

# OHE



## Individual, Health System, and Societal Impacts of Anti-seizure Medicine Use During Pregnancy

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JANUARY 2024

Nadine Henderson  
George Bray  
Chris Skedgel

Commissioned by  
**epilepsy  
society**



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**Nadine Henderson**

Office of Health Economics, London

**George Bray**

Office of Health Economics, London

**Chris Skedgel**

Office of Health Economics, London

OFFICE OF HEALTH ECONOMICS  
RESEARCH

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**Corresponding Author:**

Nadine Henderson  
[n.henderson@ohe.org](mailto:n.henderson@ohe.org)

For further information, please contact the Epilepsy Society:

**Nicola Swanborough**

Head of External Affairs

**Tel** +44 (0)7876834122

**Email** [nicola.swanborough@epilepsysociety.org.uk](mailto:nicola.swanborough@epilepsysociety.org.uk)

**Nathan Draper**

Policy and Public Affairs Manager

**Tel** +44 (0)7394566224

**Email** [nathan.draper@epilepsysociety.org.uk](mailto:nathan.draper@epilepsysociety.org.uk)



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This report concerns epilepsy, pregnancy, and the potential risks to the foetus from anti-seizure medications and is for women, non-binary and trans people who experience pregnancy. Within this document we use the terms woman and mother. However, it is important to acknowledge that it is not only women who need to navigate the complex decisions related to epilepsy and pregnancy. Provision of information on the topic must therefore be appropriate, inclusive, and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

More resources:

1. <https://www.rcm.org.uk/media/6225/inclusivity-statement.pdf>
2. <https://www.rcm.org.uk/news-views/rcm-opinion/2022/inclusive-language-in-maternity-care-to-address-inequalities/>

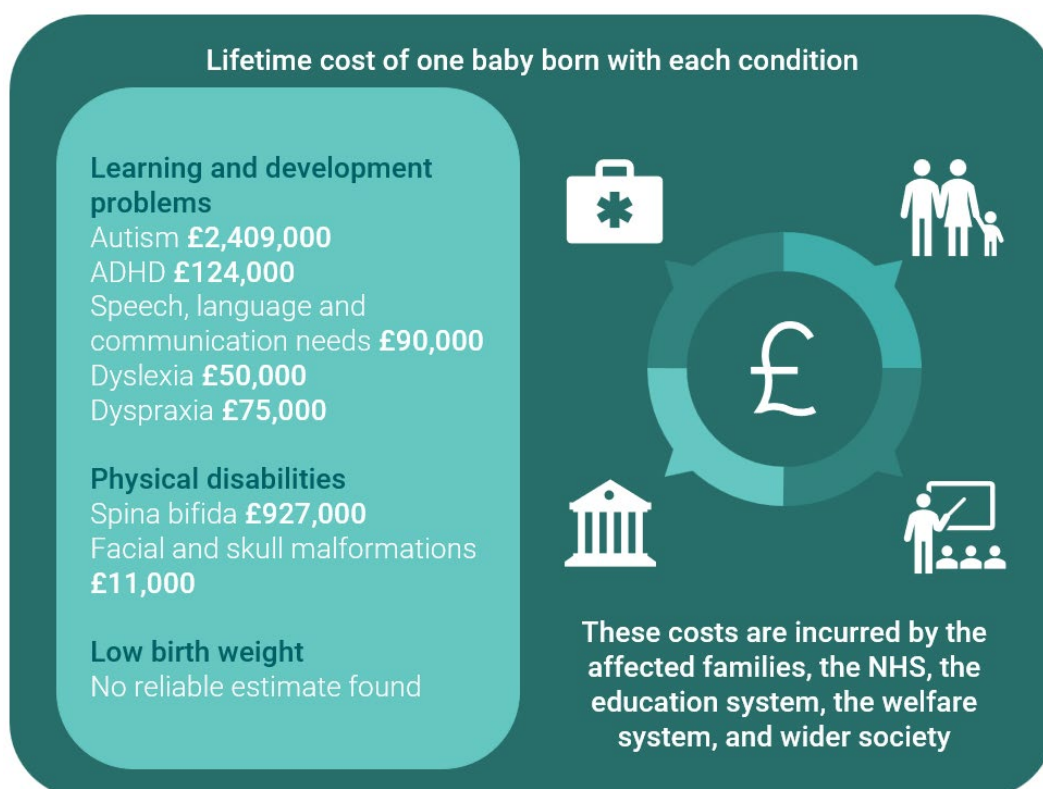
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# Executive Summary

Epilepsy is a chronic, neurological disorder characterised by spontaneous and recurrent seizures, which are a sudden onset of abnormal electrical activity in the brain that temporarily affects how it works. One of the most common ways of treating epilepsy is using medicines called anti-seizure medicines (ASMs). These can control seizures for two thirds of people with epilepsy. However, research has found that some ASMs can harm an unborn baby if the mother is taking them during pregnancy. The risks of ASMs as a class of medicines are well recognised but the specific risks of individual ASMs are much less well-understood, with some ASMs having significantly higher risks than others. Valproate, in particular, is acknowledged to have the highest risks, with up to 4 in 10 babies at risk of developmental disorders and up to 1 in 10 at risk of physical birth abnormalities. It is estimated that around 2,500 babies exposed to ASMs *in utero* are born each year, each of them at risk of physical and developmental abnormalities.

We conducted a targeted review of the literature to identify studies showing an association between *in utero* exposure to ASMs and the risk of a specific condition. The identified conditions included developmental problems such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), speech, language and communication needs (SLCN), dyslexia and dyspraxia, as well as physical abnormalities such as face or skull malformations and spina bifida. On the basis of this review, we estimated the lifetime cost per case of these conditions for affected individuals and their families, the NHS, and broader society.



These conditions were estimated to be associated with substantial lifetime costs per case to the NHS, other government sectors, the affected individuals, and their families, especially in the cases of ASD and spina bifida. These costs included medical care (medication, surgery and physiotherapy), additional educational support, social care, welfare payments, as well as out-of-pocket expenses and productivity losses to affected children and their families. Our findings suggest the aggregate costs associated with *in utero* exposure to ASMs during pregnancy are significant. There are also non-monetary impacts including decreased quality of life and loss of leisure time.

However, given the lack of detailed risk information for each ASM and its use in the UK, it is not possible to quantify the overall economic impact. The current literature on increased risks is based on studies that focus on, or include, valproate. The unacceptable risks associated with valproate are recognised and it is specifically discouraged for women of child-bearing age. Utilising estimates from such studies may therefore overestimate the ASM-attributable cases and subsequently costs of each condition. Despite lamotrigine and levetiracetam being deemed safer for use by the MHRA and recommended by the NHS, limited data is available regarding their impact on developmental conditions. These evidential limitations substantiate the call for evidence to be generated that accurately captures the elevated risks, and subsequently facilitates the estimation of the aggregate economic impact. We provide three recommendations necessary to enable the calculation of such a figure:

- I. Prescription rates of ASMs currently used by women of childbearing age**
- II. Detailed risk profiles of *in utero* exposure to these ASMs in terms of physical disabilities, neurodevelopmental problems, and low birth weight**
- III. Incidence of co-morbid conditions in the affected population if different from general population**

Highlighting the scale of the overall societal and economic impact can help target funding towards research that improves the outlook for those impacted by the adverse effects of ASMs *in utero*.

# 1 Background

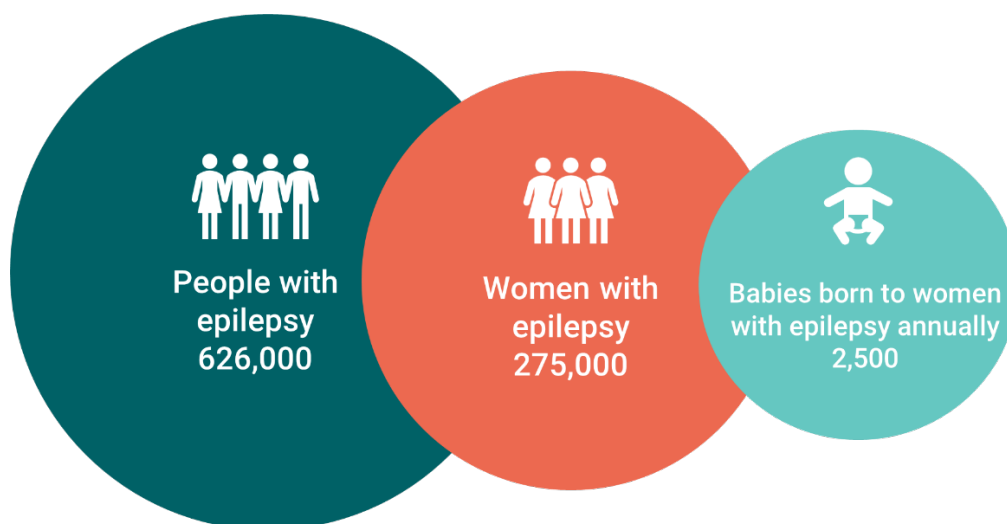
The aim of this report is to describe the socioeconomic impact of exposure to anti-seizure medication (ASMs) *in utero*, by estimating the financial impacts of associated risks for affected individuals and their families, the National Health Service (NHS), government, and wider society.

In the following sections, we provide background on epilepsy and the potential risks of *in utero* exposure to ASMs, describe the literature review we conducted to identify potential health consequences of exposure, and finally, we present estimates of the financial impacts of these consequences.

## Scale of epilepsy and *in utero* exposure to ASMs

Epilepsy is a chronic, neurological disorder characterised by spontaneous and recurrent seizures, which are a sudden onset of abnormal electrical activity in the brain that temporarily affects how it works (NHS, 2017a). These seizures can be associated with physical, cognitive, emotional or sensory symptoms. Epilepsy refers to a group of many ‘different’ epilepsies, which differ according to the cause and which part of the brain is affected. Causes include genetics, a structural change in the brain or underlying conditions. Epilepsy is usually a lifelong condition but many people with it are able to lead fulfilling lives if their seizures are well controlled.

It is estimated that epilepsy affects around 626,000 people in the UK, which is around 1 in every 100 people (Wigglesworth et al., 2023). Around 275,000 women in the UK have epilepsy and approximately 2,500 babies are born to women with epilepsy each year (Epilepsy Action, 2023; MHRA, 2021c).



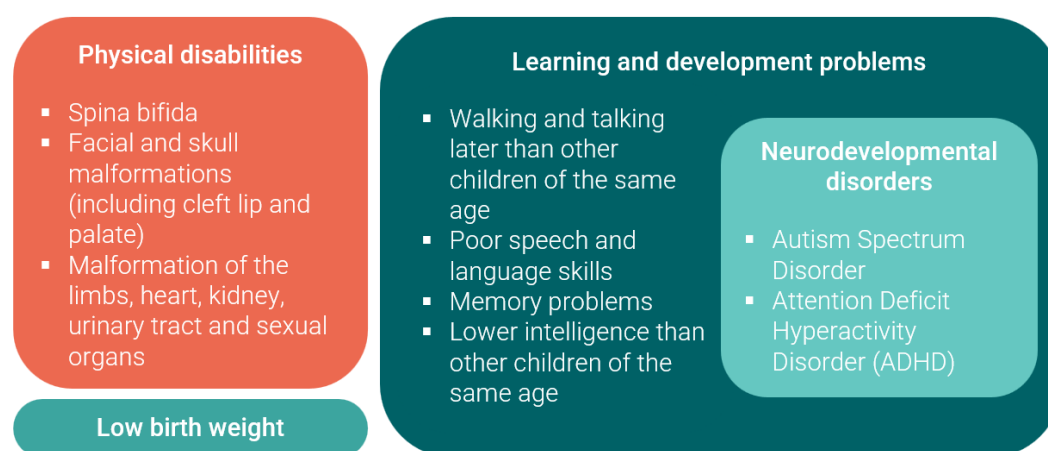
**FIGURE 1: PREVALENCE OF EPILEPSY IN THE UK**

## Risks associated with ASMs in epilepsy

One of the most common ways of treating epilepsy are medicines called anti-seizure medicines (ASMs). These can help most people have fewer seizures, and up to 70% of people could stop having seizures once the right medication regime has been established. However, this leaves approximately between 30-40% of patients with uncontrolled epilepsy as their condition fails to respond to ASMs (Laxer et al., 2014). They may also be used for various psychiatric conditions, such as in the case of valproate for bipolar disorder (Branford, Sun and Shankar, 2023).

Research has found that some ASMs can harm an unborn baby if the mother is taking them during pregnancy (Gedzelman and Meador, 2012). The risks of ASMs as a class of medicines are well recognised but the specific risks of individual ASMs are much less well-understood. Some ASMs have significantly higher risks than others. Valproate, in particular, is generally acknowledged to have the highest risks, with up to 4 in 10 babies at risk of developmental disorders, and up to 1 in 10 at risk of physical abnormalities (MHRA, 2021d).

Our review of the literature suggests that potential physical disabilities associated with ASMs include spina bifida, facial and skull malformations such as cleft lip or palate, malformations of the limbs, heart, kidney, urinary tract and sexual organs. Children exposed to valproate, and potentially other ASMs, *in utero* have an increased risk of autism and attention deficit hyperactivity disorder (ADHD). Some ASMs, particularly valproate, are also associated with potential developmental problems including delays in learning to walk and talk, lower intellectual abilities than other children of the same age, poor speech and language skills, and memory problems (Epilepsy Society, 2021).



**FIGURE 2: PHYSICAL DISABILITIES AND DEVELOPMENTAL PROBLEMS POTENTIALLY ASSOCIATED WITH *IN UTERO* EXPOSURE TO ASMs**

According to Robson et al. (2020), concerns around the risks of valproate during pregnancy were present when it was first licensed in 1972. However, it was not until 2018 that the Medicines and Healthcare Products Regulatory Agency (MHRA) published guidelines stating that valproate must not be used in any woman or girl able to have children unless there is a pregnancy prevention programme in place (MHRA, 2021d). More recently, the MHRA extended restrictions on valproate, instructing that it must not be started in any patient younger than 55 years, male or female, unless two specialists confirm there are no other treatment options or there are compelling reasons that reproductive risks do not apply. For women currently taking valproate and at risk of becoming pregnant, an annual specialist review will be undertaken to assess whether continuation is



appropriate, with a similar process being introduced for men at a later date. These recommendations are due to take effect in 2024 (MHRA, 2023a).

It has been estimated that up to 20,000 children may have been harmed as a result of the failure to communicate these risks to people with epilepsy (IMMDS Review, 2020). The Cumberlege Review was an independent review commissioned by the government to investigate three “public health scandals”, including valproate. Their report, titled “First Do No Harm”, detailed the impact of valproate on affected families and set out recommendations to improve the support and prevent further harm from ASMs (IMMDS Review, 2020).

Following an MHRA comprehensive safety review of anti-seizure medication in pregnancy, lamotrigine and levetiracetam were found to be safer to use and are recommended by the NHS (MHRA, 2021a). Other ASMs, however, including carbamazepine, phenobarbital and topiramate, are believed to be associated with an elevated risk of physical birth abnormalities compared to the general population, but evidence around the safety of these medicines is limited. For other ASMs, there is not the data to say whether they are safe or not.

In July 2022, the MHRA initiated a new safety review into topiramate as a result of an observational study reporting an increased risk of developmental disabilities in children whose mothers took topiramate during pregnancy (MHRA, 2023b; Bjørk et al., 2022). In September 2023, the European Medicines Agency implemented new guidelines that recommended to “avoid exposure of children to topiramate-containing medicines in the womb”. Research has also shown that there is a 2- to 5-fold increase in the risk of cleft lip or cleft palate in infants born to mothers who used topiramate in early pregnancy (Hernandez-Diaz et al., 2018). The use of topiramate during pregnancy has been associated with a low birth weight in 9.8% of children exposed to the drug before birth (Epilepsy Foundation, 2023).

Whilst the latest data show that while prescribing of valproate has declined substantially in girls and women of childbearing age, including during pregnancy, a number of babies continue to be exposed. Furthermore, topiramate is among the ASMs prescribed for epilepsy in women younger than 55 years of age, including during pregnancy.

There are many other ASMs for which information on their risks in pregnancy is lacking, meaning the risk of harming a baby cannot be confirmed or ruled out. In particular, MHRA specifically noted that there is not enough information to make any conclusions on safety of the following medicines during pregnancy: brivaracetam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, rufinamide, perampanel, primidone, tiagabine and vigabatrin (MHRA, 2021b).

**TABLE 1: SUMMARY OF RISKS ASSOCIATED WITH ASMS USING INFORMATION FROM THE MHRA REVIEW OF SAFETY (MHRA, 2021B)**

Anti-seizure medication	Risk during pregnancy	Risk of physical abnormality	Risk of impaired development of the brain	Risk of low growth in the womb
<b>Valproate</b>	High	about 10 out of 100 babies	about 30 to 40 out of 100	Exact risk unclear
<b>Phenobarbital</b>	High	6 to 7 out of 100	May have difficulties with learning and thinking. Exact risk is not known, not as high as valproate.	Increased risk of the baby being born smaller than expected.
<b>Phenytoin</b>	High	about 6 out of 100 babies	May have difficulties with learning and thinking. Exact risk is not known, not as high as valproate.	An increased risk cannot be ruled out due to limited data
<b>Carbamazepine</b>	High	4 to 5 out of 100 babies	Available information does not suggest an increased risk	An increased risk cannot be ruled out due to limited data
<b>Topiramate*</b>	High	4 to 5 out of 100 babies	More data needed	Increased risk of the baby being born smaller than expected.
<b>Pregabalin**</b>	High	Exact risk unclear	More data needed	An increased risk cannot be ruled out due to limited data
<b>Gabapentin</b>	Unknown	Exact risk unclear	More data needed	An increased risk cannot be ruled out due to limited data
<b>Clobazam</b>	Unknown	An increased risk cannot be ruled out due to limited data	More data needed	More data needed
<b>Zonisamide</b>	Unknown	More data needed	More data needed	Increased risk of the baby being born smaller than expected.

<b>Lamotrigine</b>	Low	Information supports that it does not increase the risk of physical birth abnormalities compared with the general population.	An increased risk cannot be ruled out due to limited data	Information supports use during pregnancy. Does not increase the risk of the baby being born small for gestational age
<b>Levetiracetam</b>	Low	Information supports that it does not increase the risk of physical birth abnormalities compared with the general population.	An increased risk cannot be ruled out due to limited data	Information supports use during pregnancy. It does not increase the risk of the baby being born small for gestational age

*\* New MHRA safety review as of July 2022. \*\*MHRA updated drug safety in April 2022 after reviewing a new study.*

Furthermore, there is also evidence to suggest that exposure to polytherapy in early pregnancy, where more than one ASM is used at a time, is associated with an increased risks of major congenital malformations compared to monotherapy, where only one drug is used at a time (Harden et al., 2009). These interactions further complicate our understanding of the safety of ASMs in pregnancy.

An Australian study found evidence to suggest that women whose last pregnancy resulted in a foetal malformation have a substantially increased risk of having further malformed foetuses if they become pregnant again while taking the same ASM, particularly valproate (Vajda et al., 2013).

Stillbirths or miscarriage are also slightly more common in infants born to mothers with epilepsy, although the absolute risk is still relatively low. Stillbirths or miscarriage occur in 1.7% of pregnancies in women exposed to ASMs, which is 2 to 3 times higher than in women without epilepsy (Epilepsy Foundation, 2023). The reason for the greater risk is unclear but it appears to be related to the mother's seizure control: the more uncontrolled the mother's seizures, the higher the infant mortality rate (Epilepsy Foundation, 2023). It is unclear whether exposure to ASMs has a direct impact on the rate of stillbirths and miscarriages.

It is also worth noting that some of the potential physical abnormalities associated with ASMs may be detected by prenatal screening, prospective parents may choose to terminate a pregnancy based on the result. Despite this decision, it is likely the quality of life of prospective parents will be affected, due to the resulting grief, isolation and shock (Blakeley et al., 2019). Furthermore, some women with epilepsy may choose not to get pregnant because they deem the risk either to their ability to control their epilepsy or of the ASM on physical abnormalities and neurological conditions to be too high. Involuntary childfree status can also be associated with a significant welfare loss for a couple (Skedgel et al., 2023). However, no information was found relating to terminations of pregnancies or involuntary childfree status among people with epilepsy.



## Awareness of risks among women and girls with epilepsy

In 2022, Epilepsy Society, Young Epilepsy and Epilepsy Action conducted a survey of women and girls with epilepsy to ask them about the information they have received around the risks of taking certain anti-seizure medication during pregnancy and how well they feel this information is being communicated to them (Epilepsy Society, Young Epilepsy and Epilepsy Action, 2023).

The results showed that a third (33%) of women and girls taking anti-seizure medications such as topiramate, carbamazepine, phenobarbital, phenytoin or pregabalin, were not aware these drugs increased the risk of physical birth abnormalities if taken during pregnancy. Furthermore, 53% of the women surveyed under the age of 24 were unaware of the potential risks related to these medications.

Awareness of the risks linked to valproate seems to have improved, with data showing that only 9% of respondents were unaware of the risks of taking valproate during pregnancy, compared with 18% in a previous 2017 survey, and 17% in 2019.

However, it remains vital that communication continues to be improved when it comes to this drug, as research shows that up to 40% of babies exposed to valproate in the womb are born with physical or developmental disabilities.

## 2 Identifying congenital abnormalities associated with *in utero* exposure to ASMs

We conducted a targeted review of the literature to identify studies showing an association between *in utero* exposure to ASMs and the risk of a specific condition, which includes a brief discussion on the quality of life impacts of the conditions. On the basis of this review, we estimated the lifetime cost per case of the included conditions for affected individuals and their families, the NHS, and broader society. The methodology for calculating these estimates is described in the next section.

We do not estimate potential QALY losses for each condition due to many conditions lacking relevant utility data across the course of an affected individual's lifetime and the lack of evidence across conditions using consistent, comparable measures of health-related quality of life (HRQoL). The scope of this paper, therefore, predominantly concerns the economic impact associated with these conditions.

### i. Autism Spectrum Disorder

Autism spectrum disorder (ASD or autism) is a lifelong neurological and developmental disorder that affects how people interact with others, communicate, learn and behave (National Institute of Mental Health (NIMH), 2023). Autism is a spectrum, some people with autism need little or no support whereas others may need help from a parent or carer every day (NHS, 2022).

A Swedish study found that the average life expectancy for autistic individuals with and without intellectual disabilities was 39.50 and 58.39 years, respectively, compared to a population average of 70.20 (Hirvikoski et al., 2016). However, it should be noted the sample of ASD patients may have been disproportionately severe, owing to the sample only including individuals who had been in contact with clinical psychiatry services. There are also HRQoL impacts as shown by a Dutch study that found the mean EQ-5D utility scores for children with ASD were significantly lower than population norms (0.67 compared to 0.94) (ten Hoopen et al., 2020). A systematic review of adults on the autism spectrum found that quality of life is lower than that of typically developing adults when using generic measures of quality of life, illustrating that the detrimental effects of ASD can persist into adulthood (Ayres et al., 2018).

In a study of 4.5 million children from Nordic population-based cohort data, for children of mothers with epilepsy who were not exposed to ASMs, 1.5% had ASD by 8 years old; in the same age children of mothers exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD (Bjørk et al., 2022).

### ii. Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a condition that affects people's behaviour. People with ADHD can seem restless, may have trouble concentrating, and may act on impulse (NHS, 2018). In a study of ADHD adults in the UK, quality of life as measured by EQ-5D utility scores was lower

than the UK population norms (0.74 compared to 0.86) (Joseph et al., 2019). ADHD is also associated with poorer physical and mental health outcomes and impaired work performance (Brook et al., 2013).

Prenatal exposure to topiramate is associated with ADHD (Adjusted Hazard Ratio (aHR) of 2.38) and exposure to levetiracetam is associated with ADHD (aHR: 1.78) and anxiety (aHR: 2.17) (Dreier et al., 2023).

### iii. Speech, Language and Communication Needs

Speech and language disorders include a broad range of conditions relating to a person's ability to create or form speech sounds, or difficulties with expressive or receptive language (Kaneshiro, 2022). Without necessary support, speech, language and communication needs (SLCN) can have long-term implications on children's academic attainment, self-esteem and emotional development. Children with developmental language disorder (DLD) have lower quality of life than their peers at 9 years of age. Their quality of life declined between 4 and 9 years, in contrast to their peers (Eadie et al., 2018).

Exposure to ASMs during pregnancy is associated with an adjusted odds ratio of 2.88 for language impairment at 8 years old (Nilsen Husebye et al., 2023).

### iv. Other Learning Disorders

Exposure to ASMs during pregnancy is also associated with other learning disorders and development problems, such as dyslexia, dyspraxia, memory problems and lower intelligence than other children of the same age (Bech et al., 2018).

Bjørk et al. (2022) found that the risk of intellectual disability in unexposed children of mothers with epilepsy is 0.8% compared to 3.1% and 2.4% in those exposed to topiramate and valproate monotherapy *in utero*.

### v. Spina Bifida

Spina bifida is a type of neural tube defect (NHS, 2017b). The neural tube is the structure that eventually develops into the baby's brain and spinal cord. In spina bifida, part of the neural tube does not develop or close properly, leading to defects in the spinal cord and bones of the spine (vertebrae). Spina bifida can be treated surgically, either whilst the baby is still in the womb or soon after birth. However, any nerve damage already present cannot be reversed and children born with spina bifida may also require physiotherapy, occupational therapy, further surgery to treat bone and joint problems and treatment for bladder or bowel problems (NHS, 2017b).

Spina bifida has a mean life expectancy of 40 years, with 1 in 3 dying before the age of 5 (Oakeshott et al., 2010). Murray et al. (2015) find evidence that children and adolescents with spina bifida are at risk for clinically reduced HRQoL, and it is possible that such trends will continue into adulthood. Grosse et al. (2008) utilised a utility score of 0.55 for children and adolescents with spina bifida when conducting an economic evaluation for a neural tube defect prevention programme. This evidence highlights the severity of spina bifida and the associated challenges of living with such a condition.

According to Gedzelman and Meador (2012), the risk of spina bifida is increased for valproate (12.7 times) and carbamazepine (2.6 times).

## vi. Low Birth Weight

Low birth weight is defined by the World Health Organisation (WHO) as weight at birth of less than 2500 grams (WHO, 2023). Low birth weight is caused by intrauterine growth restriction, prematurity or both. It contributes to a range of poor health outcomes; for example, it is closely associated with foetal and neonatal mortality and morbidity, inhibited growth, and cognitive development, and non-communicable diseases later in life. A systematic review of the quality of life of children born with very low birth weight found that school-aged children had lower health utility scores compared to their peers, but there is also evidence to suggest the impact on quality of life diminishes over time (Zwicker and Harris, 2008).

The relative risk of small for gestational age status (SGA) for infants exposed to ASMs was 2.0 (Hernández-Díaz et al., 2017). Within users of ASMs in monotherapy, the prevalence of SGA ranged from 7.3% for lamotrigine to 18.5% for topiramate, compared to a baseline for women without epilepsy without exposure to ASMs.

## vii. Face or Skull Formation Disorder

Facial and skull malformations are deformities that affect a child's head and facial bones, which commonly include cleft lip and palate, where the upper lip or facial bones are split (Boston Children's Hospital, 2023). There is limited evidence on the impact of cleft lip or palate on quality of life in the UK, possibly due to the availability of specialist treatments centres and surgical repair.

Werler et al. (2011) found an adjusted odds ratio of 4.4 for oral clefts in children exposed to valproate. Similar results are found for exposure to topiramate, with a prevalence ratio of 5.4 compared to infants of women with similar medical profiles (Mines et al., 2014).

## viii. Malformation of Organs

Exposure to ASMs *in utero* is linked with malformations of the skeleton, limbs, heart, kidney, urinary tract and sexual organs (Weston et al., 2016). Malformation of organs encapsulates many conditions so identifying an overall quality of life estimate is challenging, with the evidence base focused on more specific conditions. For example, Abassi et al. (2020) found the HRQoL for children with congenital heart disease was similar to controls. Given the wide range of potential malformations and lack of evidence on incidence and severity of those malformations, we were unable to quantify the monetary impact of this category.

The relative risks of ASMs on malformations range from 2.01 for carbamazepine to 5.69 in valproate, when compared to children born to women without epilepsy (Andrade, 2018).

## ix. Miscarriage

Whilst, this report focuses on the risks to children exposed to ASMs *in utero*, there is reason to believe that pregnant women with epilepsy taking ASMs may be more likely to experience miscarriage. A miscarriage is defined as the loss of pregnancy during the first 23 weeks. 10-20% of pregnancies end in miscarriage. Most women who suffer a miscarriage can experience stress, anxiety, depression and post-traumatic stress disorder. A study exploring quality of life in women

with recurrent miscarriage found they reported significantly lower quality of life in general health, vitality, social functioning, and mental health (Tavoli et al., 2018).

Bech et al. (2014) found pregnant women taking ASMs had a 13% higher risk of miscarriage than pregnant women not using ASMs, although the risk of spontaneous abortion was not increased in women with an epilepsy diagnosis. The authors surmise that an unmeasured confounding variable may explain the slight increased risk associated with ASM use (among women with and without epilepsy). Further research is needed to fully understand the risk of miscarriage when using ASMs. For this reason, we do not include the cost of miscarriage in the main table of costs.

## Impact on carer quality of life

Many of the above conditions require families to take on significant caring responsibilities for the affected children. Amidst the guilt and anger they are burdened with, parents must navigate caring for a child with physical and developmental abnormalities whilst living with epilepsy themselves in what has been described as a 'double disability' (IMMDS Review, 2020). Thompson et al. (2014) used a qualitative survey to investigate how caring for family members with intellectual disability and epilepsy can impact upon parents and their families. The effects ranged from practical concerns around the time commitment and meeting their child's medical needs to the emotional impact, which involved stress, anxiety and strain on relationships.

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*"I felt so guilty, I felt it was my fault for his problems and disability... not to be told what these tablets can do and have done to so many families is terrible"*

Parent perspective (IMMDS Review, 2020)

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Caring responsibilities extend to siblings of the affected children, even for those who may be affected themselves, who must provide support to both their parents and siblings. The First Do No Harm report quotes Branwen Mann, a young person affected by exposure to sodium valproate:

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*"The responsibilities we have... are essential, ensuring that medication is taken, that enough sleep is had, helping to manage appointments as they grow older, caring for them if they have had a seizure. I recently tried to get myself acknowledged as a carer, I was told that I could not be disabled and a carer. That does not fit with the experience of a Foetal Valproate Syndrome individual."*

Patient and carer perspective (IMMDS Review, 2020)

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In terms of specific conditions, a survey conducted by Sadighian et al. (2021) found that 26.7% of caregivers for individuals with spina bifida had such significant caring responsibilities that they were at risk of burning out. The treatment necessary for certain physical abnormalities can cause substantial stress for parents, as evidenced by a study that found HRQoL was significantly lower for parents of children with congenital heart disease compared to the control group, with disease severity and repeated invasive cardiac procedures predicting differences in HRQoL (Abassi et al., 2020).





For parents caring for children with ASD, 40% reported clinical depression symptoms, with HRQoL scores measured using the SF-6D significantly lower compared to the general population (Kuhlthau et al., 2014), demonstrating the health impacts beyond those experienced by the affected individual. Peasgood et al. (2021) found caring for children with ADHD had a negative impact on parents' satisfaction with leisure time, sleep hours and sleep quality. Overwhelming caring responsibilities can also adversely impact the relationships between parent and child, contributing to lower overall family wellbeing (Karst and Van Hecke, 2012).

The qualitative and quantitative evidence portraying the detrimental effects on the quality of life on both the affected individuals and their carers suggests there may also be a substantial economic impact associated with *in utero* exposure to ASMs for the health system and wider society, an issue further explored in the next section.

### 3 Estimating the economic impact of conditions associated with *in utero* exposure to ASMs

Table 2 details estimates of the lifetime costs per case of the conditions associated with *in utero* exposure to ASMs. Due to a lack of information on the ASM-specific risks of most of these conditions, we do not attempt to estimate the proportion of these conditions due to ASMs or to estimate aggregate costs. Much of the research assessing the impact of ASMs on the risk of congenital conditions is based on studies that focus on, or include, valproate (Bjørk et al., 2022; Werler et al., 2011; Gedzelman and Meador, 2012). As noted above, the unacceptable risks associated with valproate are recognised and it is specifically discouraged for women of child-bearing age. Therefore, using risk estimates from studies that include valproate may overestimate the ASM-related prevalence and impact of these conditions.

**TABLE 2: LIFETIME COSTS PER CASE OF EACH CONDITION IN TERMS OF COSTS TO THE NHS, EDUCATION SYSTEM, WELFARE SYSTEM, PRODUCTIVITY LOSSES, AND OUT OF POCKET EXPENDITURES**

	NHS	Education system	Welfare system (maximum) <sup>1</sup>	Productivity loss (of affected individual)	Out-of-pocket expenditure
<b>ASD</b>	£558,612	£403,516	£317,767	£1,037,302 <sup>2</sup>	£91,852
<b>SLCN</b>	£2,463 <sup>3</sup>	£59,998	N/A	£27,543	N/A
<b>Dyspraxia</b>	£14,899 <sup>4</sup>	N/A	N/A	£11,675 <sup>5</sup>	£48,627 <sup>6</sup>
<b>ADHD</b>	£27,041	£54,623	N/A	£42,105	N/A
<b>Dyslexia</b>	N/A	N/A	N/A	£49,001	£500-£700
<b>Spina bifida</b>	£114,467	N/A	£612,556	£200,382 <sup>7</sup>	N/A
<b>Low birth weight</b>	N/A	N/A	N/A	N/A	N/A
<b>Face/skull disorders</b>	£10,527	N/A	N/A	N/A	N/A

<sup>1</sup> Cost if an individual was receiving the maximum available payments from Disability Living Allowance (DLA), Personal Independent Payments (PIP), Carer's allowance (and a Mobility Component where applicable) over the course of their lifetime.

<sup>2</sup> Cost to affected individual and parents

<sup>3</sup> Cost during child age of 0-18

<sup>4</sup> Cost during child age of 6-18

<sup>5</sup> Cost to parents during child age of 6-18

<sup>6</sup> Cost during child of age 6-18

<sup>7</sup> Cost to affected individual and parents



Also, many of those affected by consequences of *in utero* exposure to ASMs may have multiple, or concurrent, conditions. Treating these conditions as independent (i.e. one case = one person) will tend to overestimate the number of cases in the population. To the extent that one person with multiple conditions may be associated with less costs than a collection of individuals with a single condition (e.g. any productivity losses would be limited to a single individual rather than multiplied across a number of individuals), this will also overestimate total costs. Therefore, we do not attempt to aggregate costs at a population level. The evidential limitations described above motivate the need for research into ASM-specific risks for each condition, as well as the impact on comorbidities. This evidence would enable quantification of the overall economic and societal impact of ASMs, thereby more appropriately highlighting the scale of the challenges associated with ASMs.

All costs have been inflated to 2022 prices using the NHSCII index for health sector costs and the GDP deflator for non-health costs. Further details on the source of costs and estimation methodology can be found in the appendix.

## 4 What is the economic impact on affected individuals and their families?

**TABLE 2: LIFETIME COSTS PER CASE OF EACH CONDITION IN TERMS OF COSTS TO THE NHS, EDUCATION SYSTEM, WELFARE SYSTEM, PRODUCTIVITY LOSSES, AND OUT OF POCKET EXPENDITURES**

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<b>ADHD</b>	£27,041	£54,623	N/A	£42,105	<b>N/A</b>
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<b>Spina bifida</b>	£114,467	N/A	£612,556	£200,382	<b>N/A</b>
<b>Low birth weight</b>	N/A	N/A	N/A	N/A	<b>N/A</b>
<b>Face/skull disorders</b>	£10,527	N/A	N/A	N/A	<b>N/A</b>

### Out-of-pocket expenditure

Families of children with ASD are confronted with a range of out-of-pocket expenditures necessary to manage their child's condition, including home and garden adaptations, specialist equipment such as pushchairs and toys, travel to health services, and repairs and replacement of damage to house and contents (PACT Consortium et al., 2012). There is, however, significant variability around the costs borne by families with ASD. We estimated a mean lifetime cost per case of £91,852, using annual cost estimates from a UK-based study (Buescher et al., 2014). A study in Ireland estimated annual out-of-pocket costs of €9,490 (£6,867) per family, with the largest costs including childcare, special diets, and transportation costs (Roddy and O'Neill, 2019). It also found that out-of-pocket expenditures increased as ASD severity increased, whereas state health expenditures do not, underscoring the pivotal role families have in caring for those with ASD.

Whilst many learning difficulties are associated with costs on the education system, dyslexia's financial costs fall largely onto the families of the affected children. The cost of a diagnostic assessment for dyslexia is usually between £500 and £700 in out-of-pocket expenditures for families, since it is extremely unlikely that a school will pay for such an examination (Hodgson et al., 2019). These assessments are accompanied by the lengthy and often stressful processes required to obtain Education, Health and Care Plans from local authorities, many of which are initially denied and can lead to substantial legal costs. These out-of-pocket costs raise equity concerns as those who can afford to are able to access faster and more comprehensive support for their child.

**The out-of-pocket costs borne by families for children with developmental co-ordination disorder (DCD), also known as dyspraxia, were calculated to be £48,627 over the course of their childhood (5-18 years of age).** In children with DCD, Cleaton, Lorgelly and Kirby (2020) found that private health care was commonly used by parents, especially in the case of occupational therapy. They posit that parents may deem the traditional 4-6 occupational therapy appointments provided by the NHS as insufficient for their child, which again poses the problem that children with parents who are not able to afford private treatment may get left behind. The cost of attending appointments exceeds that of the appointment itself, for both state and private attendances. Parents must take time off work, pay for petrol and parking, and organise child care, adding to the out-of-pocket financial costs caused by their child's condition. Cleaton, Lorgelly and Kirby (2020) estimate a mean cost to families of £745 over 6 months for the associated costs of attending health care appointments. Similarly, for parents with children born at low birth weight, parents are forced to pay £2,256 over the course of their infant's stay in hospital.

## 5 What is the impact on the NHS?

**TABLE 2: LIFETIME COSTS PER CASE OF EACH CONDITION IN TERMS OF COSTS TO THE NHS, EDUCATION SYSTEM, WELFARE SYSTEM, PRODUCTIVITY LOSSES, AND OUT OF POCKET EXPENDITURES**

	NHS	Education system	Welfare system (maximum)	Productivity loss	Out-of-pocket expenditure
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Dyspraxia	£14,899	N/A	N/A	£11,675	£48,627
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Dyslexia	N/A	N/A	N/A	£49,001	£500-£700
Spina bifida	£114,467	N/A	£612,556	£200,382	N/A
Low birth weight	N/A	N/A	N/A	N/A	N/A
Face/skull disorders	£10,527	N/A	N/A	N/A	N/A

### Hospital care

Surgery is necessary in the case of face and skull malformations such as cleft lip and palate, with some patients requiring multiple surgeries up to 18 years of age. Hasanally (2020) calculated that the **mean cost to NHS of treating cleft affected children between birth and 10 years of age ranged from £6,137 to £17,004 depending on the type of cleft phenotype**, with surgical costs constituting between 54.9% and 74.4% of these costs.

Surgery is usually performed 48 hours after birth for infants with spina bifida in order to prevent nerve damage. Further surgery is necessary if the child suffers from hydrocephalus, which is excess fluid on the brain (NHS, 2017b). Bowles et al. (2014) found the contribution of inpatient care is highest in these early years, when the aforementioned antenatal surgeries occur, and between 31-40 years, when a follow-up surgical intervention is sometimes required.

Children born with low birth weight are likely to need more neonatal care than babies born with a healthy weight. Whilst we were unable to find a reliable source of the cost of low birth weight babies to the NHS, a recent study estimated that the mean cost of a preterm birth (31 weeks) was around £27,000 (Yang et al., 2023).

In some cases of miscarriage, surgery is required to remove any remaining pregnancy tissue. The weighted average cost of miscarriage surgeries to the NHS was £1,720. The weighted average for all types of miscarriage treatment was £1,003. If anti-seizure medication does increase the risk of miscarriage, there is likely to be a financial impact on the NHS.

## Medications

**ASD was estimated to have the largest lifetime cost to the NHS of the considered abnormalities, at £558,612.** ASD is primarily managed in the community, as demonstrated by therapy services, outpatient visits and medication costs contributing most to the associated direct health care costs (Matin et al., 2022). Approximately two thirds of adults with ASD use psychotropic medications, with rates even higher in those with mental health and intellectual disability comorbidities.

There is an overrepresentation of individuals with ASD, ADHD, and SCLN among those with learning disabilities, along with a concerning trend of overprescribing psychotropic drugs for this population. Public Health England estimated that between 30,000 and 35,000 patients with learning disabilities are prescribed an antipsychotic without having a diagnosis that they are designed to treat (Glover et al., 2015). This not only represents poorly targeted care but substantial costs associated with medication prescriptions and their side effects.

Spina bifida can lead to lifelong treatment with medicines for the associated bowel and bladder complications, in the form of antibiotics to prevent kidney and urinary infections and laxatives to help with constipation. 12.4% of the average mean health care expenditure for patients diagnosed with Spina bifida was determined to be attributable to medicines (Bowles et al., 2014).

## Physiotherapy and Occupational Therapy

Physiotherapy and occupational therapy are usually necessary for children with spina bifida. These appointments can help children improve their independence and mobility, whilst teaching parents exercises that enable them to aid in their child's development. Whilst there is insufficient data on physiotherapy appointments specifically, Bowles et al. (2014) observed a mean of 21 outpatient appointments per year for those with neural tube defects. Families may also be directed towards expensive wheelchairs or mobility aids; 57% of those with spina bifida use wheelchairs and 23% use walking aids (Johnson et al., 2007). This is reflected in their substantial cost contribution, where between ages 2-10, 61% of the overall cost of spina bifida is attributable to medical aids.

Children with DCD often require occupational therapy to help with activities for daily living, such as getting dressed or using playground equipment. Occupational therapy was the most commonly used type of therapy appointment by children aged 6-11 in a study examining the economic cost of DCD, with 28.7% of participants attending NHS appointments and 9.8% privately (Cleaton, Lorgelly and Kirby, 2020). This led to occupational therapy having the largest mean costs for children with DCD; £144 for NHS appointments and £223 for private appointments. However, between the ages of 12-18 the numbers using occupational therapy dropped substantially despite the fact that motor problems generally persisted into adulthood. **Using estimates from this study, we calculated a childhood cost to the NHS of £14,899 for dyspraxia.**



## Legal claims and compensation

The NHS has acknowledged the damage incurred to children exposed to valproate *in utero*. NHS Resolution (as known as NHS Litigation Agency) has provided information about making a damages claim if there has been a breach of duty, factual causation and medical causation as a result of the prescription of valproate (NHS Resolution, 2022). These payments include both compensation for the affected child's injury, pain, suffering, and loss of amenity, as well as a payment to reflect the financial losses incurred by the families and the affected child due to the injury.

According to Maria Caulfield, then Parliamentary Under-Secretary for Health and Social Care, as of 31<sup>st</sup> March 2022, NHS Resolution had received 127 claims relating to sodium valproate, of which seven were still open. The total amount paid in damages and costs for the 120 closed cases was £14.6 million. As of December 2023, no further information could be obtained as to the total amount of compensation paid, but it's likely that many more cases have been opened and closed in the previous year, with the potential for more to be opened in the future. This exposes the NHS to legal liability and considerable costs; the Cumberlege review called for an ex-gratia payment scheme but this is yet to be implemented.



## 6 What is the impact on government and society?

**TABLE 2: LIFETIME COSTS PER CASE OF EACH CONDITION IN TERMS OF COSTS TO THE NHS, EDUCATION SYSTEM, WELFARE SYSTEM, PRODUCTIVITY LOSSES, AND OUT OF POCKET EXPENDITURES**

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<b>Low birth weight</b>	N/A	<b>N/A</b>	N/A	N/A	N/A
<b>Face/skull disorders</b>	£10,527	<b>N/A</b>	N/A	N/A	N/A

### Education

A large portion of the economic cost for developmental conditions arising from ASMs during pregnancy is borne by the education system. Special education represented the largest cost for children with ASD in UK studies by Knapp, Romeo and Beecham (2009) and Buescher et al. (2014), where costs peaked between ages 12-17. Using Buescher et al.'s (2014) annual cost estimates, we estimate **a lifetime cost per case of ASD to the education system of £403,516**. As with health, ASD is the linked condition with the largest educational costs. This financial impact considered alongside the current evidence base of increased risk of ASD resulting from certain ASMs during pregnancy provides strong justification for investment into research of the impact of the full range of ASMs on ASD.

**Speech and language problems require substantial investments in therapy between ages 5-15, estimated to be £59,998 in 2022 prices** (Speech and language UK, 2006). These investments may be necessary to prevent further costs later on in the lives of those with SLCN, particularly in the form

of criminal justice costs and productivity losses. Individuals with SLCN are at greater risk of contact with the criminal justice system; 60% of young people in justice settings have speech, language and communication needs (RCSLT, 2023). The educational costs of face and skull malformation disorders overlap with those described above, as 50% of children with cleft lip and/or palate have speech deviations and are referred to speech and language therapy (Sand, Hagberg and Lohmander, 2022).

71% of children with ADHD have officially recognised special education needs. This is reflected in the finding that **extra costs of educational provision account for 44% of the costs associated with ADHD, at an estimated cost of £54,623** (Parsonage, 2014). Language disorders have been found to be associated with ADHD, meaning there is a high likelihood of overlap in the resource use that makes up each cost (Lewis et al., 2012).

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*“My daughter will never be independent and will always be reliant on support throughout her life in every aspect... **she is not even able to complete forms to claim her benefits** that give her the basic requirements of life, food, roof over her head, a bed to sleep in at night and clothes to wear... I have to battle for it on her behalf because she can’t.”*

Parent perspective (IMMDS Review, 2020)

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Lastly, we were unable to identify the total financial cost of educational support for a child with dyslexia through the state education system. Mechanisms for dyslexia support in schools include additional teacher training to recognise, understand and support dyslexic pupils as well as employing teaching assistants. It’s also likely that some support costs such as additional tutoring are borne by the family.

## Welfare & Productivity Losses

The disabilities caused by ASMs during pregnancy mean those affected require state welfare support throughout their lives. These benefits include the Disability Living Allowance (DLA) for those under 16, Personal Independent Payments (PIP) for those over 16, and a Carer’s Allowance for carers whose child is in receipt of DLA or PIP. In addition, adult social care costs may also be incurred. Those with mobility issues, as is often the case with certain psychical abnormalities such as spina bifida, are eligible to receive an extra mobility component in their payments. We estimate **those with mobility issues from spina bifida and their carers could receive welfare payments of up to £612,556 over the course of their lifetime from benefit payments** directly related to their condition. **For those whom a mobility component is not applicable, the lifetime cost of these payments can reach up to £317,767.**

There may also be indirect costs of the associated risks through the impact on the productivity of carers. Evidence suggests that adults work 7 hours a week less than the general population if they have a child under 18 years of age with ASD (Cidav, Marcus and Mandell, 2012). In the case of spina bifida, between 7.5 and 11.3 work hours are displaced by caregiving (Tilford et al., 2009). These lost hours negatively impact society, as less time is utilised for economically productive means.

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Low birth weight	N/A	N/A	N/A	N/A	N/A
Face/skull disorders	£10,527	N/A	N/A	N/A	N/A

Reduced productivity is also of detriment to families themselves. A US-based study found that mothers earned 56% less and the likelihood of having both parents in work was 9% lower in families with a child with ASD, when compared to mothers and families not affected by health limitations (Cidav, Marcus and Mandell, 2012). In addition, they found the greater the severity of condition, the greater the productivity loss to caregivers. This demonstrates how increased caring responsibilities exacerbate already difficult financial situations and entrench gender inequalities.

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*“Once employers know I have ADHD, **they either don’t employ me or look for ways to fire me**”*

Patient perspective (Beaton et al., 2022)

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Productivity losses extend to the affected individuals when they become adults. **For example, lifetime earnings for those with dyslexia, ADHD and SLCN are reduced by £49,001, £42,105, and £27,543, respectively**, compared to those without these learning difficulties. The consequences of undiagnosed cases of learning difficulties or developmental problems present alternative challenges, since those affected will not be receiving treatment to help manage their condition. Employees with untreated ADHD were found to lose 22 days of productivity a year due to productivity levels lower than that of their treated counterparts (Hilton et al., 2009). Those with ADHD are also 30% more likely to have chronic employment issues (Barkley, Murphy and Fischer, 2008).

## 7 Next steps

We find that *in utero* exposure to ASMs has significant and costly consequences for affected individuals, their families, the NHS, other government sectors, and society. This is particularly true for cases of autism spectrum disorder and spina bifida, where cost per case across sectors total up to £2,409,049 and £927,405, respectively. However, the exact scale of the issue in relation to ASMs is difficult to assess given uncertainties around ASM-specific risks and the incidence of concurrent conditions.

**Exposure to anti-seizure medications in utero may lead to neurodevelopmental problems or physical disabilities**



**This is the lifetime cost of one baby born with each condition**

**Learning and development problems**

Autism **£2,409,000**

ADHD **£124,000**

Speech, language and communication needs **£90,000**

Dyslexia **£50,000**

Dyspraxia **£75,000**

**Physical disabilities**

Spina bifida **£927,000**

Facial and skull malformations **£11,000**

**Low birth weight**

No reliable estimate found

**These costs are incurred by the family, the NHS, the education system, welfare system and wider society**



**FIGURE 3 OVERVIEW OF LIFETIME COST PER CONDITION (TO THE NEAREST £1,000)**

The Cumberlege Review proposed a number of actions to minimise harm and better support those already affected by valproate, including the long-term follow-up of women on all ASMs and their children, and the introduction of measures to reduce and monitor effects of other medications which are regularly taken during pregnancy, and have a known risk above that of the general population (IMMDS Review, 2020).

We would support this call for more information on the long-term impacts of *in utero* exposure to ASMs. In particular, it will be important to understand the ASM-specific risks, particularly those representing first choice of treatment for women with epilepsy. Robust evidence exists for the risks associated with ASMs that have already been recommended for discontinuation, such as valproate, but this evidence fails to provide useful inputs for assessing the economic and societal impact of the



present utilisation of ASMs during pregnancy. To facilitate this, further data collection about the following is warranted:

- i. Which ASMs are currently used by women of childbearing age, in order to capture planned and unplanned pregnancies
- ii. Detailed risk profiles of *in utero* exposure these ASMs in terms of physical disabilities, developmental problems, and low birth weight
- iii. Incidence of co-morbid conditions in the affected population if different from general population

The occurrence of multiple conditions would exacerbate the impact on affected individuals and their families despite, potentially limiting the cost to society in terms of aggregate foregone productivity. Improving the evidence base in these directions can enable accurate estimation of the economic and societal impacts associated with ASMs and as a result, research can be appropriately directed towards reducing said impacts.

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# Appendix

**TABLE A1: LIFETIME COSTS PER CASE OF EACH CONDITION IN TERMS OF COSTS TO THE NHS, EDUCATION SYSTEM, WELFARE SYSTEM, PRODUCTIVITY LOSSES, AND OUT OF POCKET EXPENDITURES, INCLUDING THE SOURCES USED FOR EACH ESTIMATE.**

	<b>NHS</b>	<b>Education system</b>	<b>Welfare system (maximum)</b>	<b>Productivity loss</b>	<b>Out-of-pocket expenditure</b>
<b>ASD</b>	Cost: (Buescher et al., 2014)  Proportion with ID: (Wiśniowiecka-Kowalnik and Nowakowska, 2019)  Life expectancies: (Hirvikoski et al., 2016)	Cost: (Buescher et al., 2014)  Proportion with ID: (Wiśniowiecka-Kowalnik and Nowakowska, 2019)  Life expectancies: (Hirvikoski et al., 2016)	(GOV.UK, 2023)	Cost: (Buescher et al., 2014)  Proportion with ID: (Wiśniowiecka-Kowalnik and Nowakowska, 2019)  Life expectancies: (Hirvikoski et al., 2016)	Cost: (Buescher et al., 2014)  Proportion with ID: (Wiśniowiecka-Kowalnik and Nowakowska, 2019)  Life expectancies: (Hirvikoski et al., 2016)
<b>SLCN</b>	Cost: (Longfield, 2023)  For years 0-18	Cost: (I CAN TALK, 2006)	N/A	Cost: (Cronin et al., 2020)	N/A
<b>Organ disorders</b>	N/A	N/A	N/A	N/A	N/A
<b>Dyspraxia</b>	Cost: (Cleaton, Lorgelly and Kirby, 2020)  For ages 6-18	N/A	N/A	Cost: (Cleaton, Lorgelly and Kirby, 2020)  For ages 6-18	Cost: (Cleaton, Lorgelly and Kirby, 2020)  For ages 6-18
<b>ADHD</b>	Cost: (Parsonage, 2014)	Cost: (Parsonage, 2014)	N/A	Cost: (Parsonage, 2014)	N/A
<b>Dyslexia</b>	N/A	N/A	N/A	Cost: (Galluzzo, 2023)	Cost: (British Dyslexia Association, 2019)
<b>Spina bifida</b>	Cost: (Filby et al., 2019)	N/A	(GOV.UK, 2023)	Cost: (Colombo et al., 2013)  Life expectancy: (Oakeshott et al., 2010)	N/A
<b>Low birth weight</b>	N/A	N/A	N/A	N/A	N/A
<b>Face/skull disorders</b>	(Hasanally, 2020)	N/A	N/A	N/A	N/A



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- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics