalence) that may produce inaccurate estimates in the aspatial model [29], we estimated a spatial regression model in addition to the aspatial

one, fitted as a binomial generalized linear mixed model, using penalized quasi-likelihood.

To examine deviations of the observed (crude) ASD prevalence from that predicted by the locality's characteristics (observed minus predicted), additional mapping was conducted based on the regression model residuals for all localities. For reliable mapping, only those localities with >3400 births were mapped.

Spatial autocorrelation

To evaluate the spatial autocorrelation of ASD prevalence and its relation to locality-level explanatory variables, the global Moran's *I* index of spatial autocorrelation [32] was calculated for prevalence with and without adjustment for locality characteristics (i.e., for the aspatial model's prevalence residuals and for the crude prevalence, respectively).

Analyses were conducted in R statistical software, version 3.5.0/3.6.1 [31].

Results

The study population included all children born in Israel in 2000–2011: 1,786,194 children, of whom 11,699 (6.55 per 1000; 1

in 153) were diagnosed with ASD through 2016. The average age at diagnosis was 3.5 years, with 83.5% of diagnosed children as boys and 16.5% as girls. Changes in the age of diagnosis over time are presented in [Online Supplement 2](#), which shows the distribution of age at diagnosis by year of birth, from the first year of life (marked as age 0) through the age of 16. As expected, the distribution of age at diagnosis of ASD among the cases varies by year of birth because earlier birth cohorts had longer follow-up over time that captured children diagnosed in later ages as well.

Spatiotemporal distribution of ASD prevalence

Our mapping suggests that ASD prevalence varied substantially across different geographic areas in Israel, with considerably higher prevalence concentrated in central areas (around Tel-Aviv metropolitan area), in comparison with peripheral areas. The spatial distribution of ASD prevalence is presented in [Figure 1](#).

Prevalence changes with time across subdistricts are illustrated in [Figure 2](#), as a choropleth mapping for four separate 3-year birth cohorts (2000–2002, 2003–2005, 2006–2008, and 2009–2011). For the same spatiotemporal resolution as in [Figure 2](#) (subdistrict level for four separate 3-year birth cohorts), [Figure 3](#) maps local Moran's *I* clusters (highlighting only statistically significant

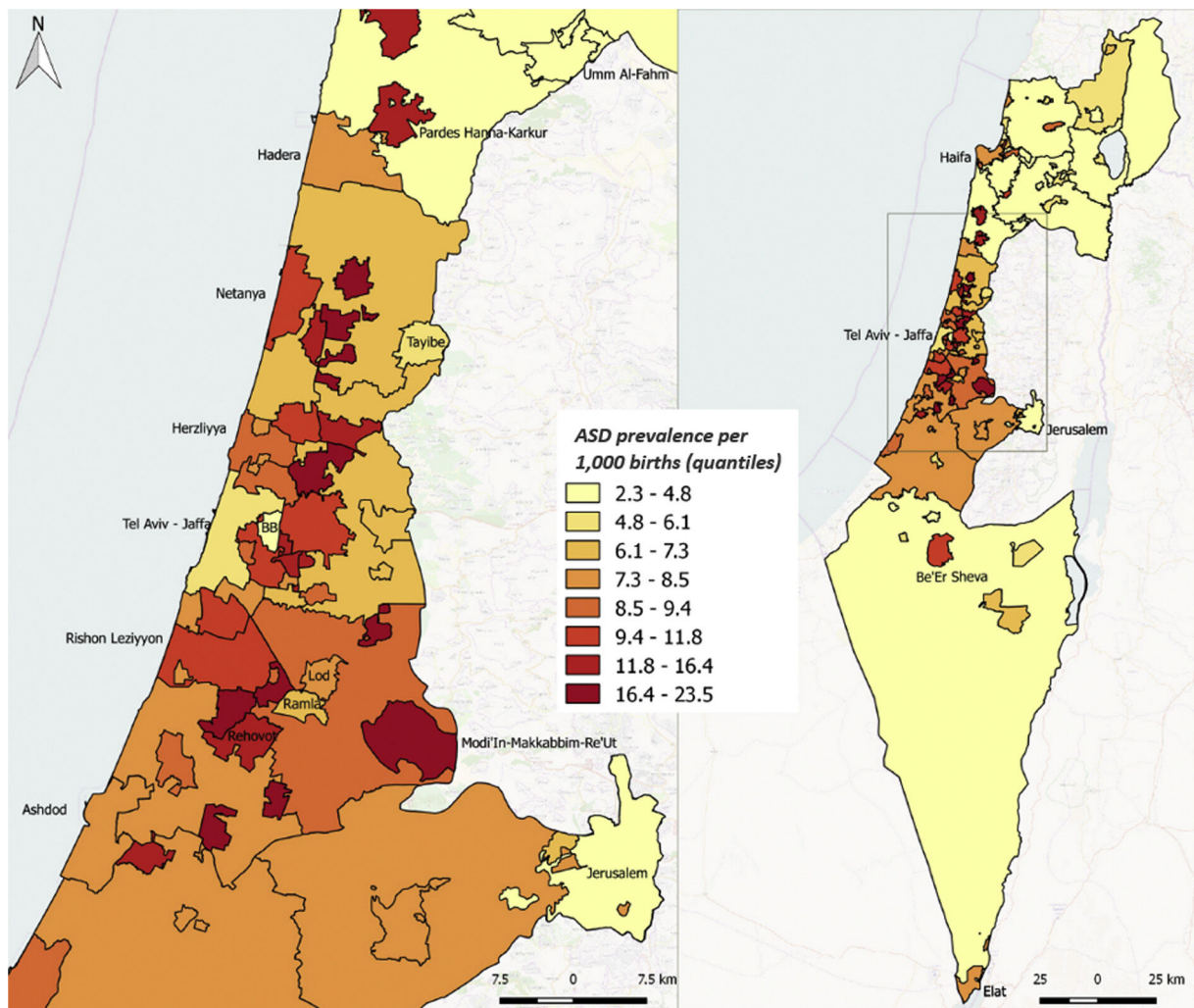


Fig. 1. Spatial distribution (choropleth map) of ASD prevalence among the total population of children born in Israel during 2000–2011, by locality/subdistrict. Caption: Localities with relative error <0.4 (see article text for additional explanations) are mapped individually, and localities with relative error > 0.4 are aggregated into their respective subdistrict. Right: The distribution across the whole country; Left: Enlargement of the framed area marked in the right map. The text appearing on both maps (right and left) refers to certain localities' names, for example, Haifa, Tel-Aviv–Jaffa, and Jerusalem.

clusters). In Figure 2, a trend of overall increase in prevalence over time is evident across most subdistricts, with some differences in the particular temporal pattern. Elevated prevalence is clearly seen in central Israel subdistricts (around Tel-Aviv metropolitan area) and low prevalence is consistently demonstrated in Jerusalem subdistrict. These subdistricts are detected and highlighted in Figure 3 as statistically significant clusters (P -value $<.05$) of relatively low or high prevalence.

Multivariable model and spatial autocorrelation

Table 1 and Online Supplement 3 present the results of the aspatial and spatial regression models, respectively. The tables show independent effect associations between locality-level characteristics (socioeconomic index, ethnicity, and peripherality) and ASD prevalence.

Higher locality SES was associated with higher ASD prevalence, independently of ethnicity and peripherality (for localities in the fourth SES Quartile, PRR = 2.01, 95% CI: 1.89–2.13 in the aspatial model; PRR = 2.01, 95% CI: 1.83–2.19 in the spatial model). Arab localities had much lower prevalence than Jewish localities (PRR = 0.38, 95% CI: 0.35–0.42 in the aspatial model; PRR = 0.38, 95% CI: 0.33–0.44 in the spatial model), and being a mixed locality was associated with intermediate prevalence. Peripherality (distance from Tel-Aviv) showed an independent inverse association with ASD prevalence.

Deviations from the prevalence predicted by the locality's characteristics (i.e., model residuals) for the overall study period are mapped in Figure 4. Three localities (colored in red) have standardized residuals (z-scores) statistically significant, with prevalence higher than predicted (z-score >1.96 , i.e. 95% CI). No localities with prevalence significantly lower than predicted (z-score <-1.96) were detected. Using the same inclusion criteria for mapping as in Figure 4, deviations are also mapped for three birth cohorts (2000–2003, 2004–2007, and 2008–2011), as presented on Online Supplement 4. The mapping, both for the overall study period and for the three separate periods, suggests that the model residuals are spatially distributed at random. This impression is supported by the global Moran's I index of spatial autocorrelation that is close to zero, indicating no spatial dependency, for both ASD prevalence (Moran's I = -0.000546 , $P = .77$) and model residuals after adjustment for locality characteristics (Moran's I = -0.00335 , $P = .42$). Standardized residuals of the spatial regression model are mapped on Online Supplements 5 (for the overall study period) and Online Supplements 6 (for three separate 4-year birth cohorts).

Discussion

Our findings suggest that ASD prevalence varies substantially across Israel, with much higher prevalence in central areas around Tel-Aviv metropolitan area, in comparison with peripheral areas. A few high SES localities within peripheral subdistricts demonstrate

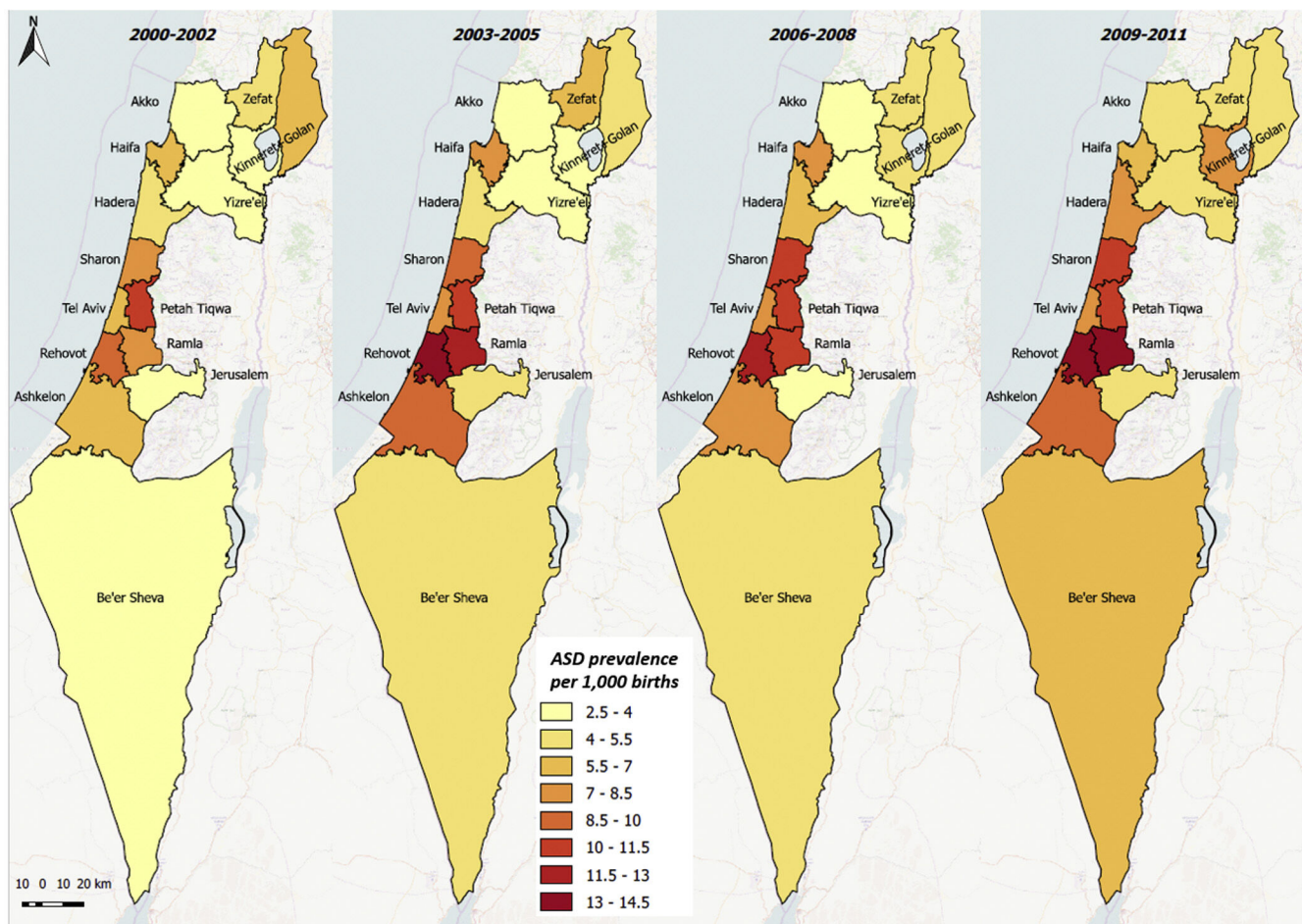


Fig. 2. Spatiotemporal distribution of ASD (choropleth map) prevalence among the total population of children born in Israel during 2000–2011. Caption: Mapping is by subdistrict per four separate 3-year birth cohorts (four separate maps, for children born during 2000–2002, 2003–2005, 2006–2008, and 2009–2011).

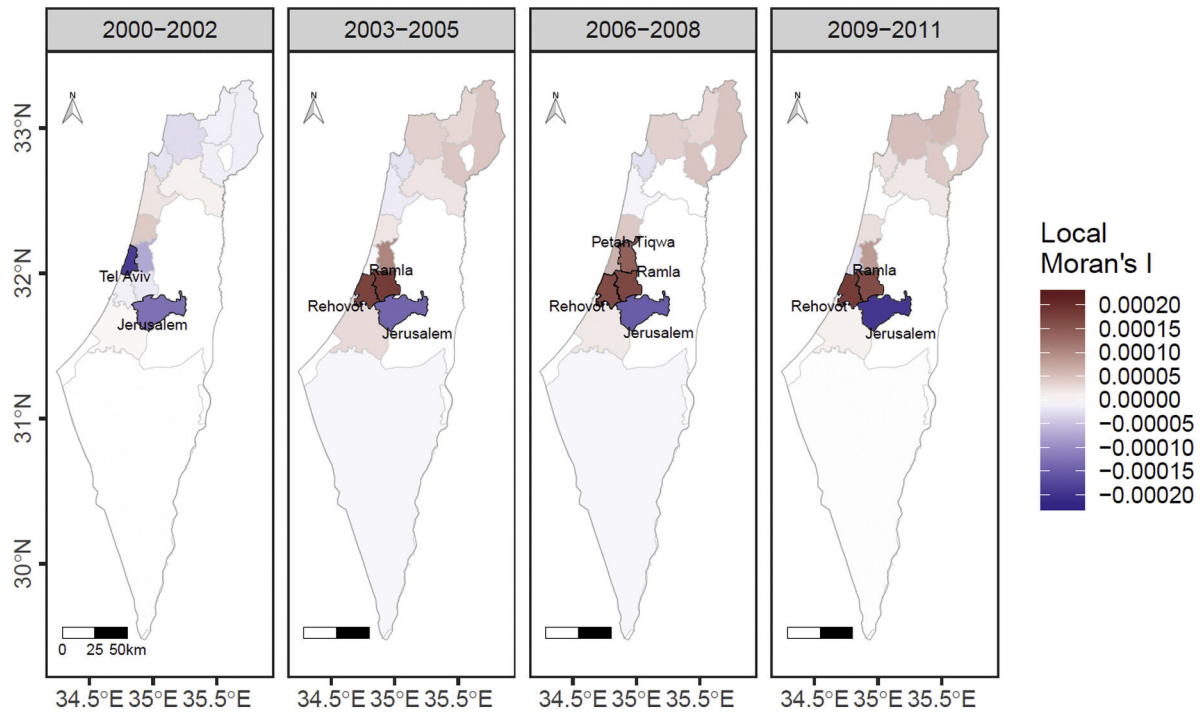


Fig. 3. Local Moran's I cluster map for ASD prevalence among the total population of children born in Israel during 2000–2011, by subdistrict per four separate 3-year birth cohorts (four separate maps, for children born during 2000–2002, 2003–2005, 2006–2008, and 2009–2011). Caption: Local Moran's I clusters of elevated prevalence (hotspots) and of low prevalence (coldspots) appear in red and blue/purple, respectively. Only subdistricts detected as statistically significant clusters (P -value of local Moran's I < .05) are highlighted on the map (the rest appear as shaded). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

higher prevalence than those of the rest of their subdistrict localities, for example, Pardes Hanna-Karkur—a Jewish locality within a relatively peripheral subdistrict (presented in the northern part of the left-hand map in Fig. 1). This pattern of higher prevalence concentrated in central Israel (and in certain high SES localities within peripheral areas) seems to be steady over the years, as demonstrated in Figure 2, and in Figure 3 in relation to the statistically significant clusters (P -value<.05) detected in central Israel subdistricts.

The small area variation in prevalence may be explained by the localities' characteristics that were found to be associated with prevalence in our analyses (Table 1). Ethnicity is probably a

prominent explanatory characteristic. Arab localities were independently associated with approximately 3-fold lower prevalence, and mixed localities with intermediate prevalence, in comparison with Jewish localities. Ascertainment of ASD in the Arabs (and ultraorthodox Jews) may be reduced because of ASD's categorization as a mental disorder (given the stigmatization of mental disorders) and possibly lower awareness of NII disability benefit for ASD [24]. A previous study comparing the clinical characteristics of Arab and Jewish children with ASD found more severe autistic manifestations among the Arab children [33]. This may indicate lower awareness or acceptance of mild cases of ASD in the Arab population in comparison with that in the general Jewish sector. A similar

Table 1
Associations between locality-level variables and ASD prevalence rate

Variable	Category/No. of localities/births*	PRR	95% CI
SES	Quartile 1 (257; 926,252)	Reference	
	Quartile 2 (257; 313,893)	1.50	1.41–1.59
	Quartile 3 (258; 267,369)	1.87	1.76–1.98
	Quartile 4 (255; 257,054)	2.01	1.89–2.13
Ethnicity	Jews (900; 946,689)	Reference	
	Arabs (118; 321,350)	0.38	0.35–0.42
	Mixed (9, 496; 529)	0.61	0.57–0.64
Peripherality	Quartile 1 (257; 733,851)	Reference	
	Quartile 2 (257; 511,396)	0.96	0.91–1.02
	Quartile 3 (256; 366,273)	0.91	0.86–0.96
	Quartile 4 (257; 153,048)	0.86	0.79–0.93

PRRs were taken from an aspatial binomial generalized linear regression model, predicting ASD prevalence in the locality. Socioeconomic index (z-scores) attributed (by Israel Central Bureau of Statistics) to the locality's population, categorized into ascending quartiles (the first quartile being the reference: the lowest SES). Quartile cut points (z-scores) are (−3.06, −0.09), (−0.09, 0.58), (0.58, 1.12), and (1.12, 3.06), for quartiles 1, 2, 3, and 4, respectively; Ethnicity: the locality's ethnic composition, in accordance with census data: Jews, Arabs, or mixed; Peripherality: distance (by shortest roads) between the locality and the boundary of the Tel Aviv subdistrict, categorized into ascending quartiles (the first quartile being the reference: the shortest distance). Quartile cut points (distance in kilometers) are (0–31.55), (31.55–75.00), (75.00–109.12), and (109.12–321.40), for quartiles 1, 2, 3, and 4, respectively.

* Variable category and the population underlying each category (indicated in parentheses and read from left to right as number of localities; number of births). 1,764,568 children across 1027 localities (not including extremely small localities for which there are no census data) were included in the regression model, of whom 11,699 cases were found.

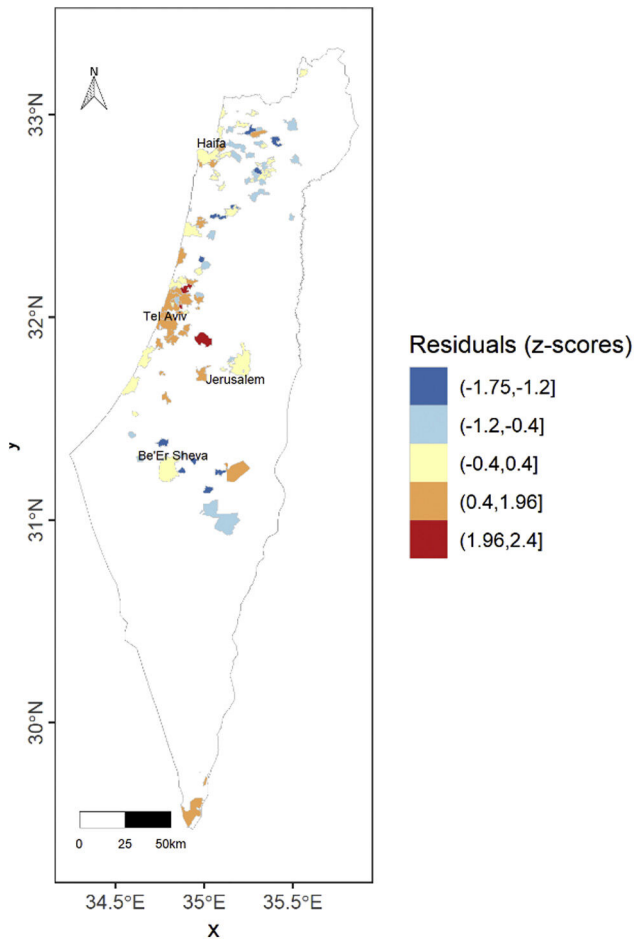


Fig. 4. Spatial distribution of deviations of ASD prevalence from values predicted by localities' characteristics (standardized residuals of a spatial regression model), for the total population of children born in Israel during 2000–2011, for the overall study period. Caption: Only localities with >3400 births are mapped (the rest of localities appear as not colored). Localities with standardized residuals (z-scores) > 1.96, that is with prevalence statistically significantly higher than predicted (95% confidence interval) are colored in red (1.96–2.4 z-score category). No localities with prevalence significantly lower than predicted (z-score < -1.96) were detected. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

phenomenon of more severe clinical phenotype in minority groups, and lack of diagnosed children with moderate-mild ASD, was found in the United States [34] and to some extent also in Europe [35,36].

A locality's peripherality (distance from Tel Aviv subdistrict) showed an inverse association with ASD prevalence (independent of SES and ethnicity). Peripherality has been found to be correlated with restricted access to health services in Israel [37]. Although the national health care applies to every Israeli resident across the country, diagnostic services for ASD, de facto, may be more at hand in central Israel than in the periphery [37,38]. Health care services, personnel, and hospitals are mainly concentrated in central Israel, with the highest population density and highest locality-level SES (mostly urban Jewish localities). In addition, private health insurance plans (as alternatives for the public ones) for diagnostic services for ASD are probably more affordable in the center than in the periphery, given the higher SES. Indeed, higher locality SES was associated with higher prevalence.

The spatial variability in prevalence may be due to differences in awareness and acceptance of ASD. Supporting such an explanation are prevalence differences between localities homogeneously inhabited by specific population subgroups: Arabs, ultraorthodox

Jews, and the general Jewish population. Comparison between such localities consistently shows highest prevalence in the general Jewish localities and considerably lower rates in ultraorthodox Jewish and in Arab localities. For example, our findings indicate that the Jewish locality Modi'in-Makkabbim-Re'ut, the ultraorthodox locality Bne-Braq (appears on Fig. 1 as 'BB'), and the Arab locality Tayibe have prevalence of 22.55, 3.05, and 4.83 cases per 1,000, respectively. Interestingly, the prevalence in the Arab locality Tayibe (which is located around the center of Israel, whereas most Arab localities are concentrated in the periphery) is higher than in more peripheral Arab localities such as Umm Al-Fahm (presented on the northern part of the left-hand map in Fig. 1, with 2.3 cases per 1000). The differences detected in spatiotemporal trends (Fig. 2) may be related to different timings across regions of increasing awareness or acceptance of ASD. Although our above-mentioned suggested explanations for the spatial and spatiotemporal variability in prevalence seem most likely, we obviously cannot rule out other possible explanations, such as lifestyle and environmental or genetic differences.

Comparability with previous studies is limited because of different approaches in spatial evaluations and aggregation levels (individual vs. locality data) [11–14,16,17]. It is nonetheless worthwhile to make some comparison and look at our findings with regard to excess prevalence after adjusting for locality characteristics associated with ASD. Similarly, in some of the aforesaid previous studies, areas of excess risk persisted after adjustment for (individual-level) SES-related factors [11,12,15]. In terms of analyzing explanatory variables for ASD, our regression results are consistent with previous studies examining the association with census tract SES [39–41]. Similar explanations for the aforementioned locality-level characteristics associations are given in the literature about ASD prevalence in the United States, for example, greater ability of higher SES families to deal with the medical system and seek a diagnosis for their children, cultural perceptions of atypical behavior, and better access to services for families with higher SES and closer residential proximity to clinical specialists [40].

This study has several limitations. First, our data analyses were performed on the locality level. Therefore, the results should be evaluated accordingly and no individual-level inference should be made. In addition, the lack of designated GIS layers and data pertaining to health care [29] restricted us to analyses on a locality (or larger) scale and did not allow for more advanced and robust spatial analyses of higher informative value (analyses on smaller spatial scales than locality resolution, had this been feasible, may have been more informative). In addition, the affiliation of the study population to their respective spatial units was made in accordance with maternal address at birth. Birth addresses may not necessarily reflect locality of actual residence in the years after birth (during which the diagnosis was made). Birth addresses may also be inaccurate, but there is no reason to assume that patterns of errors in birth addresses are different in children subsequently diagnosed with ASD. Thus, we do not expect locality misclassification in this respect to be differential, but rather to introduce random error (but not systematic error) into prevalence rates. Nonetheless, migration may contribute to locality misclassification, if, for example, cases systematically migrate to other localities more than controls do (possibly to improve accessibility to services). In the absence of available data, we could not assess this. Another limitation was the follow-up period for ASD diagnosis until December 31, 2016, which may have led to underestimation of prevalence among later birth cohorts. To limit this problem, birth cohorts after 2011 were not included in the study population, allowing for follow-up of 5 years for the youngest birth cohort of 2011. In addition, the change in definition of ASD and the shift from DSM-IV-TR to DSM-5, although the former was consistently implemented during most of the

follow-up period, for 85% of the total 11,699 diagnoses ('cases') in this study, may have had a certain impact on the prevalence among later birth cohorts. Nonetheless, that impact, for example, lower diagnostic prevalence under DSM-5 than under DSM-IV-TR [42], if any, is likely to be nondifferential (not biased) across the localities, and in any event, it does not refer to each birth cohort separately.

This study has several advantages. Overall, the complete countrywide data available in NII in relation to the total population of children born in 2000–2011 in Israel who have been diagnosed with ASD allowed a unique opportunity to gain insights into the spatial and spatiotemporal variation of ASD across the entire country and how it is associated with certain locality-level characteristics. Cases were detected individually, based on NII benefits for ASD after diagnosis ascertainment, independent of SES, income, services eligibility, or their usage. This yields a particularly high validity to case ascertainment in this study, even though it may not capture children with ASD who have not been diagnosed with ASD because of lack of awareness or for other reasons.

Our results provide insight into health disparities between localities affecting the diagnosis of ASD. These findings have utility for planning and addressing the needs for child development diagnostic and intervention services, in particular in the geographic periphery and underprivileged population groups. This, for example, by improving accessibility of services through shortening wait time and addressing language and cultural barriers in underprivileged communities at the national and local levels [43].

Adding to the current body of knowledge on spatial and spatiotemporal ASD prevalence variability, our findings may be generalizable beyond Israel and may reflect similar patterns elsewhere. Similar findings may direct to a need for additional policy intervention for diagnosis of ASD, targeting children in more peripheral regions who are at higher risk of going undiagnosed, as well as further research on possible factors that may account for significant excess or decreased prevalence, if detected in certain regions. This also calls for more sophisticated spatial analysis to be implemented in future research.

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Authors' contributions: HM-M contributed to methodology, formal analysis, investigation, data curation, visualization, writing—original draft, review and editing. RR contributed to funding acquisition, supervision, project administration, resources, conceptualization, methodology, and writing—review and editing. RH-K contributed to methodology, visualization, and writing—review and editing. OP contributed to data curation, resources, and writing—review and editing. IK contributed to conceptualization, methodology, and writing—review and editing. MD contributed to methodology, software and visualization, and writing—review and editing. HL contributed to writing—review and editing. MGW contributed to funding acquisition and writing—review and editing.

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.annepidem.2020.06.003>.

References

- [1] Presmanes Hill A, Zuckerman K, Fombonne E. Epidemiology of autism spectrum disorders. *Transl Approaches Autism Spectr Disord* 2015;13–28.
- [2] Centers for Disease Control, Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2016. CDC; 2020. https://www.cdc.gov/mmwr/volumes/69/ss/ss6904a1.htm?s_cid=ss6904a1_w. [Accessed 26 June 2020].
- [3] Fombonne E, Quirke S, Hagen A. Epidemiology of pervasive developmental disorders. *Pediatr Res* 2011;65:90–111.
- [4] French LR, Bertone A, Hyde KL, Fombonne E. Epidemiology of autism spectrum disorders. In: Buxbaum J, Hof P, editors. *Neurosci Autism Spectr Disord*. Oxford, UK: Elsevier Inc., Academic Press; 2013. p. 3–24. Chapter 1.1.
- [5] Keyes KM, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort effects explain the increase in autism diagnosis among children born from 1992 to 2003 in California. *Int J Epidemiol* 2012;41:495–503.
- [6] Nassar N, Dixon G, Bourke J, Bower C, Glasson E, De Klerk N, et al. Autism spectrum disorders in young children: effect of changes in diagnostic practices. *Int J Epidemiol* 2009;38:1245–54.
- [7] Isaksen J, Diseth TH, Schjølberg S, Skjeldal OH. Observed prevalence of autism spectrum disorders in two Norwegian Counties. *Eur J Paediatr Neurol* 2012;16:592–8.
- [8] Saemundsen E, Magnússon P, Georgrsdóttir I. Prevalence of autism spectrum disorders in an Icelandic Birth Cohort. *BMJ Open* 2013;3:e002748.
- [9] Taylor B, Jick H, Maclaughlin D. Prevalence and incidence rates of autism in the UK : time trend from 2004 – 2010 in children aged 8 years. *BMJ Open* 2013:e003219.
- [10] Mohr Jensen C, Steinhausen HC, Marlene Briciet L. Time trends over 16 years in incidence-rates of autism spectrum disorders across the lifespan based on nationwide danish register data. *Autism Dev Disord* 2014;44:1808–18.
- [11] Mazumdar S, Winter A, Liu KY, Bearman P. Spatial clusters of autism births and diagnoses point to contextual drivers of increased prevalence. *Soc Sci Med* 2012;95:87–96.
- [12] Mazumdar S, King M, Liu K-Y, Zerubavel N, Bearman P. The spatial structure of autism in California, 1993–2001. *Health Place* 2010;16:539–46.
- [13] Van Meter KC, Christiansen LE, Delwiche LD, Azari R, Carpenter TE, Hertz-Picciotto I. Geographic distribution of autism in California: a retrospective birth cohort analysis. *Autism Res* 2010;3:19–29.
- [14] Hoffman K, Kalkbrenner AE, Vieira VM, Daniels JL. The spatial distribution of known predictors of autism spectrum disorders impacts geographic variability in prevalence in central North Carolina. *Environ Health* 2012;11:80.
- [15] Hoffman K, Vieira VM, Daniels JL. Brief report: diminishing geographic variability in autism spectrum disorders over time? *J Autism Dev Disord* 2014;44:712–8.
- [16] Bakian AV, Bilder D, Coon H, McMahon W. Spatial relative risk patterns of autism spectrum disorders in Utah. *J Autism Dev Disord* 2015;45:988–1000.
- [17] Hoffman K, Weisskopf MG, Roberts AL, Raz R, Hart JE, Lyall K, et al. Geographic patterns of autism spectrum disorder among children of participants in nurses' health study II. *Am J Epidemiol* 2017;186:834–42.
- [18] Zablotsky B, Maenner MJ, Blumberg SJ. Geographic disparities in treatment for children with autism spectrum disorder. *Acad Pediatr* 2019;19(7):740–747.
- [19] Pérez-Crespo L, Prats-Urbe A, Tobias A, Duran-Tauleria E, Coronado R, Hervás A, et al. Temporal and geographical variability of prevalence and incidence of autism spectrum disorder diagnoses in children in Catalonia, Spain. *Autism Res* 2019;12:1693–705.
- [20] Gal G, Abiri L, Reichenberg A, Gabis L, Gross R. Time trends in reported autism spectrum disorders in Israel, 1986–2005. *J Autism Dev Disord* 2012;42:428–31.
- [21] Gal G, Gross R. Time trends and autism. *Isr Med Assoc J* 2009;11:577–8.
- [22] Segev A, Weisskopf MG, Levine H, Pinto O, Raz R. Incidence time trends and socioeconomic factors in the observed incidence of autism spectrum disorder in Israel: a nationwide nested case–control study. *Autism Res* 2019:1–10.
- [23] Davidovitch M, Hemo B, Manning-Courtney P, Fombonne E. Prevalence and incidence of autism spectrum disorder in an Israeli population. *J Autism Dev Disord* 2013;43:785–93.
- [24] Raz R, Weisskopf MG, Davidovitch M, Pinto O, Levine H. Differences in autism spectrum disorders incidence by sub-populations in Israel 1992–2009: a total population study. *J Autism Dev Disord* 2015;45:1062–9.
- [25] Senecky Y, Chodick G, Diamond G, Lobel D, Drachman R, Inbar D. Time trends in reported autistic spectrum disorders in Israel, 1972 – 2004. *IMAJ* 2009;11.
- [26] Raz R, Levine H, Pinto O, Broday DM, Yuval, Weisskopf MG. Traffic-related air pollution and autism spectrum disorder: a population-based nested case-control study in Israel. *Am J Epidemiol* 2017;40:1–28.
- [27] Israel Central Bureau of Statistics - CBS. CBS socio-economic index. Israel Central Bureau of Statistics; 2013. <https://www.cbs.gov.il/en/publications/Pages/2017/Characterization-and-Classification-of-Geographical-Units-by-the-Socio-Economic-Level-of-the-Population-2013.aspx>. [Accessed 26 June 2020].
- [28] Anselin L. Local indicators of spatial association - LISA. *Geogr Anal* 1995;27:93–115.
- [29] Kirby RS, Delmelle E, Eberth JM. Advances in spatial epidemiology and geographic information systems. *Ann Epidemiol* 2017;27:1–9.
- [30] Open Source Geospatial Foundation (OSGeo). QGIS Development Team. QGIS geographic information system. 2018. QGIS; 2018. <http://qgis.osgeo.org>. [Accessed 26 June 2020].
- [31] R Foundation. R: a language and environment for statistical computing. 2018.
- [32] Waller LA, Gotway CA. Applied spatial statistics for public health data. Hoboken, New Jersey: John Wiley & Sons; 2004.

- [33] Mahajnah M, Sharkia R, Shalabe H, Terkel-Dawer R, Akawi A, Zelnik N. Clinical characteristics of autism spectrum disorder in Israel: impact of ethnic and social diversities. *Biomed Res Int* 2015;2015:962093.
- [34] Jo H, Schieve LA, Rice CE, Yeargin-Allsopp M, Tian LH, Blumberg SJ, et al. Age at Autism Spectrum Disorder (ASD) diagnosis by race, ethnicity, and primary household language among children with special health care needs, United States, 2009–2010. *Matern Child Health J* 2015;19:1687–97.
- [35] Kawa R, Saemundsen E, Lóa Jónsdóttir S, Hellendoorn A, Lemcke S, Canal-Bedia R, et al. European Studies on Prevalence and Risk of Autism Spectrum Disorders According to Immigrant Status - A Review. *Eur J Public Health* 2017;27:101–10.
- [36] van der Ven E, Termorshuizen F, Laan W, Breetvelt EJ, van Os J, Selten JP. An incidence study of diagnosed autism-spectrum disorders among immigrants to the Netherlands. *Acta Psychiatr Scand* 2013;128:54–60.
- [37] Mendlovic J, Gordon ES, Haklai Z, Meron J, Afek A. Geographic variation in selected hospital procedures and services in the Israeli Health Care System. *Isr J Health Policy Res* 2017;6:4.
- [38] OECD (2012). Organization for Economic Cooperation and Development (OECD) reviews of health care quality: Israel, 2012: Raising standards. OECD Publishing; 2012. <https://doi.org/10.1787/9789264029941-en>.
- [39] Durkin MS, Maenner MJ, Baio J, Christensen D, Daniels J, Fitzgerald R, et al. Autism spectrum disorder among US Children (2002-2010): socioeconomic, racial, and ethnic disparities. *Am J Public Health* 2017;107:1818–26.
- [40] Dickerson AS, Rahbar MH, Pearson DA, Kirby RS, Bakian AV, Bilder DA, et al. Autism spectrum disorder reporting in lower socioeconomic neighborhoods. *Autism* 2017;21:470–80.
- [41] Durkin MS, Maenner MJ, Meaney FJ, Levy SE, DiGuseppi C, Nicholas JS, et al. Socioeconomic inequality in the prevalence of autism spectrum disorder: evidence from a U.S. cross-sectional Study. *PLoS One* 2010;5:e11551.
- [42] Maenner MJ, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. *JAMA Psychiatry* 2014;71:292–300.
- [43] Israel Ministry of Health. Ministry strategic plan, 2017-2020. Israel Ministry of Health; 2017. <https://www.health.gov.il/PublicationsFiles/inequality-2017-2020.pdf>. [Accessed 26 June 2020].