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# Neurodevelopmental outcomes in children and adults with Fetal Valproate Spectrum Disorder: A contribution from the ConcePTION project

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ABSTRACT

*Aim:* To describe the neurodevelopmental phenotype of older children and adults with a diagnosis of Fetal Valproate Spectrum Disorder (FVSD).

*Methods:* In this cross-sectional study, 90 caregivers were recruited and completed a series of questionnaires regarding the neurodevelopmental outcomes of 146 individuals aged 7–37 years (M = 18.1), including individuals with a formal diagnosis of FVSD ($n$ = 99), individuals exposed to Valproate but without an FVSD diagnosis ($n$ = 24), and individuals not exposed to Valproate ($N$ = 23). The mean dose of valproate exposure for individuals with an FVSD diagnosis was 1470 mg/day.

*Results:* Individuals with a diagnosis of FVSD showed significantly higher levels of moderate (43.4%) and severe (14.4%) cognitive impairment than other groups ($p$ = 0.003), high levels of required formal educational support (77.6%), and poorer academic competence than individuals not exposed to Valproate ($p$ = 0.001). Overall psychosocial problems ($p$ = 0.02), internalising problems ($p$ = 0.05) and attention problems ($p$ = 0.001), but not externalising problems, were elevated in individuals with a diagnosis of FVSD. Rates of neurodevelopmental disorders, particularly autistic spectrum disorders (62.9%) and sensory problems (80.6%) are particularly central to the FVSD phenotype. There was no evidence of a statistical dose-dependent effect, possibly due to the high mean dose of exposure having a uniformly negative impact across the sample. Individuals with FVSD had required a significant number of health and child development services.

*Interpretation:* Children and young adults with a diagnosis of FVSD are at an increased risk of a range of altered neurodevelopmental outcomes, highlighting the need for a multidisciplinary approach to clinical management across the lifespan.

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## 1. Introduction

Sodium Valproate (VPA) is an effective anti-seizure medication (ASM) (Marson et al., 2021) that has also been used in the treatment of bipolar disorder and migraine. There is now clear evidence regarding its teratogenic effects, with exposure to VPA during pregnancy being associated with an increased risk of major congenital malformations (Weston et al., 2016) and neurodevelopmental impairments (Bromley et al., 2014; Bjørk et al., 2022; Christensen et al., 2019). Fetal Valproate Spectrum Disorder (FVSD, ICD-11 LD2F.03) is a clinically recognised condition diagnosed in some individuals exposed to VPA (Clayton-Smith et al., 2019). As there is no specific physiological marker, FVSD is considered a diagnosis of exclusion. Diagnosis has historically focused on physical features, including a recognisable pattern of facial dysmorphic features, specific major and minor malformations, and functional impairments (Moore et al., 2000) but neurodevelopmental difficulties are now considered as a central part of the phenotype (Clayton-Smith et al., 2019).

Studies have demonstrated VPA exposure can alter the development of the neuronal architecture (Rice and Barone Jr., 2000) leading to later child neurodevelopmental difficulties in a number of domains, including developmental milestones (Bromley et al., 2010; Cummings et al., 2011; Meador et al., 2009), cognitive and intellectual functioning (Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Dean et al., 2002; Meador et al., 2013; Nadebaum et al., 2011), and behaviour (Dean et al., 2002; Deshmukh et al., 2016). A marked increase in risk for neurodevelopmental disorders such as Autistic Spectrum Disorder (ASD) and Attention Deficit and Hyperactivity Disorder (ADHD) has been observed (Bjørk et al., 2022; Christensen et al., 2019; Blotiere et al., 2020; Bromley et al., 2013; Christensen et al., 2013; Wood et al., 2015), as well as an increased need for educational support (Baker et al., 2015; Adab et al., 2001) and poorer educational outcomes (Elkjaer et al., 2018). A strong dose-dependent relationship has also been demonstrated by several studies, with higher dosages (e.g., doses >800 mg/d – 1000 mg/d) of VPA leading to higher levels of risk for suboptimal neurodevelopmental outcomes (Christensen et al., 2019; Bromley et al., 2010; Meador et al., 2009; Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Meador et al., 2013; Nadebaum et al., 2011; Deshmukh et al., 2016; Blotiere et al., 2020; Bromley et al., 2013; Wood et al., 2015).

Very little of this research however has focused specifically on individuals with a formal diagnosis of FVSD, instead including cohorts exposed to valproate, some of which have FVSD and others who may be unaffected. Therefore, while some characteristics may be shared, the results of previous studies do not fully represent the neurodevelopmental phenotype of individuals diagnosed with FVSD. Only two cohort studies have been conducted in patients with diagnosed FVSD to date. Moore et al., (Moore et al., 2000) carried out clinical reviews of 34 children with a diagnosis of Fetal Valproate Syndrome (FVS), defined by their physical features, aged four months to 16 years, and reported that 77% were developmentally delayed, 74% required learning support, and 77% of those aged over two years had received speech therapy. More recently, in a small cohort, Bromley et al., (Bromley et al., 2019) found high levels of additional educational needs (74%) and significantly lower levels of intellectual functioning for individuals with FVSD. These findings indicate the likelihood of a more severe presentation of neurodevelopmental difficulties in individuals diagnosed with FVSD.

There is a lack of natural history data in this population, particularly as they grow older. Extrapolation from childhood data has its limitations as the brain continues to develop into early adulthood. Increasingly complex cognitive, social and emotional demands may put further stress on developmental systems, resulting in more severe daily functioning impairments and potentially revealing novel symptoms (Adams et al., 2000). To facilitate optimum care and clinical management at each developmental stage, we first must understand how FVSD presents in adolescents and young adults.

This report is based on data collected as part of a cross-sectional pilot study to design and feasibility test routine integration of a questionnaire set, developed within the Conception project (https://www.imi-conception.eu/), for collecting long term outcomes for pregnancy pharmacovigilance. This aspect of the project aimed to understand the domains which require investigation by generating information regarding the FVSD phenotype in older children and adults.

## 2. Materials and methods

### 2.1. Study design

This was a cross- sectional, observational study, collecting primary data regarding neurodevelopmental outcomes via parent reports. The study was completed according to a pre-established protocol (EUPAS 45205). Ethical approval for this study was granted by the University of Manchester Research Ethics Committee (Ref: 2021–11,241-21,470).

### 2.2. Participants

Mothers or other primary caregivers of individuals with FVSD were recruited through advertisements on social media and through participating charities based in the UK, Ireland, New Zealand and Australia. Participants were able to complete the study on behalf of more than one child.

Participants were eligible to take part in this study if they were the mother (or other primary caregiver) of an individual with a formal diagnosis of FVSD aged 7 years or older (no upper age limit). Caregivers of individuals exposed to VPA but not diagnosed with FVSD and individuals not exposed to VPA in utero were also invited to participate to form comparison groups. No restrictions were placed on exposure to other ASMs.

### 2.3. Procedure

This study was completed online using the Qualtrics online survey platform. Participants who preferred not to participate online took part over the phone with a member of the research team. If participants did not return the completed questionnaire, they were sent a reminder email after three weeks, and then a final reminder after an additional three weeks.

### 2.4. Measures

The online questionnaire was developed in collaboration with clinical and academic partners, and with experts by experience, as part of the IMI funded ConcePTION project (https://www.imi-conception.eu/). Experts by experience highlighted the areas of health and neurodevelopment they felt were important in individuals with FVSD. The clinical and academic members also provided expert input and included experts with experience of fetal alcohol spectrum disorder. Not all individuals are within the validated age-range of certain questionnaires. The questionnaire set was selected after extensive consideration of available measures including known challenges for individuals with a diagnosis of FVSD, the importance of caregiver-report, cost, and geographical availability.

*Background Information:* Participants completed a background questionnaire to provide information regarding medication exposure (e.g., dose, timing and duration of exposure), FVSD diagnostic status, maternal health during pregnancy, and demographic factors. Caregivers were provided with the standardised EUROCAT list of malformations and indicated which had been diagnosed in their child or young person, including information regarding operations and ongoing impact to daily life. This information was reviewed by a clinical geneticist (JCS), blinded to exposure status, and malformations were categorised as major or minor (EUROCAT, 2013).

**Table 1**
Caregiver and Infant Factors.

| Caregiver Factors[a] | FVSD | | | VPA Exposed | | | Non Exposed | | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | Mean (SD) | N | % | Mean (SD) | N | % | Mean (SD) | N | % | Mean (SD) |
| **Current Age (years)** | 67 | | 48.9 (8.6) | 13 | | 50.1 (7.3) | 8 | | 49.3 (2.9) | 88 | | 49.1 (8.0) |
| **Education** | | | | | | | | | | | | |
| Up to Secondary | 14 | 20.6% | | 3 | 23.1% | | 2 | 22.2% | | 19 | 21.1% | |
| Above Secondary | 54 | 79.4% | | 10 | 76.9% | | 7 | 77.8% | | 71 | 78.9% | |
| **Household Income[b]** | | | | | | | | | | | | |
| ≥ UK Median (£31,400) | 25 | 52.1% | | 5 | 45.5% | | 2 | 25.0% | | 32 | 47.8% | |
| < UK Median (£31,400) | 23 | 47.9% | | 6 | 54.5% | | 6 | 75.0% | | 35 | 52.2% | |
| **Maternal Epilepsy** | | | | | | | | | | | | |
| Yes | 66 | 97.1% | | 12 | 92.3% | | 5 | 55.6% | | 83 | 93.3% | |
| No | 1 | 1.5% | | 1 | 7.7% | | 4 | 44.4% | | 6 | 6.7% | |
| **Maternal Seizures during pregnancy[c]** | | | | | | | | | | | | |
| No | 64 | 68.1% | | 12 | 52.2% | | 7 | 53.8% | | 83 | 63.8% | |
| Yes, Convulsive | 17 | 18.1% | | 6 | 26.1% | | 2 | 15.4% | | 25 | 19.2% | |
| Yes, Non Convulsive | 6 | 6.1% | | 1 | 4.3% | | 2 | 15.4% | | 9 | 6.9% | |
| Yes, Both | 7 | 7.1% | | 4 | 17.4% | | 2 | 15.4% | | 13 | 10.0% | |
| **Child Factors** | | | | | | | | | | | | |
| **Age (years)** | 99 | | 18.4 (7.1) | 23 | | 20.6 (6.9) | 23 | | 14.2 (5.3) | 145 | | 18.1 (7.0) |
| <10 years | 10 | 10.1% | | 1 | 4.3% | | 5 | 21.7% | | 16 | 11.0% | |
| 10–19 years | 46 | 46.5% | | 9 | 39.1% | | 15 | 65.2% | | 70 | 48.3% | |
| 20–29 years | 36 | 36.4% | | 12 | 52.2% | | 3 | 13.0% | | 51 | 35.2% | |
| 30–39 years | 7 | 7.1% | | 1 | 4.3% | | 0 | 0.0% | | 8 | 5.5% | |
| **Sex (%)** | | | | | | | | | | | | |
| Male | 54 | 54.5% | | 10 | 41.7% | | 13 | 56.5% | | 77 | 52.7% | |
| Female | 45 | 45.5% | | 14 | 58.3% | | 10 | 43.5% | | 69 | 47.3% | |
| **Plurality (%)** | | | | | | | | | | | | |
| Singleton | 91 | 91.9% | | 23 | 95.8% | | 23 | 100% | | 138 | 94.5% | |
| Twin | 7 | 7.1% | | 1 | 4.2% | | 0 | 0.0% | | 7 | 4.8% | |
| Other | 1 | 1.0% | | 0 | 0.0% | | 0 | 0.0% | | 1 | 0.7% | |
| **Gestational Age (weeks)** | 98 | | 35.6 (7.4) | 24 | | 37.4 (6.6) | 22 | | 36.6 (6.5) | 144 | | 36.0 (7.2) |
| **Birthweight (KG)** | 81 | | 3.2 (0.9) | 21 | | 3.5 (0.6) | 19 | | 3.3 (0.6) | 121 | | 3.25 (0.8) |
| **Diagnostic Group** | | | | | | | | | | | | |
| FVSD Diagnosed | | | | | | | | | | 99 | 67.8% | |
| VPA Exposed | | | | | | | | | | 24 | 16.4% | |
| Non Exposed | | | | | | | | | | 23 | 15.7% | |

[a] Restricted to 90 unique caregivers. [b] Participant income from non-UK countries converted to GBP at current exchange rate; missing data $n = 23$. [c] As this information differs between individual pregnancies, this includes data from multiple pregnancies for individual participants.

*MacArthur Health Behaviour Questionnaire (HBQ) (Essex et al., 2002):* The HBQ is a parent-report measure to assess physical health, social functioning, and academic performance in children aged 4–18 years. The following subscales were included in the current study: Neurodevelopmental Disorder Checklist (NDD), Service Utilisation Checklist, Academic Competence. The NDD and service utilisation checklists include a list of items rated as yes/no and were extended for this study to reflect common NDDs, contextually relevant healthcare services (i.e., in UK, Ireland and New Zealand), and those reported as relevant by the experts by experience and previous research (Supplementary File 1). The academic competence subscale contains 5-items rated using a 5-item Likert-scale, with a higher score indicating higher competence, as well as individual items regarding formal educational support and academic qualifications. Where individuals were no longer in school, caregivers were instructed to base their responses on past academic experience.

*Pediatric Symptoms Checklist – 17 (PSC-17) (Murphy et al., 2016):* The PSC-17 is a 17-item parent-report screening tool for current psychosocial problems in children aged 4–16 years. The measure yields a total problem score, and three subscale scores: internalising, externalising and attention problems. Higher scores indicate greater risk and a score of ≥15 on the total problems scale has been validated as indicative of overall mental health risk. Scores ≥7 indicate risk on both the attention and externalising subscales, and ≥ 5 indicate risk on the internalising subscale.

*Patient Reported Outcomes Measurement – Perceived Cognitive Function (PROMIS-PCF) (Lai et al., 2011)*: The PROMIS-PCF is an item bank that measures current everyday cognitive functioning. The full item-bank is 43 items but is designed to allow users to tailor it to specific needs without compromising the validity of the measure or output. This study used a 30-item version to reduce participant burden. The scale produces a total cognitive raw score which is converted into a standardised T-score (M = 50, SD = 10) based on a US general population sample. T-scores of <40 represent moderate cognitive impairment, scores of <30 represent severe cognitive impairment.

*Sensory Issues:* A bespoke set of questions were developed after a review of the literature regarding sensory issues in other populations. Existing measures were either aimed at younger ages or added disproportionately to participant burden. Participants were asked if the individual has current significant sensory difficulties, if they are over- or under-sensitive to sensory stimulation, and which specific stimuli they find difficult.

### 2.5. Statistical analysis

All data were analysed using SPSS 28. This study was primarily concerned with identifying the pattern of risk in individuals with a diagnosis of FVSD. Therefore, analyses focused on comparisons of FVSD group with other study groups and general population data. Data were checked for normality and the distribution of responses described in terms of mean scores and percentages. Where cut-offs were available, data were dichotomised and group differences were explored using cross-tabulations and chi-square analysis. Continuous data from the PROMIS-PCF, PSC-17 and the HBQ Academic Competence Scale were compared using ANOVA, Mann-Whitney U, or Kruskal-Wallis test statistics The HBQ NDD and Service Utilisation and the Sensory Difficulties questionnaire were examined descriptively. Dose-dependent effects in VPA monotherapy exposed individuals were explored using the

**Table 2**
ASM treatment regimen for each group.

| ASM Group, N (%) | FVSD Diagnosed | VPA Exposed | Non-Exposed to VPA |
|---|---|---|---|
| VPA Monotherapy | 72 (75.8%) | 16 (66.7%) | – |
| VPA Polytherapy | 23 (24.2%) | 8 (33.3%) | – |
| Other Monotherapy[a] | – | – | 6 (26.1%) |
| Other Polytherapy[b] | – | – | 5 (21.7%) |
| None | – | – | 12 (52.2%) |

[a] Including: Carbamazepine, Levetiracetam, Lamotrigine, Oxcarbazepine. [b] Including: Clobazam, Lamotrigine, Levetiracetam, Topiramate, Ethosuximide, Phenobarbital.

**Table 3**
Information regarding Valproate exposure for the FVSD and the VPA Exposed participant groups.

| VPA Dose (>1000) | FVSD Diagnosed | VPA Exposed | Combined |
|---|---|---|---|
| N | 57 | 9 | 66 |
| % | 60.6% | 39.1% | 56.4% |
| **VPA Whole Pregnancy (Yes)** | | | |
| N | 96 | 20 | 115 |
| % | 99.0% | 83.3% | 95.9% |
| **Dose Changed (Yes)** | | | |
| N | 24 | 10 | 34 |
| % | 25.8% | 45.5% | 29.6% |
| **Dose (g/day), M (SD)** | | | |
| Max Dose During Pregnancy | 1470.2 (694.2) | 1432.6 (1061.7) | 1462.8 (774.9) |
| 2nd Trimester | 1399.2 (716.8) | 1167.4 (1153.4) | 1353.23 (821.1) |
| 3rd Trimester | 1408.6 (676.5) | 1393.5 (1153.4) | 1405.6 (772.7) |

maximum dose during pregnancy as a continuous outcome and by splitting participants into high (>1000 mg/d) or low (≤1000 mg/d) dose groups using a median split. Sensitivity analyses investigated differences in results by age using the validated cut-off of the primary measure PROMIS-PCF (<18 vs ≥18) as the cut-off.

## 3. Results

### 3.1. Descriptive results

102 caregivers initially consented to report on 175 individuals. The final sample consisted of completed questionnaire data from 90 caregivers regarding 146 children and adults. Eighty-five caregivers were the birth mother (94.4%), two were the adoptive mother (2.2%), and there was one foster mother, one grandmother, and one father (1.1%). Seventy-one caregivers (78.9%) were educated above secondary school level, and 35 caregivers (38.9%) reported an income above the UK median (Table 1).

The mean age of the young people was 18 years 1 month (Range = 7–37 years, Mdn = 17 years 0 months) and included 77 males and 69 females (Table 2). There were 99 individuals with a formal diagnosis of FVSD, 24 who had been exposed to VPA but had not received an FVSD diagnosis, and 23 who had not been exposed to VPA. Ten of the VPA exposed group and 11 of the non-exposed group were the sibling of an individual in the group with an FVSD diagnosis. Within the group with an FVSD diagnosis, 75.8% were exposed to VPA monotherapy and 24.2% were exposed to VPA polytherapy (Table 3). In the group of individuals with a diagnosis of FVSD, caregivers reported that four (4.0%) individuals had a least one minor malformation, 11 (11.1%) individuals had at least one major malformation, and additionally 10 (10.1%) individuals had at least one minor and one major malformation.

**Table 4**
Scale and subscale scores for neurodevelopmental measures, split by group across the full sample, and split by age in the Fetal Valproate Spectrum Disorder group only.

| Scale | N | Mean | SD | Median | *p* |
|---|---|---|---|---|---|
| **Cognitive Function** | | | | | |
| Overall | 142 | 41.5 | 10.2 | 40.2 | |
| FVSD | 97 | 38.5 | 8.8 | 38.4 | 0.001[a] |
| VPA Exposed | 22 | 47.1 | 11.2 | 46.2 | |
| Non Exposed | 23 | 48.3 | 9.5 | 48.4 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 49 | 40.3 | 10.2 | 40.0 | 0.128a[a] |
| < 18 years | 48 | 36.7 | 6.9 | 36.7 | |
| **Academic Competence** | | | | | |
| Overall | 134 | 2.5 | 1.2 | 2.2 | |
| FVSD | 91 | 2.2 | 1.0 | 2.2 | 0.001[a] |
| VPA Exposed | 22 | 2.7 | 1.2 | 2.4 | |
| Non Exposed | 21 | 3.5 | 1.3 | 3.8 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 48 | 2.1 | 1.1 | 2.1 | 0.515[a] |
| < 18 years | 42 | 2.2 | 0.9 | 2.2 | |
| **Total Psychosocial Problems** | | | | | |
| Overall | 143 | 15.8 | 6.6 | 17.0 | |
| FVSD | 98 | 16.8 | 6.4 | 18.0 | 0.02[b] |
| VPA Exposed | 22 | 13.1 | 6.1 | 14.0 | |
| Non Exposed | 23 | 14.0 | 6.9 | 14.0 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 50 | 16.4 | 6.7 | 17.5 | 0.511[b] |
| < 18 years | 48 | 17.3 | 5.9 | 18.0 | |
| **Externalising Problems** | | | | | |
| Overall | 143 | 4.6 | 2.9 | 4.0 | |
| FVSD | 98 | 4.7 | 2.9 | 4.0 | 0.32[b] |
| VPA Exposed | 22 | 3.8 | 2.8 | 3.0 | |
| Non Exposed | 23 | 4.9 | 2.8 | 5.0 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 50 | 4.3 | 2.9 | 4.0 | 0.209[b] |
| < 18 years | 48 | 5.1 | 2.9 | 4.5 | |
| **Internalising Problems** | | | | | |
| Overall | 143 | 5.6 | 3.1 | 6.0 | |
| FVSD | 98 | 5.9 | 3.1 | 6.0 | 0.05[b] |
| VPA Exposed | 22 | 5.7 | 3.0 | 6.0 | |
| Non Exposed | 23 | 4.1 | 2.9 | 3.0 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 50 | 6.2 | 3.1 | 7.0 | 0.217[b] |
| < 18 years | 48 | 5.5 | 3.1 | 6.0 | |
| **Attention Problems** | | | | | |
| Overall | 143 | 5.6 | 2.8 | 6.0 | |
| FVSD | 98 | 6.2 | 2.5 | 7.0 | 0.001[b] |
| VPA Exposed | 22 | 3.7 | 2.9 | 3.5 | |
| Non Exposed | 23 | 5.0 | 2.8 | 5.0 | |
| Age (FVSD only) | | | | | |
| ≥ 18 years | 50 | 5.8 | 2.6 | 6.5 | 0.083[b] |
| < 18 years | 48 | 6.7 | 2.4 | 7.0 | |

[a] Non-Parametric Tests.
[b] Parametric Tests.

**Table 5**
Number of neurodevelopmental risk indicators within the full group of individuals diagnosed with FVSD, and in those with or without a reported malformation (major and/or minor).

| Group | | Neurodevelopmental Risk Indicators | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 |
| Overall FVSD Group | | 2.0% | 1.0% | 7.1% | 20.2% | 24.2% | 45.5% |
| Reported Malformation | Yes | 0.0% | 0.0% | 12.0% | 16.0% | 16.0% | 55.0% |
| | No | 2.7% | 1.4% | 5.4% | 21.6% | 27.0% | 41.9% |

Note: Risk indicators include PROMIS-PCF (Moderate/Severe Impairment), PSC-17 (At-risk in ≥1 subscale), Sensory Problems (Yes), Neurodevelopmental Disorders (≥1 reported diagnosis), Service Utilisation (≥1 service).

### 3.2. Neurodevelopmental outcomes

Individual domains are reported below and rates of impairment and risk in the FVSD group are provided in Table 4, for the overall sample

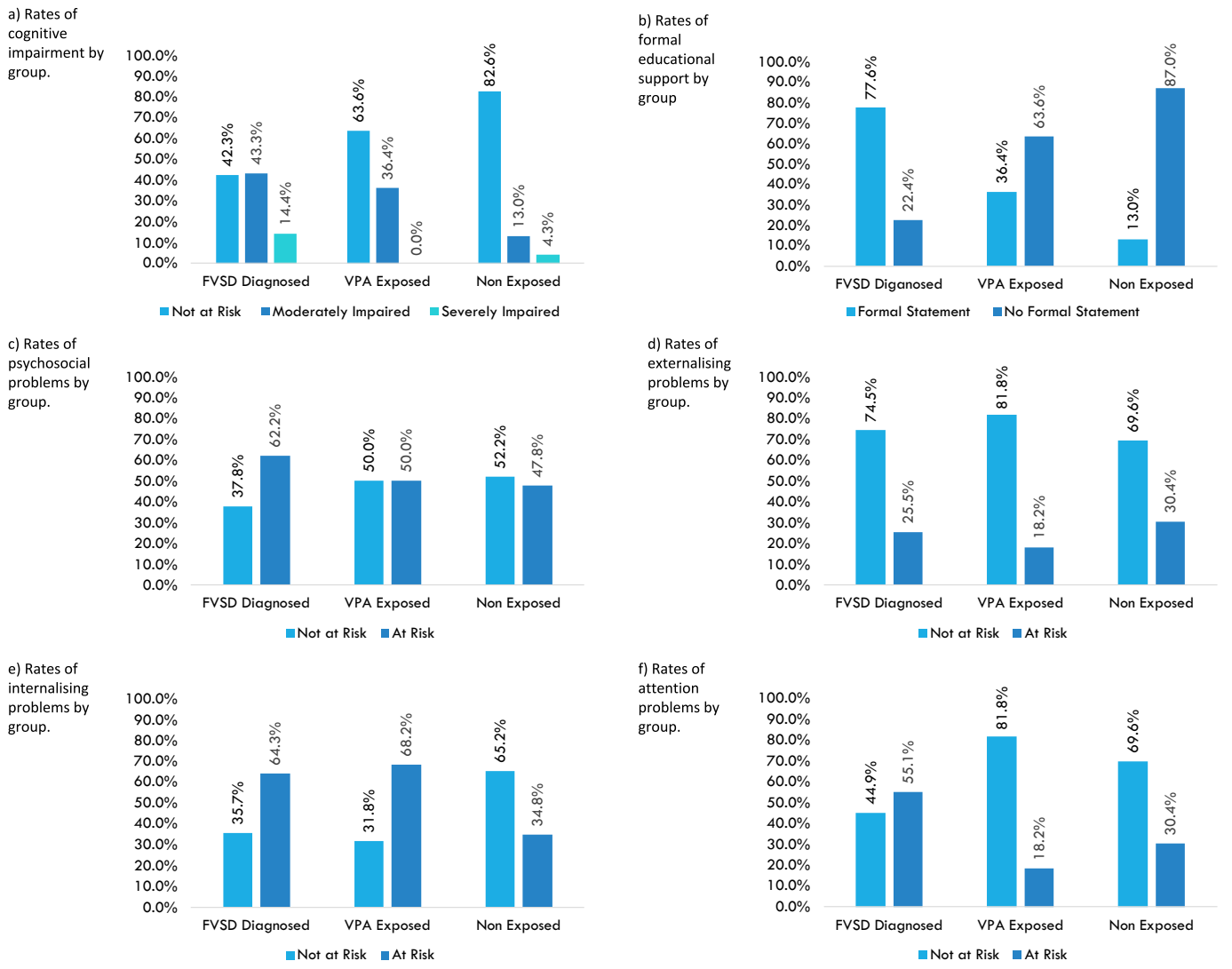



**Fig. 1.** Cognitive Development, Educational Support and Psychosocial Development.

and split according to the presence of a reported malformation.

### 3.3. Cognitive development (PROMIS-PCF)

The group mean for individuals with an FVSD diagnosis was in the "moderately impaired" range (M = 38.5, SD = 10.2) (Table 5) and was lower than both VPA exposed individuals (M = 47.1, SD = 11.2) and non-exposed individuals (M = 48.3, SD = 9.5) (H(2)) = 24.93, $p < 0.001$). Using established cut-offs, there was a significantly increased number of young people with FVSD scoring within the moderately (43.4%) or severely impaired (14.4%) ranges compared to the VPA exposed and non-exposed groups ($p = 0.003$, Fisher's Exact test) (Fig. 1a).

### 3.4. Academic functioning (HBQ)

Individuals with an FVSD diagnosis (M = 2.2, SD = 1.0) and those exposed to VPA but not diagnosed with FVSD (M = 2.7, SD = 1.2) had more academic difficulties than individuals who were not exposed to VPA during pregnancy (M = 3.5, SD = 1.3) (H(2)) = 14.06, $p = 0.001$). Consistently, there was a significant association between group affiliation and formal educational support ($x^2$ (2) = 26.56, $p < 0.001$), with 77.6% of individuals with a diagnosis of FVSD receiving a formal statement of need from the school or local authority (Fig. 1b).

### 3.5. Behavioural and emotional development (PSC-17)

Total psychosocial problems were highest for the group with a diagnosis of FVSD (M = 16.8, SD = 6.4) (F(2, 140) = 4.0, $p = 0.02$) and 62.6% of individuals in this group were classed as at-risk (Fig. 1c). Internalising problems were raised in this group (M = 5.9, SD = 3.1) (F (2, 140) = 2.9, $p = 0.05$), with 64.3% of individuals being classed as at-risk (Fig. 1d). Attention problems were also raised (M = 6.2, SD = 2.5) (F (2, 140) = 9.3, $p < 0.001$), with 55.5% of individuals in this group classed as at-risk (Fig. 1e). However, externalising problems were not raised in the FVSD group (M = 4.7, SD = 2.9) (F(2, 140) = 1.2, $p = 0.32$), with just 25% being classed as at-risk (Fig. 1f). Scale scores for the VPA exposed and non-exposed groups are reported in Table 5.

### 3.6. Sensory issues

Caregivers reported that 80.6% of individuals with FVSD experienced significant difficulties with sensory problems, in comparison to 63.6% of VPA exposed individuals, and 34.8% of non-exposed individuals (Fig. 2a). How these sensory problems were categorised and which specific difficulties were experienced are shown in Fig. 2b and c.

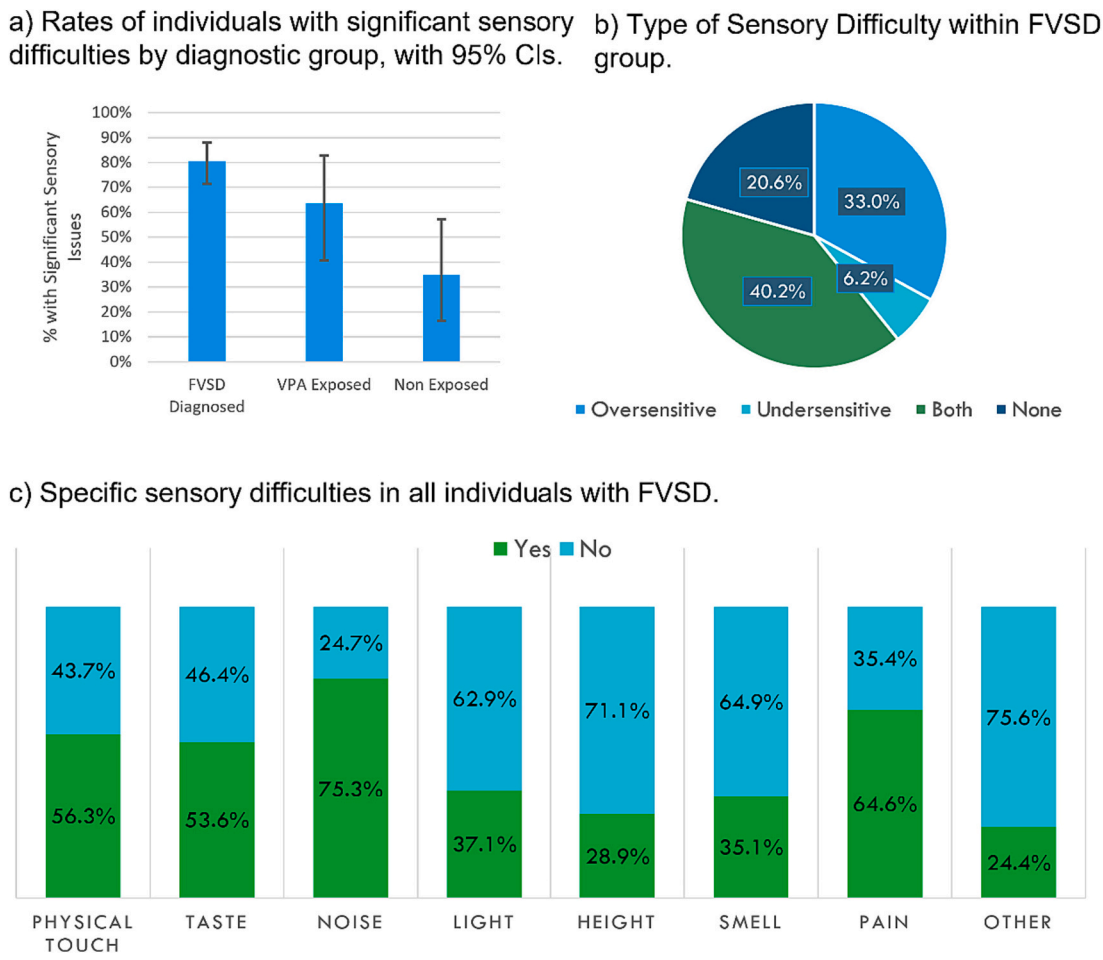



**Fig. 2.** Exploration of Significant Sensory Difficulties in Individuals with FVSD.

### 3.7. Neurodevelopmental disorders

The prevalence of many specific neurodevelopmental disorders (NDD) was considerably higher in individuals with a diagnosis of FVSD compared to current UK background rates (Fig. 3a). The only exceptions were Conduct Disorder and Oppositional Defiant Disorder which were both lower in the FVSD sample.

### 3.8. Health and child development service utilisation

There were generally high rates of health service utilisation reported by parents and caregivers of individuals with a diagnosis of FVSD (Fig. 3b). Utilisation of social care was lower than other services, as was support from the family support worker.

### 3.9. Dose -dependent associations

When the associations between maximum VPA monotherapy dose ($n$ = 86) and outcomes were examined, univariate correlations were non-significant for cognitive development (Fig. 4a) and emotional and behavioural development. However, it is observed that 88.2% of those exposed to VPA monotherapy scored below the general population mean (Fig. 4a). There was a significant but weak association between dose and Academic Competence ($r = -0.29$, $p = 0.007$), indicating that academic competence declined as dose increased.

Individuals exposed to VPA monotherapy were also stratified by High dose ($n$ = 53) and Low dose ($n$ = 33) exposure (>1000 mg/d vs =/< 1000 mg/d). There were no significant differences by dose group for cognitive development, academic functioning, behavioural and emotional problems, or neurodevelopmental disorders. Examples are provided in Fig. 4 b and c that demonstrate the lack of difference between groups for cognitive functioning and ASD diagnoses, respectively.

### 3.10. Sensitivity analyses

Sensitivity analyses were conducted to determine whether the neurodevelopmental outcomes observed in the whole group were representative of adults with FVSD (≥ 18 years). There were some small differences between age groups but these did not reach significance. For example, individuals aged ≥18 years scored 3.56 points higher on the measure of cognitive functioning than individuals aged <18 years. Overall, participants aged ≥18 years ($n = 50$) exhibited a similar pattern of impairments to the overall sample and to those <18 years ($n$ = 49) (Table 5).

Dose analyses showed no significant differences when including participants exposed to VPA polytherapy in the analyses.

## 4. Discussion

This study characterised the neurodevelopmental phenotype of older children and adults with a diagnosis of FVSD. Caregivers reported high levels of cognitive impairment, neurodevelopmental disorders, service utilisation, and sensory difficulties. Individuals with FVSD were also reported to have more academic difficulties than non VPA exposed individuals, and higher levels of psychosocial challenges, including internalising and attention problems but not externalising problems. Outcomes were not significantly different for older (≥18 years) and younger (<18 years) participants, demonstrating that substantial

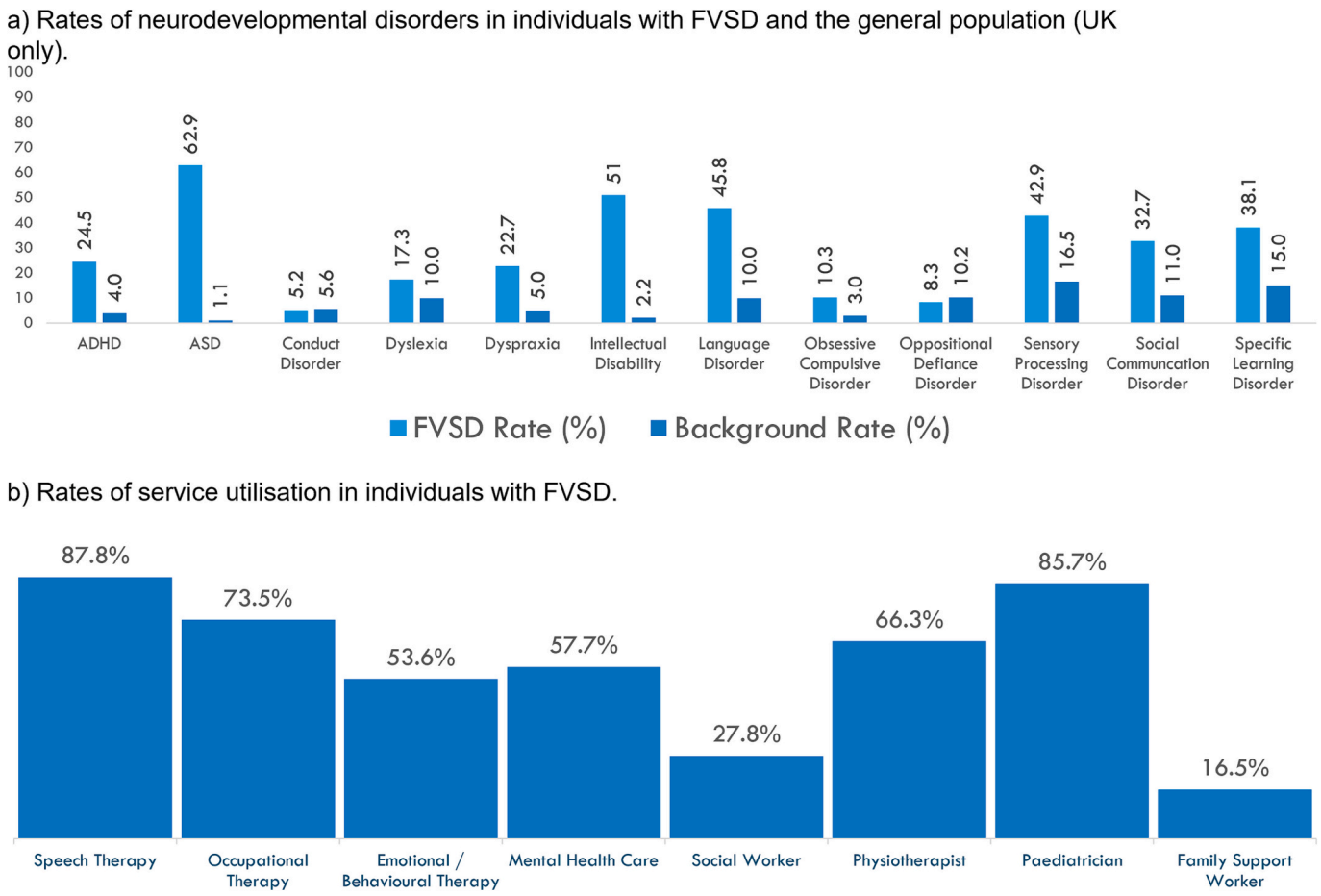



**Fig. 3.** Rates of Neurodevelopmental Delay and Service Utilisation in Individuals with FVSD.

neurodevelopmental impairment continues throughout adolescence and into adulthood for individuals with a diagnosis of FVSD.

In the present study, over half of individuals with FVSD were rated as experiencing severely or moderately impaired cognitive functioning, which was higher than the groups without a diagnosis of FVSD. This supports previous evidence of a more severe presentation of cognitive difficulties in children and young people with diagnosed FVSD than in the heterogeneous group of all those exposed to VPA but who had not been diagnosed as having the clinical syndrome (Bromley et al., 2019). Such cognitive difficulties appear to be associated with real life challenges in an education setting where participants with FVSD were rated as showing significant academic difficulties and increased rates of formalised educational support. This replicates earlier findings by Bromley et al., (Bromley et al., 2019) and Moore et al., (Moore et al., 2000) who reported, in smaller groups, similar high levels of educational support.

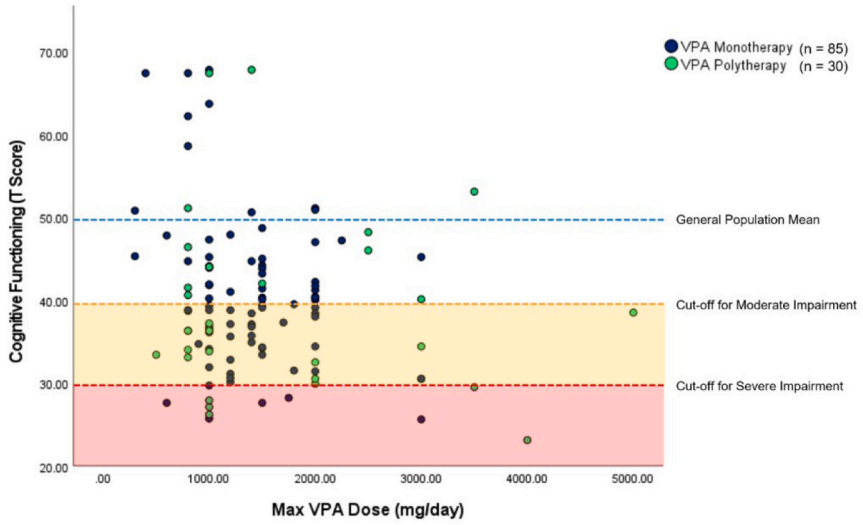
Significant sensory difficulties were more prevalent in individuals with a diagnosis of FVSD than has been found previously in the general population (80.6% vs 5–16%) (Miller et al., 2017). This is the first time this has been reported in this population. Sensory difficulties can impair the development of adaptive behaviours and impact on an individual's quality of life through their capacity to participate in education and social activities, thereby potentially limiting employment opportunities (Miller et al., 2017; Daly et al., 2022).

The prevalence of ASD in the group of individuals with a diagnosis of FVSD was extremely high (62.9%). This is roughly 60 times the rate observed in the general population, and higher than the rates generally reported in VPA exposed populations (Bjørk et al., 2022; Christensen et al., 2013). Similarly high prevalence rates were reported for intellectual disability diagnoses, language disorders, sensory processing disorder, specific learning disorder, ADHD, and dyspraxia. Utilisation rates of specialist services such as speech therapy, occupational therapy and physiotherapy were also high for the group with FVSD, as was the need for mental health care and emotional or behavioural therapy.

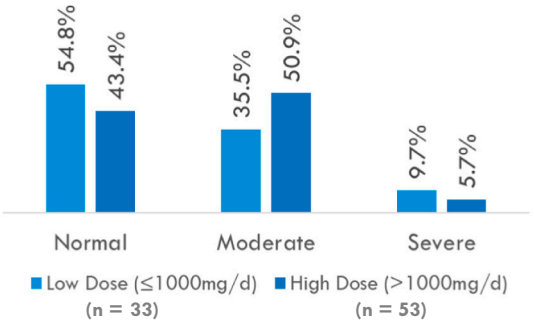
Children with a history of valproate exposure are at higher risk of neurodevelopmental difficulties (Bjørk et al., 2022; Christensen et al., 2019; Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Christensen et al., 2013; Wood et al., 2015), but it was observed here that their rate of neurodevelopmental difficulties are lower than those diagnosed with FVSD. Therefore, it is proposed that a continuum of neurodevelopmental effects is found following valproate exposure which ranges from no observable effect through to severe disruption of neurodevelopmental functioning; with those with FVSD representing the moderate to severe end of the continuum. Although it should also be noted that there may be additional unmet need in individuals exposed to VPA who have not received a diagnosis of FVSD, for whom the relative lack of service utilisation and diagnoses may reflect lack of access rather than lack of need.

Interestingly, the risk of impaired neurodevelopmental outcomes was not observed to be statistically dose-dependent in individuals with a diagnosis of FVSD, with the exception of academic competence. Lower levels of risk have been consistently reported for individuals exposed to <1000 mg/day of VPA for both congenital anomaly and neurodevelopmental risk (Bromley and Bluett-Duncan, 2021). An important distinction for the current study is that the mean daily exposure of participants with a diagnosis of FVSD was high at ~1400 mg/day. In this high dose cohort, 91.9% of individuals exposed to VPA (monotherapy and polytherapy) scored below the general population mean on the cognitive functioning scale (Fig. 4a) suggesting that the observed effect on neurodevelopmental functioning may plateau once above a critical dose level.

a) Scatterplot of Cognitive Functioning by Max VPA Dose during pregnancy.




b) Rates of cognitive impairment by VPA dose (monotherapy only)




c) Rates of Autistic Spectrum Disorder diagnoses by VPA dose (monotherapy only)

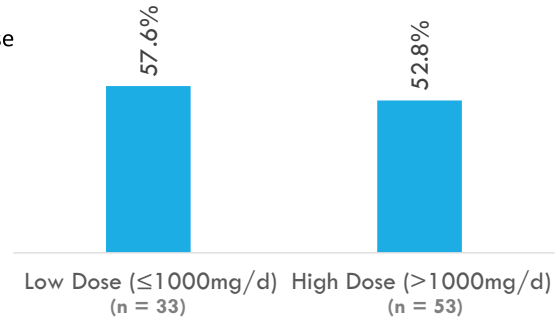



**Fig. 4.** Analysis of dose-dependent effects,
Note: 4a: Scatterplot of Cognitive Functioning by Max Valproate (VPA) Dose during pregnancy for participants exposed to VPA monotherapy and polytherapy, 4b: rates of cognitive impairment for high and low dose exposures to VPA, 4c: rates of Autistic Spectrum Disorders diagnoses for high and low dose exposures to VPA.

### *4.1. Strengths and limitations*

It was not possible to formally confirm FVSD diagnostic status, however participants were asked which professional group made the diagnosis to decrease the likelihood of inaccurate reports. Parent-report is an approach open to bias. However, caregivers are well placed to observe the difficulties faced by individuals with FVSD in daily life and most parent-report measures utilised have been shown to be valid and reliable predictors of clinical outcomes. Only the sensory difficulties questionnaire has not been validated or standardised, meaning that findings require further investigation with standardised instruments. Recall bias may also be more likely in caregivers of older individuals.

The opportunistic sampling method may have introduced bias towards more severe presentations of FVSD, but the pattern of findings reflects previous studies in FVSD and VPA exposed population. Additionally, some caregivers reported on more than one individual, potentially introducing within-family effects to the data. However, given that this is a first report of this group it was considered important to take broad inclusion criteria. The size of the control group and the small number of individuals with exposures below 1000 mg/d limited conclusions that could be drawn to a degree. Finally, a number of the measures have been validated in younger age populations (e.g., <18 years) but due to the known risk of impairment in individuals with a diagnosis of FVSD and because of limited caregiver-report tools available for older populations these tools were considered to be the most appropriate available. No age-dependent patterns were observed in the data, however future studies should consider bespoke adult and pediatric assessment batteries.

This project was designed and undertaken in collaboration with experts by experience, including parents of individuals with a diagnosis of FVSD, representing a key strength of the study (Wiering et al., 2017). This is also the largest known cohort of individuals with FVSD and a broad range of outcomes is included. As such, the data provides a valuable overview of the neurodevelopmental phenotype of FVSD in older children and adults as observed by their parents/caregivers. While these findings should be further examined with blinded characterisation, the present study provides a clear indication of the extent and diversity of challenges experienced by individuals with a diagnosis of FVSD.

### *4.2. Implications clinical management and support*

The results of this study indicate that the neurodevelopmental difficulties observed during early childhood endure throughout later childhood, adolescence and into adulthood. Around 90% of individuals with a diagnosis of FVSD were, conservatively, identified as having three or more significant neurodevelopmental symptoms (Table 5). These findings demonstrate that individuals with a diagnosis of FVSD continue to require substantial support across a wide array of areas as they age and highlight the breadth of expertise and specialist experience required to adequately support this population throughout the lifespan. This emphasises the importance of establishing networks of specialists to provide comprehensive diagnosis, clinical management, care and advice for those affected, as recommended in a recent UK government review (Cumberlege, 2020). It is additionally important that educators and employers are aware of the likelihood of these difficulties so that strategies and support can be put in place to provide individuals with the best opportunity to participate in society, reach their potential, and enjoy a higher quality of life.

While further investigation is required to understand the correlation between physical features of the syndrome and neurodevelopmental outcomes, this range of difficulties appears to be experienced both with and without accompanying major congenital malformations (Table 5), indicating that an apparent lack of physical effects should not preclude further neurodevelopmental assessment and referral.

## 5. Conclusions

Children and young people with a diagnosis of FVSD are at an increased risk of a range of altered neurodevelopmental outcomes, including cognitive, sensory, emotional, and behavioural functioning, which are pervasive into the adult years. While the presence of physical symptoms or a higher dose may increase the risk of difficulties, the current results demonstrate that neurodevelopmental effects may plateau above a certain level of exposure and are not exclusive to those with a major structural anomaly. A multidisciplinary focus is required for the clinical management of children and adults with FVSD.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Rebecca L. Bromley reports a relationship with UCB Pharma that includes: consulting or advisory. Laura M. Yates reports a relationship with Sanofi Genzyme South Africa that includes: consulting or advisory.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ntt.2023.107292.

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