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Early Manifestations of Neurodevelopmental Copy Number Variants in Children: A Population-Based Investigation

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ABSTRACT

BACKGROUND: There is clinical interest in recognizing copy number variants (CNVs) in children because many have immediate and long-term health implications. Neurodevelopmental (ND) CNVs are associated with intellectual disability, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), conditions typically diagnosed by medical practitioners. However, ND CNVs may have additional, early developmental impacts that have yet to be examined in unselected populations.

METHODS: Carriers of known ND CNVs were identified in 2 UK birth cohorts: ALSPAC (Avon Longitudinal Study of Parents and Children) (carriers = 144, controls = 6217) and MCS (Millennium Cohort Study) (carriers = 151, controls = 6559). In ALSPAC, we assessed associations between CNV carrier status and birth complications; preschool development; cognitive ability; ND conditions (ASD, ADHD, reading, language, and motor difficulties); and psychiatric, social, and educational outcomes. Corresponding phenotypes were identified in MCS and meta-analyzed, where available.

RESULTS: In ALSPAC, ND CNVs were associated with low cognitive ability, ADHD, and ASD. ND CNV carriers showed a greater likelihood of preterm birth, fine and gross motor delay, difficulties in motor coordination, language, and reading, and special educational needs (SEND). Meta-analysis with available measures in MCS identified elevated likelihood of ASD, ADHD, low birth weight, reading difficulties, SEND, and peer problems.

CONCLUSIONS: ND CNVs are associated with a broad range of developmental impacts. While clinicians who see children with intellectual disability, ASD, or ADHD may be aware of the impacts of CNVs and consider genetic testing, our investigation suggests that this training and awareness may need to extend to other professional groups (e.g., speech and language therapists).

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Copy number variants (CNVs) are a type of genetic variation that include deletions and duplications of chromosomal segments. Known neurodevelopmental (ND) CNVs, although rare with a population frequency <1%, are potentially important to recognize clinically due to large effect sizes on risk for intellectual disability (1,2), autism spectrum disorder (ASD) (3,4), attention-deficit/hyperactivity disorder (ADHD) (5,6), schizophrenia (7,8) and physical ill health (9,10). Accumulating insights into the health impacts of CNVs, as well as the benefits to patients of disclosing genetic findings (11), have led to questions about the appropriateness of early genetic screening in high-risk groups. This raises the question of who should be considered as being at high risk of carrying an ND CNV. Many high-income countries already recommend the screening of individuals with developmental delay/intellectual disability for ND CNVs. A recent report further recommended that people with schizophrenia also should be offered the opportunity for CNV testing in certain circumstances (12).

Most studies conducted and reported to date have focused on adult or highly selected clinical (13,14) or volunteer (15,16) samples and defined ND CNVs in diverse ways (17). These studies suggest elevated rates of cognitive impairment, learning problems, ADHD, ASD, and psychiatric diagnoses among rare-CNV carriers compared with controls (15,16,18–21). The early developmental indicators of ND CNVs have yet to be fully characterized in unselected birth cohorts. Guidance on appropriate referral to clinical genetics services and screening requires this evidence. Another uncertainty is whether risk estimates for outcomes from CNVs may have been overestimated by selection bias (21).

In this study, we set out to examine associations between known ND CNVs and a range of developmental outcomes spanning birth and childhood, specifically birth complications, early motor and communication development, cognitive ability, broadly defined DSM-5 ND conditions, and social and educational outcomes, in 2 large UK birth cohorts.

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METHODS AND MATERIALS

Participants

Full details of the cohort are provided in Supplemental Methods. Pregnant women residing in Avon, United Kingdom, with an expected delivery date between April 1, 1991, and December 31, 1992, were invited to participate in ALSPAC (Avon Longitudinal Study of Parents and Children). The total sample size for analyses using any data collected after the age of 7 was 15,447 pregnancies; from these pregnancies, 14,901 children were alive at 1 year of age (22,23). The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool (https://www.bristol.ac.uk/alspac/researchers/our-data). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local research ethics committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Families with a child born in the UK between September 1, 2000, and January 11, 2002, were invited to participate in the MCS (Millennium Cohort Study) (24). Children living in recruitment areas across the UK at 9 months of age whose families were eligible to receive child benefit were able to participate, which was almost all families in the UK at the time. The total number of enrolled children was 19,870, of whom 10,757 remained in the cohort at age 17. Ethical approval was obtained from the National Health Service Research Ethics Committee. Parents provided informed consent for their child to participate, and children provided assent. Data availability is described in the Supplement.

CNV Calling and Annotation

Details of genotyping are provided in Supplemental Methods. Genetic ancestry was inferred using the GenoPred pipeline (https://github.com/opain/GenoPred) (25), as described previously (26). CNV calling, quality control, and annotation were performed using the Cardiff Pathfinder pipeline (https://github.com/CardiffMRCPathfinder) in both cohorts. CNV calling is described in the Supplement.

CNV annotation was performed in R. CNVs in 54 regions have been robustly associated with ND conditions as grouped in DSM-5 (defined as intellectual disability, ASD, developmental delay, and ADHD); are widely accepted to be pathogenic (1,27,28); and have been investigated extensively in the literature (9–11,29). We defined these CNVs according to previously published criteria (30) (Table S1). To meet our criteria for an ND CNV, CNVs that spanned multiple genes were required to cover >50% of the critical interval and known key genes (defined in Table S1). For CNVs spanning 1 gene, deletions were required to cover at least 1 exon, while duplications were required to cover the whole gene. The presence of an ND CNV was confirmed through visual inspection of log R ratio and B allele frequency plots for each identified ND CNV.

Outcomes

All outcome measures were dichotomized, using previously published cut points, to facilitate clinical interpretation. For measures derived from multiple time points, individuals were included in the analysis if they had data for at least 1 time point. Individuals with data at multiple time points were coded as having the phenotype if they met the threshold/criteria at least once.

Birth Complications

In ALSPAC, preterm birth (<37 weeks), low birth weight (<2500 g), and Apgar score <7 at 5 minutes were identified through obstetric records or through parent report when records could not be identified. In MCS, preterm birth (<37 weeks) and low birth weight (<2500 g) were defined by parent report. Preterm birth and low birth weight were only defined in singleton births.

Early Motor and Language Development

In ALSPAC, preschool development items included communication, fine motor, and gross motor delays. Each item was defined using the corresponding scores from the developmental milestones questions at approximately 18 months, which were residualized against age, and the lowest-scoring 5% were defined as having delay. Measures of preschool development were unavailable in MCS.

Cognition

Cognitive measures in ALSPAC were low performance, low verbal, and low general cognitive ability. Low cognitive ability was defined as the lowest-scoring 5% after age correcting the scores from the total IQ scale of the Weschler Intelligence Scale for Children (WISC) (31) at age 8 years. Low performance and low verbal cognitive ability were defined as the lowest-scoring 5%, after age correction, of the WISC performance and verbal IQ scales, respectively. We could not derive measures of cognitive ability in MCS.

Child ND Conditions

Detailed information on the definition of each ND condition is provided in Supplemental Methods and described briefly below. In ALSPAC, a DSM-IV diagnosis of ADHD was generated via the Development and Wellbeing Assessment (32), a research diagnostic interview conducted with parents at ages 7, 10, and 13. Individuals who met criteria at ≥1 time points were defined as having ADHD. Probable ASD was defined categorically as a score >12 on the parent-reported Social Communication Disorders Checklist (SCDC) (33) at ages 7, 10, and/or 13 years. Children who scored below the fifth percentile on the reading subtest of the Wechsler Objective Reading Dimensions (34) were defined as having reading difficulties (35). Similarly, children who scored below the fifth percentile of the structural language score of the Children's Communication Checklist (CCC) (36) were defined as having structural language difficulties, and those who scored below the fifth percentile of the pragmatic scale of the CCC were defined as having pragmatic language difficulties (35). Children were defined as having motor coordination difficulties if they scored below the fifth percentile on a composite score from the Movement Assessment Battery for Children (35). Tics were defined as the presence of motor and/or vocal tics occurring

more than once per week and were measured by parent report at age 13.

ADHD, ASD, and reading difficulties were assessed in MCS. Probable ADHD was defined by the parent-rated Strengths and Difficulties Questionnaire (SDQ) (37) hyperactivity subscale as a score >8 at any of the following time points: 5, 7, 11, or 14 years. ASD was defined as a parent report of a clinician diagnosis between ages 5 and 14 years. Children were defined as having reading difficulties if they scored below the fifth percentile for the reading subscale of the British Ability Scales (38) at age 7.

Psychiatric Conditions

In ALSPAC, emotional problems were defined using the parent-reported emotional symptoms subscale of the SDQ (37). Individuals who scored >6 at any point from ages 4 to 17 years were defined as having emotional problems. Conduct problems were defined as scoring >5 at any time point on the parent-reported conduct problems subscale of the SDQ, measured at the same ages as above. In MCS, emotional problems and conduct problems were defined using the parent-rated SDQ subscale cut points as above, measured at ages 5 to 17.

Social and Educational Outcomes

Special educational needs (SEND) in ALSPAC were defined by parent report at ages 8 or 11 that the child had "ever been recognised as having special educational needs." Social difficulties were defined as having peer problems, classified as a score >4 on the parent-reported SDQ peer subscale at any point between ages 4 to 17 years. In MCS, SEND were defined by parent report at ages 7, 11, and 14 years. Peer problems were defined by the SDQ peer problems subscale, as in ALSPAC, at ages 5 to 17.

Analyses

Primary. Logistic regressions were used to test for associations between ND CNV carrier status and each outcome in ALSPAC. CNV status was coded with noncarriers as the reference category (0) and carriers as 1. Replication was sought in MCS where corresponding measures were available, followed by meta-analysis of ALSPAC and MCS data using random-effects models from the R package meta (39). The false discovery rate ($p < .05$) was used to correct for multiple comparisons within each phenotype category.

Infrequent Versus Ultrarare CNVs. While all the ND CNVs are rare, some occur more commonly than others, in particular 15q11.2 deletion and duplication and 16p11.2 duplication. To investigate whether effect sizes in the primary analyses were driven by the more common CNVs, we tested for association between these 3 specific CNVs, which we term infrequent CNVs, and all outcomes, in comparison to noncarriers. We also tested for associations between the remaining ultrarare CNVs and all outcomes in comparison to noncarriers.

Deletions Versus Duplications. For some loci, deletions may have a more severe impact than their reciprocal duplication (40); accordingly, we compared all duplication carriers with CNV noncarriers for association with each ND phenotype, and all deletion carriers were compared with CNV noncarriers separately.

Continuously Measured Outcomes. For ease of clinical interpretation and translation, the continuous measures were dichotomized to create binary traits. We repeated the above analyses in ALSPAC and MCS using continuous traits where appropriate. A detailed description of the continuous measures is provided in Supplemental Methods.

Excluding ASD, ADHD, and Low Cognitive Ability. We tested ND CNV carrier status for an association with each phenotype in our primary sample, ALSPAC, after excluding individuals with ASD, ADHD, and low cognitive ability from the sample, to assess whether associations were driven by comorbidity with these phenotypes.

Sex Differences. Consistent with recommended best practice (41), we explored sex differences as a secondary analysis. Logistic regressions were repeated in male-only and female-only subsamples of ALSPAC, and effect sizes and confidence intervals were compared. Interactions between each phenotype and sex were examined to investigate whether effect sizes differed significantly between males and females.

Missing Data. To investigate the impact of missing data on our results, we used logistic regressions to assess associations between 1) missing exposure (i.e., CNV) data and developmental phenotype and 2) missing outcome (i.e., developmental phenotype) data and ND CNV carrier status. We also tested for associations between ND CNVs and nonparticipation in ALSPAC clinic and questionnaire assessments at a variety of ages (42) and MCS nonparticipation at age 17, because DNA was not collected until age 14 in this cohort.

RESULTS

A total of 8721 participants in ALSPAC had genetic data available, 6361 (73%) of whom passed CNV quality control. In MCS, 8117 participants had genetic data, 6710 (83%) of whom passed CNV quality control. In ALSPAC, 144 (2.3%) people carried an ND CNV, while 151 (2.3%) people in MCS carried an ND CNV. The frequencies of each ND CNV are displayed in Table S2; we identified carriers of 23 of the 54 known ND CNVs. The frequencies of demographic and outcome measures for ND CNV carriers compared with noncarriers are shown in Table 1. ND CNV carrier status was not associated with female sex in either sample (ALSPAC: odds ratio [OR] = 0.91 [95% CI, 0.65–1.27], $p = .58$; MCS: OR = 1.04 [95% CI, 0.75–1.44], $p = .83$).

The percentage of people with an ND CNV by number of ND conditions and the percentage of ND conditions by ND CNV carrier status are shown in Figures S1 and S2.

Primary Analysis

Full results of the primary and replication analyses and meta-analysis are presented in Table 2 and Figures 1 and 2.

After correcting for multiple comparisons in ALSPAC, carrying an ND CNV was significantly associated with a greater

Table 1. Frequency of Demographic and Outcome Measures by ND CNV Carrier Status in ALSPAC and MCS

			ALSPAC		MCS	
Category	Phenotype	Group	Noncarriers, *n* = 6217	ND CNV Carriers, *n* = 144	Noncarriers, *n* = 6559	ND CNV Carriers, *n* = 151
Demographics	Sex	Female	3206 (51.7%)	71 (49.3%)	3088 (48.8%)	72 (49.7%)
		Male	3000 (48.3%)	73 (50.7%)	3244 (51.2%)	73 (50.3%)
	Genetic ancestry	African	0	0	154 (2.6%)	<5[a]
		European	6217 (100%)	144 (100%)	5057 (86%)	124[a]
		South Asian	0	0	667 (11.3%)	11[a]
Birth Complications	Preterm birth	No	3289 (93.9%)	76 (87.4%)	5735 (93.7%)	137 (95.8%)
		Yes	213 (6.1%)	11 (12.6%)	386 (6.3%)	6 (4.2%)
	Low birth weight	No	3289 (95.3%)	79 (90.8%)	5805 (94.1%)	131 (90.3%)
		Yes	161 (4.7%)	8 (9.2%)	364 (5.9%)	14 (9.7%)
	Apgar score <7	No	3456 (98.8%)	85[a]	NA	
		Yes	43 (1.2%)	<5[a]		
Early Motor and Language Development	Gross motor delay	No	4929 (95.4%)	101 (89.4%)	NA	
		Yes	236 (4.6%)	12 (10.6%)		
	Fine motor delay	No	4991 (96.6%)	101 (89.4%)	NA	
		Yes	174 (3.4%)	12 (10.6%)		
	Communication delay	No	4996 (96.6%)	106 (93.8%)	NA	
		Yes	174 (3.4%)	7 (6.2%)		
Cognition	Low performance cognitive ability	No	4096 (95.4%)	80 (87%)	NA	
		Yes	196 (4.6%)	12 (13%)		
	Low verbal cognitive ability	No	4113 (95.8%)	79 (84.9%)	NA	
		Yes	182 (4.2%)	14 (15.1%)		
	Low cognitive ability	No	4089 (95.5%)	81 (88%)	NA	
		Yes	191 (4.5%)	11 (12%)		
ND Conditions	ADHD	No	4962 (97%)	109 (92.4%)	6094 (96.9%)	138 (93.9%)
		Yes	154 (3%)	9 (7.6%)	192 (3.1%)	9 (6.1%)
	ASD	No	4618 (90.7%)	99 (84.6%)	6063 (96.5%)	140 (95.2%)
		Yes	474 (9.3%)	18 (15.4%)	223 (3.5%)	7 (4.8%)
	Reading difficulties	No	4537 (95.9%)	86 (88.7%)	5678 (95.8%)	118 (91.5%)
		Yes	193 (4.1%)	11 (11.3%)	250 (4.2%)	11 (8.5%)
	Motor coordination difficulties	No	3559 (95.8%)	65 (89%)	NA	
		Yes	156 (4.2%)	8 (11%)		
	Pragmatic language difficulties	No	4149 (96%)	89 (89%)	NA	
		Yes	174 (4%)	11 (11%)		
	Structural language difficulties	No	4250 (96.5%)	90 (89.1%)	NA	
		Yes	153 (3.5%)	11 (10.9%)		
	Tics	No	3167 (82.9%)	75 (89.3%)	NA	
		Yes	654 (17.1%)	9 (10.7%)		
Psychiatric Conditions	Emotional problems	No	5222 (94.4%)	120 (93.8%)	5403 (82.4%)	121 (80.1%)
		Yes	312 (5.6%)	8 (6.3%)	1154 (17.6%)	30 (19.9%)
	Conduct problems	No	5228 (94.5%)	122 (95.3%)	5783 (88.2%)	118 (78.1%)
		Yes	307 (5.5%)	6 (4.7%)	772 (11.8%)	33 (21.9%)
Social and Educational Outcomes	SEND	No	3210 (74.2%)	53 (52%)	5374 (87.8%)	117 (81.3%)
		Yes	1115 (25.8%)	49 (48%)	747 (12.2%)	27 (18.8%)
	Peer problems	No	4873 (90.3%)	113 (89%)	5452 (83.2%)	114 (75.5%)
		Yes	523 (9.7%)	14 (11%)	1103 (16.8%)	37 (24.5%)

Values are presented as *n* (%) or *n*. Percentages are calculated vertically to indicate the percentage of people with/without a CNV who endorsed each phenotype.

ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; CNV, copy number variant; MCS, Millennium Cohort Study; NA, not available; ND, neurodevelopmental; SEND, special educational needs.

[a]Cell counts <5 and corresponding percentages are not specified to maintain anonymity as required by ethics guidelines.

Table 2. Results of the Analysis in ND Copy Number Variant Carriers Versus Noncarriers in ALSPAC, MCS, and the Meta-Analysis

		ALSPAC			MCS			Meta-Analysis		
Category	Phenotype	OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Birth Complications	Preterm birth	2.23	1.17–4.27	.04	0.65	0.29–1.48	.31	1.24	0.37–4.15	.73
	Low birth weight	2.07	0.98–4.35	.08	1.70	0.97–2.99	.13	1.83	1.17–2.86	.02
	Apgar score <7	0.95	0.13–6.95	.96		NA			NA	
Early Development	Gross motor delay	2.48	1.34–4.58	.01		NA			NA	
	Fine motor delay	3.41	1.84–6.32	3.0×10^{-4}		NA			NA	
	Communication delay	1.90	0.87–4.13	.11		NA			NA	
Cognition	Low performance cognitive ability	3.13	1.68–5.85	4.9×10^{-4}		NA			NA	
	Low verbal cognitive ability	4.00	2.23–7.21	1.1×10^{-5}		NA			NA	
	Low cognitive ability	2.91	1.52–5.55	1.2×10^{-3}		NA			NA	
ND Conditions	ADHD	2.66	1.32–5.35	.01	2.09	1.33–3.28	4.4×10^{-3}	2.24	1.53–3.28	9.1×10^{-5}
	ASD	1.77	1.06–2.95	.03	1.36	0.63–2.94	.43	1.63	1.07–2.50	.02
	Reading difficulties	3.01	1.58–5.72	2.4×10^{-3}	2.15	1.20–3.85	.03	2.51	1.60–3.94	9.1×10^{-5}
	Coordination difficulties	2.81	1.32–5.95	.01		NA			NA	
	Pragmatic language difficulties	2.95	1.55–5.61	2.4×10^{-3}		NA			NA	
	Structural language difficulties	3.40	1.78–6.48	1.5×10^{-3}		NA			NA	
	Tics	0.58	0.29–1.17	.13		NA			NA	
Psychiatric Conditions	Emotional problems	1.12	0.54–2.30	.77	1.16	0.78–1.74	.47	1.15	0.81–1.64	.44
	Conduct problems	0.84	0.37–1.92	.77	2.09	1.41–3.10	4.6×10^{-4}	1.43	0.59–3.46	.44
Social and Educational Outcomes	SEND	2.66	1.79–3.95	2.3×10^{-6}	1.66	1.08–2.54	.02	2.12	1.33–3.36	3.0×10^{-3}
	Peer problems	1.15	0.66–2.03	.62	1.60	1.10–2.34	.02	1.45	1.06–1.98	.02

p Values are corrected for multiple comparisons using false discovery rate.

ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; MCS, Millennium Cohort Study; NA, not applicable; ND, neurodevelopmental; OR, odds ratio; SEND, special education needs.

likelihood of preterm birth; gross and fine motor delay; and low performance, verbal, and general cognitive ability. ND CNVs were also associated with ADHD, ASD, reading difficulties, motor coordination difficulties, and pragmatic and structural language difficulties but not with tics. ND CNV carrier status was not associated with child emotional or conduct problems. ND CNVs were associated with SEND but not with peer problems (Figure 1).

Consistent with findings in ALSPAC, carrying an ND CNV in MCS was associated with ADHD, reading difficulties, and SEND and was not associated with low birth weight or emotional problems. In contrast to ALSPAC, ND CNVs in the MCS cohort were not associated with preterm birth or ASD (parent-reported diagnosis) but were associated with conduct and peer problems (Figure 1 and Table 2).

In the meta-analysis, ND CNVs were associated with low birth weight, ADHD, ASD, reading difficulties, SEND, and peer problems (Figure 2 and Table 2). We did not find evidence of associations between ND CNVs and preterm birth or conduct or emotional problems in the meta-analysis.

Infrequent Versus Ultrarare CNVs

In ALSPAC, effect sizes were generally stronger for the ultrarare CNVs in than for the relatively infrequent CNVs, i.e., 15q11.2 deletion or duplication or 16p11.2 duplication (Figure S3 and Table S3). These differences were particularly pronounced for low cognitive ability, reading difficulties, coordination difficulties, and SEND. In MCS, effect sizes between infrequent and ultrarare CNV carriers were more comparable, with the exception of peer problems, which had a noticeably stronger association with ultrarare CNV carriers (Figure S3 and Table S4).

Deletions and Duplications

Effect sizes were generally consistent between deletions and duplications, with a few exceptions. In ALSPAC, stronger effects were observed between deletions and pragmatic and structural language difficulties and SEND than were seen between duplications and these items (Figure S4 and Table S5). In MCS, stronger associations were observed between deletions and conduct problems and SEND than for duplications and these items (Figure S4 and Table S6).

Continuously Measured Outcomes

In ALSPAC, when defining outcomes on a continuous scale, ND CNVs were associated with lower gross and fine motor skills; lower communication skills; lower performance, verbal, and general cognitive ability; and lower reading, coordination,

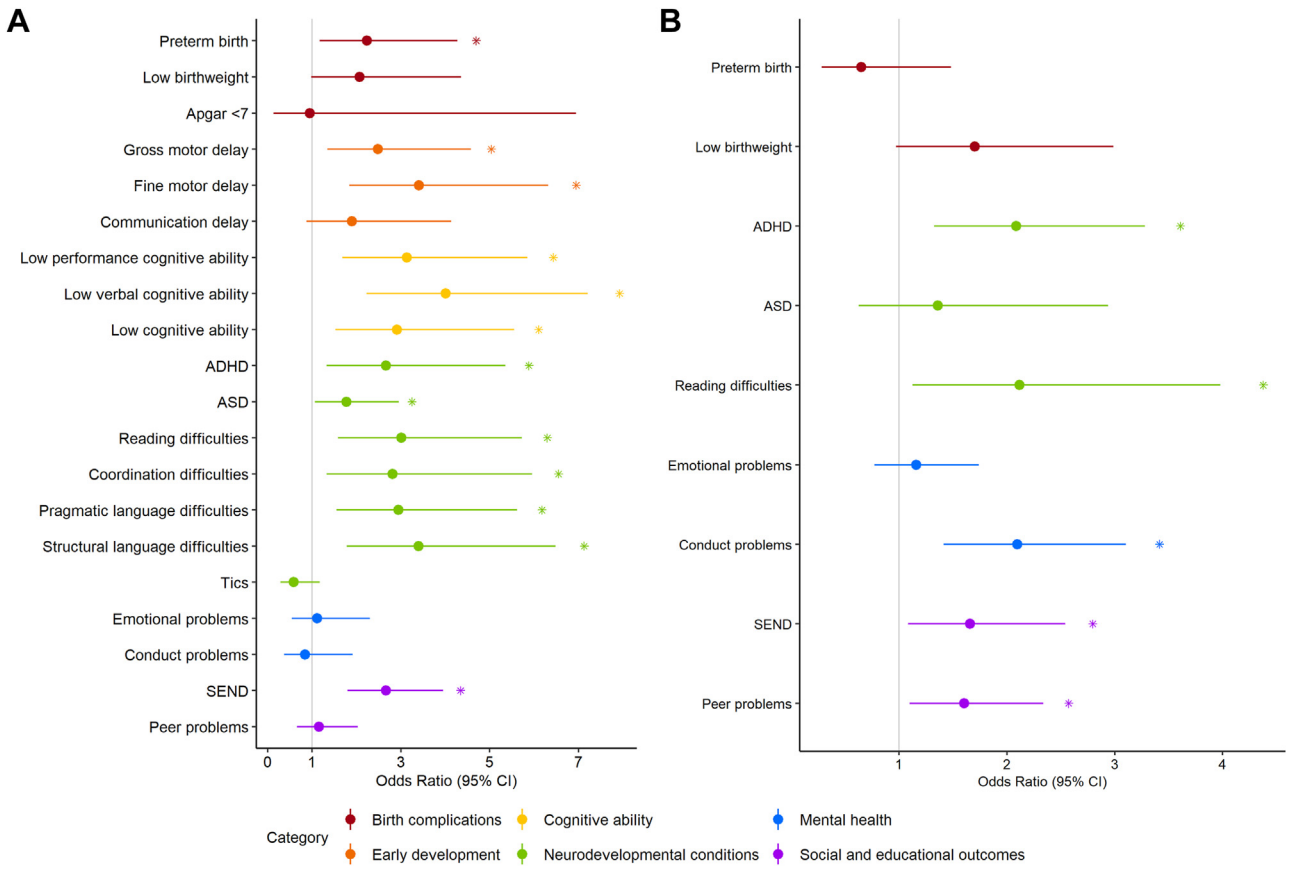

Figure 1. Results of primary analyses in ALSPAC and MCS. Odds ratios and 95% CIs for the association between each outcome and neurodevelopmental copy number variant carrier status in the **(A)** ALSPAC and **(B)** MCS cohorts. Asterisks indicate false discovery rate–corrected $p < .05$. ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; MCS, Millennium Cohort Study; SEND, special educational needs.

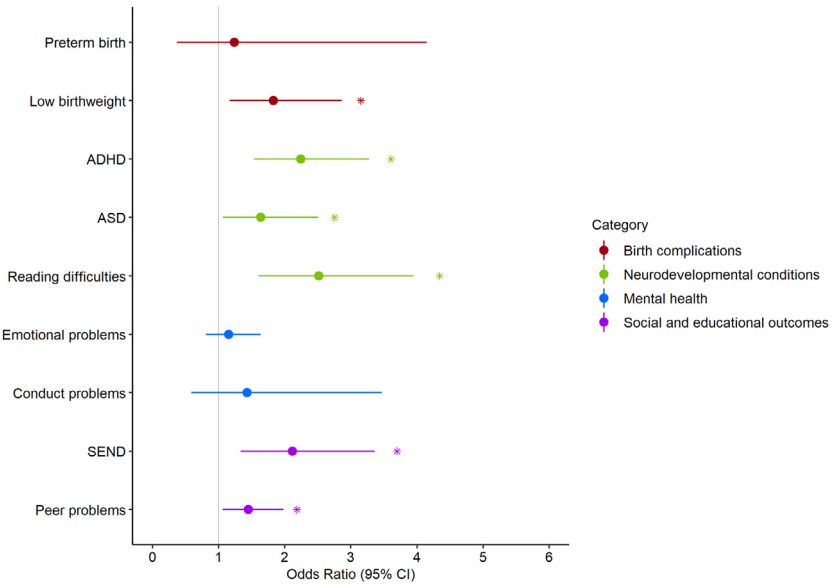

Figure 2. Results of the meta-analysis of ALSPAC and MCS. Odds ratios and 95% CIs for the association between each phenotype and neurodevelopmental copy number variant carrier status. Asterisks indicate false discovery rate–corrected $p < .05$. ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; MCS, Millennium Cohort Study; SEND, special educational needs.

and pragmatic and structural language abilities (Table S7). In MCS, when using continuous outcomes, ND CNVs were associated with lower birth weight, higher ADHD traits, and poorer reading ability (Table S8). These findings were consistent with those observed using our primary outcomes, which were defined as binary items.

Results of analyses investigating infrequent compared with ultrarare CNVs and deletions compared with duplications against continuously measured outcomes were consistent with the findings using binary outcomes (Figures S5 and S6; Tables S9–S12).

Excluding ASD, ADHD, and Low Cognitive Ability

Patterns of association were consistent when we excluded individuals with ADHD, ASD, and low cognitive ability (Figure S7 and Table S13).

Sex Differences

Sex differences were examined as a secondary analysis, and the results are presented in Figures S8 and S9 and Table S14. A significant interaction with sex was observed only for low cognitive ability in the direction of low cognitive ability being associated with ND CNVs in males but not females.

Missing Data

Carrying an ND CNV was associated with ALSPAC clinic nonattendance only at age 7 (OR = 1.62 [1.14–2.31], p = .007). Full missingness results are displayed in Figure S10 and Tables S15 and S16.

DISCUSSION

Using 2 UK population birth cohorts, we found that children carrying a known ND CNV were at a higher chance of birth complications, lower cognitive ability (tested in ALSPAC only), ND conditions, and SEND. In ALSPAC, which contained a wider range of ND measures, all broadly defined DSM-5 ND conditions except tics were associated with carrying an ND CNV. Our study provides an extensive population-wide assessment of the early impacts of CNVs in childhood and highlights a broad range of developmental indicators that may be useful for clinicians to evaluate when a CNV is suspected or genetic testing is being considered.

It is well established that ND CNVs are enriched in those who are autistic or have ADHD or intellectual disability (43,44). To date, there have been no population-based studies of ND CNVs that have focused on other DSM-5 child ND conditions including specific learning difficulties (e.g., reading difficulties) and speech and language or communication difficulties, and only a limited number of studies have investigated developmental motor coordination disorder and difficulties in ND CNV carriers (45,46). However, one volunteer population cohort of children, which examined CNVs defined differently, suggested an association with learning problems as well as ASD and ADHD (15). We observed ND CNV effect sizes in ALSPAC for communication, motor coordination, and reading difficulties (OR range = 2.81–3.40) that were similar to those for ADHD, ASD, and low cognitive ability (OR range = 1.77–4.00) and persisted even after we excluded individuals with the latter 3 conditions. However, little research has focused on the genetic underpinnings of these ND difficulties (35). In many countries, reading, coordination, and language difficulties are typically assessed and managed by therapists, psychologists, and other specialists in educational or other contexts where the possibility of examining genetic contributions, including by genetic screening, may not be considered or available. Our findings suggest that clinicians working with children and young people with a recognized CNV should consider screening for a broad range of ND difficulties, beyond ADHD, ASD, and cognitive difficulties.

While all the CNVs included in our study are rare, with a population frequency <1, some CNVs are relatively more common, namely 15q11.2 deletion, 15q11.2 duplication, and 16p11.2 duplication. Sensitivity analyses comparing these 3 relatively more common CNVs, i.e., infrequent CNVs, with noncarriers and comparing the remaining ultrarare CNVs with noncarriers suggested that the ultrarare CNVs had stronger effects on low cognitive ability, reading difficulties, coordination difficulties, and SEND in ALSPAC and on peer problems in MCS. These findings also suggest that associations in the primary analysis were not driven by the more prevalent CNVs. Similarly, deletions were associated with greater effect sizes for language difficulties in ALSPAC, conduct problems in MCS, and SEND in both cohorts. Our findings are consistent with previous research that identified stronger associations with neuropsychiatric conditions in deletions than in their reciprocal duplications (14,40), although others have not observed this effect (19).

ASD and preterm birth were significantly associated with ND CNVs in ALSPAC but not MCS, while conduct and peer problems were significantly associated with ND CNVs in MCS but not ALSPAC. These disparities may be due in part to differences in measurement and power. For example, ASD was measured using the SCDC questionnaire in ALSPAC, which captured a broader phenotype, while in MCS parents were asked whether their child had ever been diagnosed with ASD, to which only a small number of parents responded “yes.” These differences in power are reflected in the wider confidence intervals of the estimate in MCS compared with ALSPAC, despite similar effect sizes. Other differences may reflect variation in the sociodemographic makeup of each cohort and/or secular trends in these phenotypes (47).

The meta-analysis of 2 large birth cohorts afforded us greater power to detect associations between CNV carrier status and several of the phenotypes, which allowed us to overcome some limitations of study design in the literature. However, only ALSPAC included the full range of ND assessments, and some conditions (e.g., ASD, tics) were not assessed as rigorously as they are in clinical studies. Nevertheless, previous research has focused predominantly on either clinically ascertained childhood samples of those who carry a specific CNV; those with ADHD, ASD, or developmental delay; or adult-based population cohorts. Clinical samples, while invaluable for studying the clinical presentation of specific CNVs, are typically biased toward selecting individuals with more overt physical phenotypes (e.g., cleft lip), more severe ND conditions (e.g., intellectual disability), males, and specific socioeconomic and ethnic groups. Therefore, clinical studies may overestimate prevalence rates of ND conditions in CNV carriers. This was suggested by a large Danish study that

examined associations between recurrent CNVs and ADHD, ASD, and schizophrenia (19). Similarly, we found that in ALSPAC, carrying an ND CNV increased the risk of ASD by an OR of 1.77 (95% CI, 1.06–2.95), whereas research in a UK clinical sample, which used similar questionnaire methods to define ASD, reported an OR of 44.1 (95% CI, 15.3–127.5) (18). Adult population samples overcome certain biases, but some, e.g. the UK Biobank, are subject to strong ascertainment bias (e.g., higher socioeconomic status), and all adult studies are subject to survivor bias. Only a few studies have investigated nonclinical childhood samples (15–17), and there has been limited investigation of known ND loci (17). By utilizing birth cohorts, we were able to minimize the impact of survivor bias in adult samples, without the selective recruitment bias seen in clinical or volunteer samples. Nevertheless, ALSPAC is overrepresentative of individuals from higher socioeconomic classes, and genetic data are available only for individuals of European genetic ancestry. The MCS is more representative of the UK population due to targeted recruitment of individuals from ethnic minority and economically deprived backgrounds and thus provides a less biased estimate of effect size. However, fewer ND and psychiatric measures were available in MCS than in ALSPAC. Additionally, MCS did not collect DNA until age 14, and individuals with ND CNVs might have dropped out of the sample by this age, although we note that in ALSPAC, ND CNVs did not appear to strongly predict attrition other than clinic attendance at age 7.

We observed associations between various developmental phenotypes and missing genetic data and between CNV carrier status and missing data for coordination and reading difficulties. Complete case analysis may bias estimates when missingness is associated with both the outcome and exposure (48). This was true for coordination difficulties in ALSPAC and reading difficulties in MCS, which suggests that the association that we observed for these phenotypes may be attenuated. Additionally, in MCS, not having emotional problems and not having peer problems were associated with missing genetic data. For these results, nonrandom missingness might have led to inflated effect sizes.

Another limitation is that associations with clinical and social/educational phenotypes likely vary by the specific CNV. Due to limitations of sample size, in the current study, we pooled all ND CNVs into a combined measure to analyze as a group. While we conducted sensitivity analyses comparing deletions and duplications and relatively more common and ultrarare CNVs, we did not have the power to examine the effect of individual CNVs or the ability to determine whether CNVs were de novo or inherited. Thus, the findings of our study should be considered alongside clinical studies of specific CNVs. Furthermore, we defined ND CNVs on the basis of evidence from the literature (1) and the DECIPHER database (https://www.deciphergenomics.org/disorders/syndromes/list) and also to maintain consistency with other studies (10,30). It is possible that other loci are associated with ND conditions, and the strength of evidence will increase with higher-powered studies. Future research should aim to integrate new loci into our list of ND CNVs, using other databases such as ClinVar to evaluate the robustness of the evidence.

Conclusions

Our findings highlight widespread early impacts of ND CNVs on development that encompass nearly all DSM-5 ND conditions. They suggest that it may be helpful to evaluate a range of developmental indicators when considering genetic testing. Our results further highlight the need for genetics training to be extended to other types of professional groups who may work with children with CNVs, such as speech and language therapists, physiotherapists, and psychologists.

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