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Can Early Childhood Motor Developmental Delay be an Indicator of a Future Autism Spectrum Disorder Diagnosis?

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Abstract

Purpose: This study assessed whether Motor Developmental Delay (MDD) can be regarded as an indicator of ASD.

Methods: Retrospective cohort study. The study's population included 240,299 children from Israel, born between 2011 and 2017. MDD definition was based on at least one recorded developmental physiotherapy visit before age two years. Association of MDD, demographic and health characteristics and later diagnosis of ASD were evaluated.

Results: MDD was significantly more frequent in children subsequently diagnosed with ASD. Additional characteristics associated with ASD were male gender and a sibling with ASD. The average age of ASD diagnosis in children with MDD was 7 months younger than those without MDD.

Conclusions: An in-depth examination of communication skills within the MDD population is recommended, especially when associated with male babies, siblings with ASD, premature birth, and low birth weight. Appropriate training of developmental physiotherapists should aim to identify suspicious early indications of ASD.

Keywords: Motor Developmental Delay (MDD); Autism Spectrum Disorder (ASD); Developmental Physiotherapy

Introduction

Autism Spectrum Disorder (ASD) is a group of developmental disabilities including social, speech, and emotional issues with a high impact on cognitive, motor, and sensory abilities [1]. In the past two decades increasing ASD prevalence rates has been reported worldwide. In 2018, the United States Center for Disease Control and Prevention (CDC) reported an ASD prevalence rate at 1 in 44 or an incidence rate of 2.3% [2]. These rates have public health consequences regarding appropriate treatment for children and adults with ASD. The number of new cases each year holds high financial burden for patients, their families, and the nations. Early and intensive therapeutic and behavioral intervention have shown to produce favorable results in children with ASD in all areas of intervention including cognitive, speech, motor and behavioral fields [3]. Hence, it is important to detect infants at risk for ASD as early as possible. ASD's early markers are in the social-communication field with low use of pointing, waving, mimicry, poor eye contact, and inconsistent response to being called by name at one year of age and speech delays and lack of pointing at two years of age [4]. Yet, accurate assessment of these markers necessitates child observation under favorable conditions that are sometimes lacking due to circumstances such as fatigue, fear of strangers, or parental lack of awareness and misinterpretation. In the first year of life,

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infants acquire new motor and perception skills at a rapid rate. Failure to keep up with motor developmental milestones leads to Motor Developmental Delay – MDD .It may be a sign for various non-motor development gaps, among those with a diagnosis of ASD [5]. Although motor impairment is not part of ASD diagnosis criteria, recent studies reported deficiencies in gross motor functions in children with ASD [6,7] including deficiencies in balance, gait, planning, reaching, and fine motor skills. Delays and differences in typical development are described in children with ASD starting at 20 weeks of age [8] and throughout the first year of life [9]. Several studies showed that gross motor performance is delayed and presents abnormal characteristics when compared to typical development [10] and therefore should be part of the criteria supporting ASD diagnosis [11].

Retrospective studies on infants diagnosed with ASD included parents' questionnaires and coding of videos in the first year of life [12,16]. The infants showed a variety of motor difficulties including MDD, poor movement quality, delayed motor development and poor posture. The infants showed concomitant social difficulties such as lack of smiling, poor eye tracking, delayed or no reaction when called by name, in addition to nervousness, poor mobility, stereotypical play, or over-staring at objects. Yet, the main limitation of retrospective studies is parental recall information bias. Cohort studies on siblings of children with ASD who are at increased likelihood of ASD [13], mainly included small groups. In a retrospective small cohort study (n=47) in Japan [14] of the infants referred before age 2 years due to MDD, 23% (n=11) were later diagnosed with ASD. In 2019, a large study (n=648) compared siblings of children with ASD to a control group [15]. The infants were assessed for gross and fine motor level at 6 months and underwent communication evaluation (Autism Diagnostic Observation Schedule -ADOS) at 3 years. Delayed fine motor skills at 6 months were significantly associated with the ADOS evaluation result at 3 years. Moreover, gross motor scores in children at high risk were lower than in children at low risk and without classic symptoms.

Early intervention in children with ASD is important [3], so indicators for clinical suspicion such as Motor Developmental Delay should be explored [5]. The current study was aimed at assessing the association between MDD in early life, demographic and health characteristics and a later diagnosis of ASD in childhood in a large cohort.

Methods

This retrospective cohort study was carried out in Meuhedet Health Services (MHS). MHS is Israel's third largest health fund, serving over 1.2 million (14% of the national population) clients nationwide. Ethical approval was provided by the MHS IRB as a "retrospective survey of health records without intervention". The study objectives were to evaluate MDD and other characteristics as indicators for ASD.

MDD variable definition: MDD was defined as at least one recorded developmental physiotherapy visit before the age of two. Parents concerned about their infant's motor development approach the pediatrician. If the pediatrician recommends a developmental evaluation, the child is referred to the Child Development Institute (CDI). If MDD is suspected – the referral will be to a developmental physiotherapist (DPT). The DPT's target diverse population including children with delay in acquiring age-appropriate motor milestones. DPT sessions are recorded in the MHS administrative data system (AS400 software) from which the MDD variable was therefore retrieved. In addition, data were collected on age (in months) at the first DPT visit and total number of sessions up to the age of two years. The number of sessions can indicate severity, as in mild cases the treatment is usually short-term, less than 10 sessions. Generally, sessions occur weekly so that a series of 11 sessions will last some 3 months. In complex cases the treatment lasts over three months (>10) and may take place more than once a week.

ASD Variable Definition: According to Israel's Ministry of Health guidelines [16], ASD diagnosis is performed by a qualified physician (a child and adolescent psychiatrist, a child neurology and development specialist or a developmental pediatrician with 3 years' experience at an accredited child development institute). The diagnostic process includes full physical, neurological, developmental, and emotional evaluation. Concomitantly, the child must be examined by an expert psychologist and standard assessment tools such as ADOS are used. ASD diagnoses are recorded in accordance with the diagnostic codes of the International Classification of Diseases (ICD) which are based on DSM-4 and DSM-5, depending on the year of diagnosis. In the study, diagnoses based on ICD codes were extracted from the children's computerized health records. A child who had been diagnosed with one of the ICD codes was defined as an ASD case.

Additional variables: Additional variables were evaluated for association with ASD: gender, siblings diagnosed with ASD, parental age and age difference between parents, socioeconomic status (SES), residential area, and population sector (Distribution based on MHS clinic location)- General population (GP), Ultra-orthodox Jews (UO) and Israeli Arab (IA).

Inclusion and exclusion criteria - The original data file consisted of the health records of 279,510 children, MHS members, who were born between the years 2011 and 2017.

According to the State Health Law of the State of Israel, it is possible to switch between four health funds (such as MHS) every three months. Children who joined the MHS after the

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age of 24 months (N=39,206) were excluded from the study. Another 5 children with incorrect MDD developmental data or with no documentation in the child's file were also excluded. The study population description is in Table No. 1 and additionally includes ASD rates and 95% Confidence Interval (CI) unadjusted OR.

Table 1: Description of the study population, ASD rates and CI 95% Unadjusted OR.

Variable	N=240,299	ASD (N1821=)	CI 95% Unadjusted OR
Gender			
Boys	123752 (51.5%)	1437 (79%)	3.5 (3.1-3.9)
Siblings with ASD			
Yes	2546 (1.1%)	177 (9.7%)	10.7 (9.1-12.5)
Father's age			
Mean ±SD (years)	32.5±5.5		
Father's age>33 years	117872 (49.1%)	1146 (63%)	1.7 (1.5-1.9)
Mother's age			
Mean ±SD (years)	29.5±5.7		
Mother's age>30 years	105853 (44.1%)	1028 (56.4%)	1.6 (1.5-1.8)
Sector			
GP	113592 (47.3%)	1209 (66.3%)	2.2 (2.0-2.4)
UO	92824 (38.6%)	338 (18.5%)	
IA	33855 (14.1%)	274 (15%)	
District of residence			
Jerusalem	119407 (49.7%)	565 (31%)	
Center	46589 (19.4%)	510 (28%)	1.6 (1.4-1.8)
South	39596 (16.5%)	382 (21%)	1.3 (1.2-1.5)
North	34676 (14.4%)	364 (20%)	1.4 (1.3-1.6)
SES			
Rank 1-3	96666 (40.3%)	517 (28.3%)	
Rank 4-6	10505 (43.6%)	849 (46.6%)	1.1 (1.0-1.2)
Rank 7-10	38619 (16.1%)	454 (25%)	1.7 (1.5-1.9)
Year of Birth			
2011	31404 (13.1%)	280 (15.3%)	
2012	32246 (13.4%)	291 (16 %)	
2013	33048 (13.8)	299 (16.4%)	
2014	34869 (14.5%)	298 (16.3%)	
2015	35420 (14.7%)	240 (13.1%)	
2016	36681 (15.3%)	257 (14.1%)	
2017	36631 (15.2%)	156 (8.5%)	

Statistical methods

Statistical analysis Data analysis was performed with IBM SPSS Statistics for Version 25.0. Armonk, NY: IBM Corp. Categorical variables are presented as rate and proportion; continuous variables as mean ± Standard Deviation (SD) and median. Results are presented as odds ratio (OR) with a 95% CI. In addition, the association with ASD was examined using ROC analysis, which was used to find the point with the best sensitivity and specificity for predicting ASD.

A bivariate analysis was performed for calculating an OR for ASD among children with and without MDD background. Odd ratio were examined. In addition, since each child contributes a different time for monitoring, a regression model of Cox's proportional hazards was used. The study population was allocated as to the dichotomous variable MDD yes/no with comparison of later ASD rates and the age of ASD diagnosis in the 2 groups. In order to examine whether There is a difference in age at diagnosis of ASD between children with or without MDD, a Kaplan -Meier survival analysis was used.

Then, a multivariate model using logistic regression for ASD including MDD and other variables was produced. Associations between the variables and ASD are presented as OR and a 95% CI. P-values less than 0.05 were considered significant and all were two-sided. For this purpose, all study variables were divided into four blocks:

Block 1: Demographic variables - gender, sector, SES, and district of residence.

Block 2: Family characteristics - father age, mother age and siblings with ASD.

Block 3: MDD dichotomous variable

Block 4: Age at first session of DPT and the Total number of visits at DPT.

Since there is a likelihood that the younger the age of the first visit the more visits there will be in total, the relationship between the two variables was examined in an appropriate statistical test. Finally, the CDI files of children who had MDD and later were diagnosed with ASD (MDD + ASD group) were reviewed and the following data which is not included in the general data set was gathered –the referral form to DPT as prescribed by an MHS physician, week of birth, and birth weight. The birth week and birthweight were compared with data of the national population of Israel based on data from Israel's Ministry of Health [17].

Results

The flow chart of the research process, criteria for exclusion, first division according to children with or without background of MDD and final division according to ASD diagnosis is shown in Figure 1.

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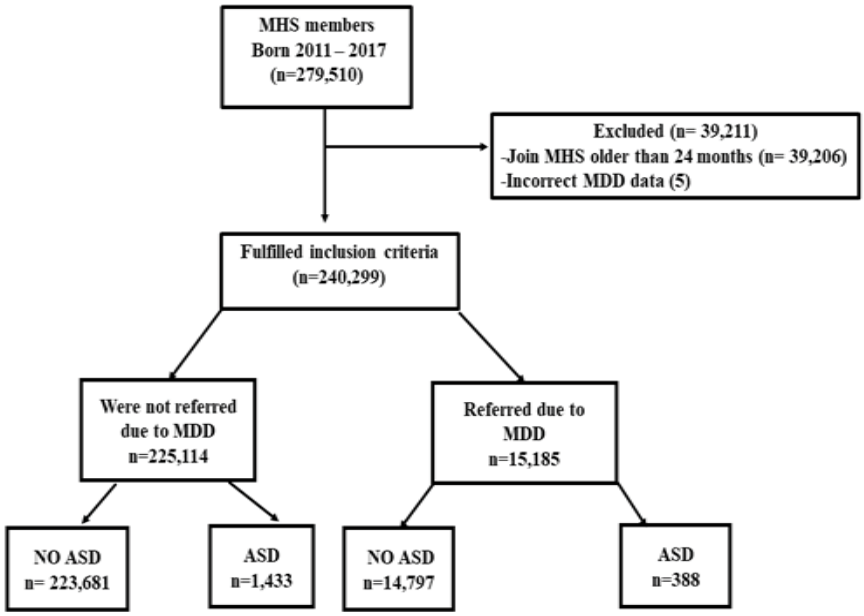
The final data file included 240,299 children of whom 15,185 (6.3%) were referred to DPT due to MDD and 225,114 were not referred to DPT due to MDD and the number of children with a registered diagnosis of ASD was 1,821 children - 0.75%. Cross-referencing data between MDD and ASD showed that 388 children were diagnosed with ASD in the MDD group which constituted a rate of 2.6% compared to 1,433 children diagnosed with ASD from the non MDD group who were not in DPT and constituted 0.64%. The Odd Ratio is 4.1 (95% CI 3.6-4.6). The Cox proportional-hazards regression model between MDD and the non MDD group has a Hazard Ratio of 5.1(95% CI 4.7-5.5).

Table 2 shows that among children diagnosed with ASD the proportion of background of MDD increases over the years, from 11% in 2011 to 34% in 2017. In addition, the median ASD diagnosis age's drops from 55 months in 2011 to 27 months in 2017.

Among all children of the cohort the mean age for the first visit was 8±5 months and the mean number of DPT treatments for an infant in two years was 8.67±11.2 treatments (median=5).

ROC Analyses for Continuous Variables – First, the two variables that characterize MDD were examined - age of first visit to DPT and the number of total treatments in two years. The age of first visit to DPT from which the risk of diagnosing ASD increases is 8.2 months. The number of treatments in the two years from which the risk of diagnosing



MHS= Meuhedet Health Services; MDD=Motor Developmental Delay; ASD= Autism Spectrum Disorder

Figure 1: Flow chart of the research process: Criteria for exclusion, first division according to backgrounds of MDD and without background of MDD and final division according to ASD diagnosis.

Table 2: Description of children diagnosed with ASD by year of birth: crude number and rate of MDD backgrounds and median age of diagnosis.

Year of Birth	MDD	No MDD	%	Median age for diagnosis of ASD (months)
2011	32	248	0.11	55
2012	33	258	0.11	50
2013	37	262	0.12	45
2014	88	210	0.29	41
2015	64	176	0.28	37
2016	80	177	0.31	32
2017	54	102	0.34	27
Total	388	1433	0.21	

MDD=Motor developmental Delay; ASD= Autism Spectrum Disorder

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ASD increases is 5 treatments. In addition, risk of diagnosing ASD in relation to parents' age was also examined. The predictive age of mothers was 30.15 years and above, the predictive age of fathers was 33.65 years and above and the predictive age difference between both parents was found as 2.8 years.

The Kaplan-Meier survival curve (Figure 2) shows that children with MDD were diagnosed with ASD earlier than children without MDD. The mean age for diagnosis of ASD among children who displayed motor delay was 38.6 months (SD= 17.7, median 34 months) compared to children without background of MDD who were diagnosed with a mean age of 45.5 months (SD= 20.5, median 40 months). The difference in the diagnosis age is 6.9 months, 95% CI 4.6 - 9.1.

The logistic regression results are shown in Table 3 and show OR adjusted for demographic or familial variables (P <0.05). The variables that were found to have an OR value higher than 3 are siblings to ASD (OR=10.3, 95% CI 8.7-12.2), male gender (OR=3.5, 95% CI 3.1-4.0) and MDD (OR=3.4, 95% CI 3.0-3.8). In addition, increased OR can be seen for ASD in infants who reached treatment aged 10 months or older for the first DPT session (OR 2.1, 95% CI 1.6-2.8) or who were treated with more than 10 DPT treatments (OR 1.6, 95% CI 1.5-2.0). To avoid multicollinearity, the relationship between these two variables was examined and a negligible negative relationship was found (Spearman test = 0.26).

Children with MDD background and subsequent ASD diagnosis (n=388)

To characterize in-depth the group of 388 children with MDD backgrounds later diagnosed with ASD, an individual review of the child health files in the MHS' software of the Institute for Child Development. Indication for referral – based on the initial doctor's referral or the medical file documentation, 48 infants had two reasons listed for referral, and for 15 infants the referral was not documented in the medical file (N = 420). Of the 420 referrals, 194 infants (46.3%) were referred due to motor delay -i.e. MDD diagnosis or specific description of delay in achieving a motor milestone such as crawling, standing or walking, 82 infants (19.6%) were referred due to torticollis, 65 infants (15.5%) were referred due to developmental delay (motor delay and delay in another developmental area- Most often cognitive or language delay), 31 infants (7.4%) were referred due to pre-term birth, 15 infants (3.6%) were referred due to birth defects, 12 infants (2.8%) were referred due to hypertonia and 12 infants were referred due to other reasons. Additionally, for 9 infants (2.1%) the reason for the referral included communication difficulty (poor eye contact, language delay, etc.). The rates of pre-term birth (birth before week 37) and infants born with low birth weight (LBW- below 2,500 grams) in the MDD + ASD group was 17.1% and 18.1% respectively - twice as high as in the general population in Israel in 2017 (7.7% & 7%) respectively. Description of pregnancy - 81.7% of pregnancies were defined as normal (N = 388).

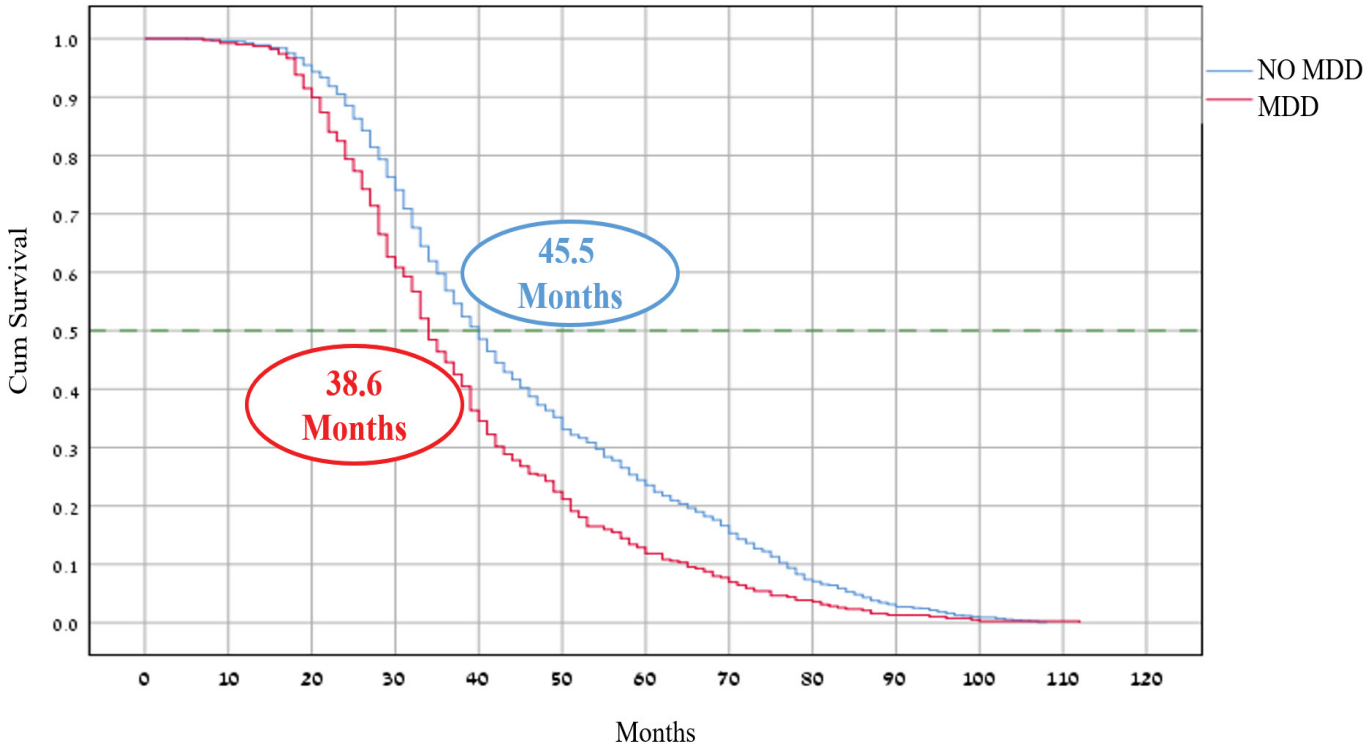

Figure 2: Kaplan-Meier curve describing the age of diagnosis of ASD in children with and without a background of MDD.

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Table 3: Logistic Regression Results for ASD prediction. Divided into 4 models.

	Model1: Demographic Variables	Model2: Demographic Variables + Family Variables	Model3: All variables + MDD Variable	Model4: All variables + MDD characterization variables
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
N	239738	237875	237875	15007
Number of ASD cases	1820	1805	1805	386
Gender				
Boys vs. Girls	3.5 (3.1-4.0)	3.5 (3.2-4.0)	3.5 (3.1-4.0)	2.9 (2.2-3.7)
Sector				
IA vs. UO	2.1(1.7-2.5)	2.0 (1.8-2.4)	2.2 (1.8-2.6)	1.9 (1.2-3.0)
GP vs. UO	2.2 (1.8-2.5)	2.0 (1.7-2.4)	2.0 (1.7-2.4)	1.3 (0.9-1.7)
District of Residence				
South vs. Jerusalem	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.2 (1.04-1.4)	1.3 (0.9-1.8)
North vs. Jerusalem	1.5 (1.3-1.8)	1.5 (1.3-1.8)	1.4 (1.2-1.6)	1.8 (1.3-2.6)
Center vs. Jerusalem	1.7 (1.5-2.0)	1.7 (1.5-2.0)	1.6 (1.4-1.8)	1.8 (1.3-2.4)
SES				
Rank 1-3 vs. Rank 4-6	1.3 (1.1-1.4)	1.3 (1.1-1.4)	1.3(1.1-1.5)	1.5 (1.1-1.9)
Rank 1-3 vs. Rank 7-10	1.4 (1.2-1.6)	1.4 (1.1-1.6)	1.3(1.1-1.5)	1.4 (0.9-1.9)
Siblings with ASD				
Siblings vs. No Siblings		11.0 (9.3-13.0)	10.3 (8.7-12.2)	7.2 (5.0-10.5)
Mother's age				
Mother's age over 30 years vs Mother's age under 30 years				
		1.3 (1.1-1.4)	1.3 (1.2-1.4)	1.1 (0.9-1.3)
The parental age difference Age difference above 2.8 years vs age difference below 2.8 years				
		1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.2 (1.02-1.5)
MDD				
MDD vs. No MDD			3.4 (3.0-3.8)	
Age of first visit DPT				
4-9 Months vs. 0-3 Months				1.2 (0.9-1.6)
10-24 Months vs. 0-3 Months				2.1 (1.6-2.8)
Number of DPT Treatments				
3-9 Treatments vs. 1-2 Treatments				0.8 (0.6-1.1)
10+ Treatments vs. 1-2 Treatments				1.6 (1.5-2.0)

OR=Odd Ratio; CI= Confidence Interval; ASD= Autism Spectrum Disorder; GP=General Population; UO=Ultra-orthodox; Jews IA-Israeli Arabs; SES=Socio-Economic; Status on the rating of "points(*Points Location Intelligence – Because Everything Happens Somewhere, n.d.*)" MDD=Motor developmental Delay; DPT= Developmental physiotherapists

Discussion

This retrospective cohort study was aimed to examine the association between motor delay in infancy and a later diagnosis of ASD. The association between MDD and ASD (adjusted OR of 3.4 ;4.1 unadjusted) corresponds with previous studies and constitutes another supportive milestone in recognizing motor delay in infancy as an early marker for autism [5,12,14,15,18].

The research method has dealt with difficulties raised in previous studies on this topic. The study is based on a general population with no selection biases and uses a significantly larger sample size compared to the studies mentioned. Second, the use of the cohort model shows temporalities between MDD and ASD without being exposed to information biases such as recall bias in studies based on parent questionnaires and observer bias in studies based on video observation.

However, in retrospective cohort studies based on administrative data, problems of information quality (validity and reliability) may arise. ASD diagnoses were given by MHS doctors. In contrast, the classification for MDD was based on an administrative registration of DPT. However, analysis of indication for referral shows that 46% were referred due to MDD, one-fifth of infants were referred due to torticollis, and 15% were referred due to developmental delay, i.e., motor delay in addition to delay in another developmental area. Torticollis is a condition of asymmetrical head tilt, congenital or acquired, which can appear with head rotation

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to the opposite side [19]. In a study that examined infants with torticollis about a year after starting treatment, it was found to be a risk factor for MDD [20]. From this analysis, one can deduce the validity of the use of DPT administrative information as describing MDD.

The multivariate model results showed a significant and strong association between ASD and ASD in siblings, supporting the genetic-familial component of ASD. Previous studies have indeed shown that siblings of children with ASD are at high risk of being diagnosed with ASD [13,21]. In addition, the model showed a link to gender, corresponding with a meta-analysis published in 2017 showing male/female ratio of OR=4.20 ,95% CI 3.84- 4.60 [22].

The ROC analysis showed that from the fifth DPT treatment onwards there is an increased risk of an ASD diagnosis. Usually, by the fifth treatment a connection is established between the therapist and the patient and his family. As a result, there is room to routinely check communication markers from the fifth treatment using questionnaires such as Communication Scales Behavior Symbolic Profile Developmental (DP-CSBS). This parental questionnaire consists of 24 questions and is divided into three areas: social, verbal, and symbolic. A pilot study conducted in MHS in 2019 showed that this questionnaire was effective in detecting and promoting language and communication difficulties [23]. Additionally, tools such as the M-CHAT-R/F, a highly reliable and sensitive ASD screening tool for toddlers 16-24 months old, can be used [24].

The strength of this study is the use of the MDD variable definition through documentation of a DPT visit. DPTs are trained at detecting atypical movement patterns common in children with ASD. They also treat and monitor motor development of pre-term infants, who are at greater risk of ASD diagnosis [25]. Often, the motor problems of the child with ASD will arise at a young age and therefore most often, the DPT is the first professional in the child development system who treats the youngest clients [26]. The place of DPT in the treatment of children with ASD has greatly expanded in recent years and includes several options for intervention27, including early detection [28]. The findings of the present study support the urgent need to establish a base of knowledge regarding early detection of ASD among DPT's along with other health professionals. When comparing age of diagnosis, the mean age of diagnosis of ASD was 38 months among children with a background of MDD compared to 45 months among children without a background of MDD. These are young ages relative to the 2019 meta-analysis that examined the mean age of ASD diagnosis and reported an average age of 60.5 months ,95% CI 50.1-70.8 [29].

Among the 388 children with a background of MDD and a late diagnosis of ASD the rates of pre-terms infants and LBW =were twice as high as in the general population in Israel in 2017. Pre-term infants, were found to be at a higher risk for ASD – with an incidence rate of 7.1% [30] among pre-term infants compared with 1.85% in general pediatric population (CDC). LBW (2,500g>) was also found to be associated with ASD. A study conducted in Sweden found an OR of 2.2, 95% CI = 3.2-1.4 for ASD in infants born with LBW [31].

Limitations of the study

As with all cohort studies the main limitation of this study is the lack of data on children who left the MHO (Lost to follow up) by age two and up to 2020 mainly of children from the MDD group. Another limitation is that the study is based on data from only one in four health maintenance organizations in the State of Israel. Also, the rate of the UO sector in MHS is higher than their rate in the GP within the State of Israel. Also, the SES variable which is based on the residential address and the sector variable is based on the MHS branch and therefore they are not necessarily accurate at the individual level. In addition, some variables such as week and birth weight can only be obtained by entering individual files and therefore were not included in the general data set of the study.

Conclusions

Based on the study data, MDD can be regarded as one of the early (but not necessary) signs of ASD. Thus, the first caregiver to encounter the child with ASD is frequently the DPT. It is recommended that DPT who treat infants up to the age of 2 years focus on examining communication skills, especially in instances of siblings with ASD, male gender, pre-term infants, or LBW. It is further recommended to use questionnaires that examine communication in infants such as CSBS-DP, when the DPT suspects other alarming signs typical of ASD, from the fifth treatment onwards. In addition, appropriate training of physiotherapists at child development centers should be considered to identify early signs of ASD in infants. It is advised to conduct further studies including MDD as a visit to DPT allowing the use of relatively large samples in other areas of child development research, and especially ASD research. In addition, it is recommended to perform an in-depth and high-quality study of the files of children diagnosed with ASD who have an MDD background.

Author Contributions: Conceptualization: MKL, CSZ and ML; Methodology: MKL; Data curation: MKL; Writing—original draft preparation: MKL, Writing—review and editing: CSZ and ML; Supervision: OBB, CSZ and ML; Project administration. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the declaration of Helsinki, and Ethical approval was provided by the MHS IRB as a "retrospective survey of health records without intervention.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to Medical Confidentiality.

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Competing Interests: The authors declare that they have no competing interests.

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