The association of childhood attention deficit/hyperactivity disorder (ADHD) with socioeconomic disadvantage

Submitted by Abigail Emma Russell to the University of Exeter

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature:

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is commonly reported to be more prevalent in children from socioeconomically disadvantaged backgrounds. In this thesis I will explore in more detail the association between socioeconomic disadvantage and ADHD. This thesis comprises six studies, starting with a systematic review in order to evaluate existing published evidence, which is followed by a qualitative study that explores educational practitioners' conceptualisation of the causes of ADHD. A series of three analyses utilising existing data from the Avon Longitudinal Study of Parents and Children (ALSPAC) then explore which measures of socioeconomic status (SES) are associated with a research diagnosis of ADHD and potential mediators of this association, and whether timing, duration or changes in exposure to financial difficulty impact on the SES-ADHD association. In the final study in this thesis, I explore whether SES-health associations in general are likely to be due to epigenetic differences in children exposed to low SES.

Existing literature provides evidence that an association between SES and ADHD is commonly detected. The facet of SES most predictive of ADHD was mother-reported experience of difficulty affording basic necessities (financial difficulty), associated with an increased risk of a research diagnosis of ADHD of 2.23 (95%CI 1.57, 3.16). Exposure to financial difficulty between birth and age seven was associated with higher levels of ADHD symptoms across childhood of 0.78 points on the Strengths and Difficulties Questionnaire Hyperactivity subscale (95% CI 0.54, 1.00, $p<0.001$), whereas later exposure to financial difficulty was not associated with ADHD symptoms. In addition, I found tentative evidence that different patterns of SES exposure are associated with different levels of ADHD symptoms, with those consistently low SES having symptom scores 0.41 points higher than those in difficulty (95% CI 3.46, 3.57, $p<0.001$). I did not find strong evidence that low SES impacts on epigenetic profiles across childhood.

These findings add to emerging evidence of an association between SES and ADHD that has implications for theory and policy.

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The candidate's contribution to all papers and chapters (AER):
Conception and design, data analysis (except for Chapters 7 and 9), interpretation of data, write-up of articles, critical revision for important intellectual content and final approval of the version to be published.

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All co-authors contributed to critical revision of draft manuscript for important intellectual content and approval of final version to be published. Additional contributions are outlined below.

Chapter 4: The association between socioeconomic disadvantage and attention deficit/hyperactivity disorder (ADHD): a systematic review (AER, TF, RW and GR)

Tamsin Ford (TF) and Ginny Russell (GR): Advised on study conception and design

Rebecca Williams: Acted as independent reviewer to select studies and extract data

Chapter 5: Educational practitioners' beliefs and conceptualisation about the cause of ADHD: A qualitative study (AER, DM and TF)

TF: Advised on study conception

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Chapter 6: Socioeconomic associations with ADHD: findings from a mediation analysis (AER, TF and GR)

TF: Study design, guidance with interpretation

GR: Study conception and design, guidance with analysis and interpretation

Chapter 7: Longitudinal associations between socioeconomic disadvantage and childhood hyperactivity: a cohort study (AER, JM, WH, TF and GR)

TF and GR: Advised on study conception and design, advised on interpretation of findings

William Henley: Advised on design and analysis, interpretation of data, methodological guidance

Justin Matthews: Advised on design, conducted analysis, aided with interpretation of data, drafting manuscript methods section and tables.

Chapter 8: Trajectories of socioeconomic status over childhood and their association with symptoms of ADHD: a UK longitudinal cohort study (AER, TF and GR)

TF and GR: Advised on study conception and design

Chapter 9: Associations of early life socio-economic position in DNA methylation throughout childhood (AER, and MS, chapter)
Matthew Suderman: Advised on study design, undertook analysis, led writing of methods and results, assisted in interpretation of results

Abbreviations

ADHD	Attention deficit/hyperactivity disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
ASD	Autism spectrum disorders
DAWBA	Development and Well-Being Assessment
DSM (II, III, IV and 5)	Diagnostic and Statistical Manual of Mental Disorders (versions 2, 3, 4 and 5)
EWAS	Epigenome-wide association study
GP	General Practitioner
HKD	Hyperkinetic Disorder
ICD-10	International Classification of Diseases, 10th edition
IMD	Index of Multiple Deprivation
MCS	Millennium Cohort Study
NICE	National Institute for Health and Care Excellence
SDQ	Strengths and Difficulties Questionnaire
SED	Socioeconomic disadvantage
SENCo/SENDCo	Special Educational Needs (and Disabilities) Co-ordinator
SES	Socioeconomic status
TA	Teaching assistant

Chapter One: Attention deficit/hyperactivity disorder (ADHD) and child development (Introduction part 1/2)

1.0 Chapter Overview

In this chapter I will provide a brief overview of the history and diagnostic criteria of attention deficit/hyperactivity disorder (ADHD), its symptoms and current commonly-used diagnostic criteria. I will move on to discuss how ADHD is assessed and treated, and outline the theoretical stances that are taken around its aetiology and mechanisms.

1.1 A brief history

ADHD is currently classified as a developmental disorder, and is diagnosed when an individual shows a pattern of inattentive and/or hyperactive and impulsive behaviours, which are inappropriate for their age and that cause significant impairment across settings (American Psychiatric Association, 2013). A widely accepted estimate of ADHD prevalence is 2-5% of children and young people (Polanczyk et al., 2007).

ADHD was first diagnostically conceptualised nearly fifty years ago as Hyperkinetic Disorder of Childhood in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (2nd ed, DSM-II, American Psychiatric Association, 1968). Debates arise, however, when examining historical clinical records for cases of ADHD, leading to questions over whether the ADHD diagnosis is socially constructed in response to demands of twentieth century living or a valid clinical disorder.

It is clear that ADHD or disorders with similar symptoms have been described in medical case studies and texts since the 1700s. Lange et al. (2010) credit Sir Alexander Crichton in 1798 with the first written account of a disorder similar to ADHD, in the aptly named chapter of his book “On attention and its diseases”. In this chapter, Crichton’s account draws several parallels that dovetail with what we currently consider to be ADHD- for example that the problems generally diminish with age and can have an impact on education. Crichton defines the key issue in his disorder as “the incapacity of attending with a necessary degree of constancy to any one object”; what we would describe as inattention today.

Moving forward in history, another popularly cited example of the “first” description of ADHD is from an 1844 book of children’s stories by Henrich Hoffman. He was a physician who created the books for his children, with characters similar to those in the “Mr Men” books in that they were all named by their actions. “Fidgety Phil”, who cannot sit still and does not listen is described by Lange et al. (2010) as an example of a child with hyperactive behaviours, although they concede that other researchers consider this character to show more oppositional than hyperactive behaviours. Hoffman had another relevant character, known as “Johnny look-in-the-air” who, depending on the interpretation of the researcher, has been considered to either have inattentive-type ADHD or be experiencing petit-mal absence seizures. Whilst Hoffman’s work is of historical importance and interest, conclusions drawn about the particular afflictions of his characters are at best speculative. This does however demonstrate that as early as the 1800’s, children with problematic behaviours were being recognised and perhaps treated by physicians such as Hoffman.

The most-commonly cited “first” accounts of ADHD, although still hotly debated among academics, were during the Goulstonian lectures of Sir George Frederic Still in 1902 (Lange et al., 2010). Still was a British paediatrician who in his series of lectures described case studies of children under his care. Forty three of the case studies describe children with problems both in sustained attention and self-regulation (Barkley, 2006): today self-regulatory deficits are often posited as a core deficit in children with ADHD, and problems sustaining attention is a key symptom (American Psychiatric Association, 2013). Barkley (2006) describes many of these case-study children as also being overactive, another core symptom. Other parallels between Still’s descriptions and what we consider ADHD include his observation of a differential male: female ratio, onset mostly prior to age eight, that both parents and teachers had noted problems with the child’s ability to sustain attention, and many of the cases having co-occurring disorders, for example oppositional behaviour and tic disorder. Still described these cases as having an “abnormal defect in moral control” (Lange et al., 2010).

It seems that the centre of the debate around whether some of Still’s cases could be described as having ADHD is due to the heterogeneity of the cases he describes. Conners (2000) suggests that throughout the cases, all the core symptoms of ADHD are described, but that Still’s cases do indeed cover

the whole range of behavioural disorders. As noted by Barkley (2006), 43 of Still's cases have symptoms consistent with ADHD, but as Still himself described, some of these fell into a category defined by physical disease as the cause of the problem, for example children who had a history of epilepsy or meningitis (Lange et al., 2010). Still describes 20 case studies without physical disease or intellectual impairment (Lange et al., 2010, Barkley, 2006), of these there was a 3:1 male: female ratio (a gender imbalance is commonly observed in identified cases of ADHD today). For the nine children with age-of-onset information, seven of them showed symptoms prior to the age of seven. Although Still may not have described children with symptoms unique to ADHD, it is known to have substantial comorbidity with other disorders, for example conduct disorder and oppositional defiant disorder (Ford, Goodman and Meltzer, 2003).

Still is also credited with being the first to recognise the connection between brain damage and abnormal behaviour in children, which has influenced theory throughout the twentieth century. The brain-damage/disorder connection became more prominent during the global pandemic of encephalitis lethargica from 1917-1928. This affected millions of people and it is estimated that more than a million individuals were left with "severe neurological disease" (Ravenholt and Foege, 1982). Affected children who survived the disease that killed over half a million individuals displayed marked hyperactivity and distractibility and were described as having "post-encephalitic brain disorder" (Vilensky, Foley and Gilman, 2007).

In the 1930's, Kramer and Pollnow describe what I consider to be the first clear cases of a disorder similar to that which we call ADHD today. Their "Hyperkinetic disease of infancy" has key symptoms of restlessness and hyperactivity, lack of purpose in motor activity and distractibility (Lange et al., 2010). Interestingly, Kramer and Pollnow were the first to clearly state that although the pathological manifestation had been recognised already, they differentially defined it as a distinct disorder. Again, there were key similarities with modern-day ADHD: severe education problems, peak of cases/symptoms around age 6, and that if a child found an activity to be of particular interest they could pursue it for hours on end, not unlike what we see now with children and video games.

Following this, Strauss and Lehtinen (1947) systematically compared children with intellectual impairment with and without brain damage, and found differences in domains of hyperactivity and distractibility, reinforcing the notion that although brain damage could cause intellectual and behavioural problems in children, these problems were qualitatively different from those with no history of brain damage (Conners, 2000). ADHD, however, continued to be conceptualised as a neurological disorder, not least because of the accidental discovery of an effective treatment by Charles Bradley in 1937. He found that of the children in his hospital with neurological impairments, when he treated them with the stimulant Benzedrine (for severe headaches caused by loss of spinal fluid during pneumo-encephalograms), half of the children showed a dramatic change in behaviour. By the 1950's he had developed Ritalin (methylphenidate), named after his wife Rita, and deduced that the children it was effective for were those with a short attention span, hyperactivity, impulsivity, poor memory, mood lability and dyscalcula (Conners, 2000, Lange et al., 2010).

From the 1970's ADHD-like symptoms were classified under the terms "minimal brain damage" and "minimal brain dysfunction". Minimal brain damage was used due to beliefs that ADHD-like behaviours were the result of generally undetectable damage to the child's brain. Due to lack of evidence of this, and a decree from the Oxford International Study Group of Child Neurology in 1963 that brain damage could not in fact be inferred from problem behaviour, it was reclassified as minimal brain dysfunction, reflecting underlying defects in neurological pathways as a causal mechanism instead of brain damage: theories and evidence for which are still prevalent today (Lange et al., 2010, Conners, 2000). Only five years later, in 1968, the Diagnostic and Statistical Manual of Mental Disorders II (DSM-II) included "Hyperkinetic reaction of childhood".

Since its original occurrence as a diagnostic category in the DSM-II, the symptom criteria for ADHD have fluctuated in subsequent editions of the DSM. The focus in DSM-II was on hyperactivity as a core symptom, along with distractibility, restlessness and attention problems. The emphasis changed with the publication of the DSM-III in 1980, where the term Attention Deficit Disorder (ADD) was coined, and could be either with or without hyperactivity as a feature. This switch to attention as the core focus was due to the continuing

prevalence of mechanistic theories attributing the symptoms to a deficit in attention-sustenance. The DSM-III criteria for ADD were structured into three symptom lists: one for inattentive symptoms, one hyperactive and the last impulsive. DSM-III-R in 1987 combined these into a single list of symptoms due to the lack of empirical evidence defining subtypes of the disorder, and it was renamed ADHD.

The notion of subtypes of ADHD was reintroduced in the DSM-IV in 1994, with two subtypes: hyperactive-impulsive and inattentive, and the further option of a combined subtype. This is the pattern in which ADHD is categorised today, and this has allowed for theories about gender differences to flourish. Many suggested that girls were more likely to have the inattentive type and therefore be less likely to be disruptive and so under-recognised, whereas boys were considered more likely to have the hyperactive-impulsive type, which causes more external disruption and so is more likely to result in boys being recognised as in need of services (Gershon and Gershon, 2002). Regardless of possible gender differences, the notion of three subtypes as defined by the DSM-IV was supported by field trials conducted by Lahey et al. (1994), and ADHD has essentially continued to be defined in this manner.

This overview captures the diagnostic and symptomatic history of ADHD, and in addition a body of literature addresses sociocultural factors that may have impacted on such a cluster of traits being identified as a disorder in need of intervention. Theories include ADHD being a creation of American society increasingly focussing on the need for highly educated individuals in order to compete against the world market. Linked to this an intolerance for disruptive children in schools would have developed, with these children subsequently identified as a problem and labelled as such (Smith, 2013). Others believe ADHD to be a myth and part of a conspiracy generated by pharmaceutical companies to sell stimulants (Conners, 2000). Further theories discuss ADHD as being a way to categorise and control ‘naughty boys’ (Timimi, 2005b), and export of the US product of “ADHD” around the world (Matthew Smith, author of Smith (2013), verbal communication).

In spite of differing psychiatric diagnostic systems, children (and adults) with ADHD show a pattern of inattentive and/or hyperactive and impulsive behaviours. Children with ADHD are at increased risk for a wide range of negative outcomes, both short and long term. A recent systematic review of

long-term outcomes for children and adults with ADHD concluded that individuals with ADHD are at an increased risk, relative to those without ADHD, in all nine domains of published research identified in the review: drug use or addictive behaviour, poor academic outcomes, antisocial behaviour, problems with social function, problems with occupation, low self-esteem, driving and car accidents, use of services and obesity (Shaw et al., 2012). The authors also conclude that treatment for ADHD reduces some of these long term risks, but not to the levels of the control populations.

1.2 ADHD: Underlying symptoms and current diagnostic criteria

The majority of recent research has used either the DSM-IV criteria for ADHD or the International Classification of Diseases, 10th Revision (ICD-10) criteria for hyperkinetic disorder. Publication of the DSM-5 in 2013 has further refined the criteria: by current definition a child with ADHD must present with "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development". There are then two symptom constellations which allow for different subtypes of the disorder to be defined. An individual must have at least six symptoms from each domain to have the "combined" version of ADHD, or six or more symptoms within one constellation allows diagnosis of "predominantly inattentive" or "predominantly hyperactive/ impulsive" subtypes (American Psychiatric Association, 2013). These basic criteria are commonly used by researchers in the form of a symptom checklist, often completed by parents or teachers of the child concerned. The DSM-5, as in the DSM-IV (see Table 1 for DSM-IV diagnostic criteria and Table 2 for DSM-5 diagnostic criteria), specifies that the symptoms must be present during childhood (prior to age 12 in the latest version of the DSM, although previously the criterion was prior to age 7), and that several symptoms must be present across at least two settings, i.e. home and school. Symptoms also have to significantly interfere with a child's functioning and not be better explained by another disorder.

There has been some criticism of the approach taken by the DSM-5, that has updated DSM-IV criteria to reflect the fact that some children with ADHD will go on to suffer with symptoms throughout adulthood (Shah and Morton, 2013, Rohde, Verin and Polanczyk, 2012). The age threshold for symptom onset has been adjusted to allow the possibility of adults being retrospectively

diagnosed. It has been argued that with the publication of the DSM-5, thresholds are being altered which will potentially drive over-diagnosis, and that those who suffer from 'severe' ADHD are actually less than 15% of those classified as having ADHD in the USA (Thomas, Mitchell and Batstra, 2013).

Table 1: DSM –IV-TR Attention Deficit/Hyperactivity Disorder criteria (American Psychiatric Association, 2000)

A. Persistent pattern of inattentive and/or hyperactivity-impulsivity that interferes with functioning or development	
Inattention (6 or more, ≥ 6 months)	**Hyperactivity/Impulsivity** (6 or more, ≥ 6 months)
Careless errors, inattentive to detail	Often fidgets or squirms
Difficulty sustaining attention in tasks	Cannot stay seated (e.g. classroom)
Appears to not be listening when spoken to directly	Runs about of climbs excessively when not appropriate
Follows through poorly on instructions (loses focus/easily side-tracked)	The above may present as subjective feelings of restlessness in adolescents/adults
Difficulty organising tasks or activities	Difficulty playing quietly
Avoids, dislikes or reluctant to engage in tasks with require sustained mental effort	Always 'on the go'
Loses essential objects for tasks or activities	Blurts out answers before questions are completed
Easily distracted by extraneous stimuli	Difficulty awaiting turn
Forgetful in daily activities	Often interrupts or intrudes on others
Combined subtype: 6 or more symptoms in both the inattentive and hyperactive-impulsive domains. **Inattentive subtype**: 6 or more symptoms in inattention domain but less than 6 in hyperactivity-impulsivity domain. **Hyperactive/impulsive subtype**: 6 or more symptoms in hyperactive/impulsive domain, less than 6 in inattention domain	
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 7	
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. home, school, work)	
D. Clinically significant impairment in social, academic, or occupational functioning	
E. The symptoms do not occur exclusively in pervasive developmental disorder, during the course of schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder	

Table 2: DSM-5 Attention Deficit/Hyperactivity Disorder criteria (American Psychiatric Association, 2013)

A. Persistent pattern of inattentive and/or hyperactivity-impulsivity that interferes with functioning or development	
Inattention (6 or more, ≥ 6 months)	**Hyperactivity/Impulsivity** (6 or more, ≥ 6 months)
Careless errors, inattentive to detail	Often fidgets or squirms
Sustains attention poorly	Cannot stay seated (e.g. classroom/office)
Appears to not be listening when spoken to directly	Restless
Follows through poorly on instructions (loses focus/easily side-tracked)	Loud, noisy
Difficulty organising tasks or activities	Always 'on the go'
Avoids, dislikes or reluctant to engage in tasks with require sustained mental effort	Talks excessively
Loses essential objects for tasks or activities	Blurts out
Easily distracted by extraneous stimuli	Impatient
Forgetful in daily activities	Often interrupts or intrudes on others
Combined subtype: 6 or more symptoms in both the inattentive and hyperactive-impulsive domains. **Inattentive subtype**: 6 or more symptoms in inattention domain but less than 6 in hyperactivity-impulsivity domain. **Hyperactive/impulsive subtype**: 6 or more symptoms in hyperactive/impulsive domain, less than 6 in inattention domain	
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12	
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. home, school, work)	
D. Clear evidence that the symptoms interfere with, or reduce quality, of social, academic, or occupational functioning	
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder	

International Classification of Diseases, 10th Revision (ICD-10)

The ICD-10 (World Health Organization, 2004) is used by the World Health Organisation and in many countries worldwide, particularly Europe, with the DSM being a primarily North American system. The ICD-10 includes diagnostic criteria for a disorder very similar to the DSM's ADHD: hyperkinetic disorder (HKD). If anything, these criteria are more stringent (Polanczyk et al., 2007) as the ICD-10 does not allow for subtypes of only one symptom cluster: for a diagnosis of HKD symptoms of both inattention and hyperactivity/impulsivity must be present, and a range of comorbid disorders must not occur (World Health Organization, 2004). The diagnostic criteria for HKD in the ICD-10 are summarised in Table 3.

Comparing DSM and ICD

Inherent in there being different diagnostic systems and criteria for disorders that are considered to be essentially identical are differing reports of costs, prevalence and impact that ADHD has across the world. A highly cited systematic review (Polanczyk et al., 2007) went some way towards ending the debate on whether ADHD was an international phenomenon by demonstrating that much of the variation in prevalence was due to the diagnostic criteria and methodology used by different researchers across different countries. The review concluded that the worldwide prevalence of ADHD was 5.29%, making it one of the most common childhood psychiatric disorders (Polanczyk et al., 2007). This differing of prevalence by diagnostic criteria was further illustrated in a German study (Döpfner et al., 2008), that found a 4% difference in prevalence depending on criteria used- with DSM-IV prevalence of 5% and ICD-10 prevalence of 1%. This is also the case with updates to diagnostic criteria: Wolraich et al. (1996) found that there was a 57% increase in those eligible for diagnosis in a large community sample if DSM-IV criteria were used as opposed to DSM-III-R.

Table 3: ICD-10 Hyperkinetic Disorder diagnostic criteria (World Health Organization, 2004)

<table>
<tr><th colspan="3">G1. Demonstrate abnormality of attention, activity and impulsivity at home, for the age and developmental level of a child</th></tr>
<tr><td>Inattention
At least 3 of the following:</td><td>Hyperactivity
At least 3 of the following:</td><td>Impulsivity
At least 1 of the following:</td></tr>
<tr><td>Short duration of spontaneous activities</td><td>Runs or climbs excessively in inappropriate situations</td><td rowspan="2">Difficulty awaiting turns in games or group situations</td></tr>
<tr><td>Often leaves play activities unfinished</td><td>Excessive fidgeting and wriggling</td></tr>
<tr><td>Over-frequent changes between activities</td><td>Excessive activity in situations expecting relative stillness</td><td rowspan="2">Often interrupts or intrudes others</td></tr>
<tr><td>Undue lack of persistence at tasks set by adults</td><td>Cannot stay seated (e.g. classroom/office)</td></tr>
<tr><td>High distractibility during study</td><td>Loud, noisy</td><td>Blurts out</td></tr>
<tr><th colspan="3">G2. Demonstrable abnormality of attention and activity at school or nursery (if applicable), for the age and developmental level of the child, as evidenced by both:</th></tr>
<tr><td colspan="2">Attention
At least 2 of the following:</td><td>Activity
At least 3 of the following:</td></tr>
<tr><td colspan="2">Lack of persistence at tasks</td><td>Excessive motor restlessness in situations allowing free activity</td></tr>
<tr><td colspan="2">High distractibility</td><td>Excessive fidgeting and wriggling</td></tr>
<tr><td colspan="2" rowspan="2">Over frequent changes between activities when choice is allowed</td><td>Off-task activities during tasks</td></tr>
<tr><td>Cannot stay seated</td></tr>
<tr><td colspan="2">Short duration of play activities</td><td>Loud, noisy</td></tr>
<tr><th colspan="3">G3. Directly observed abnormality of attention or activity (can be those stated in G1 or G2). This must be excessive for the child's age and developmental level.</th></tr>
<tr><th colspan="3">G4. Does not meet criteria for pervasive developmental disorder, mania, and depressive or anxiety disorder.</th></tr>
<tr><th colspan="3">G5. Onset before age of seven years</th></tr>
<tr><th colspan="3">G6. Duration of at least six months</th></tr>
<tr><th colspan="3">G7. IQ > 50</th></tr>
</table>

Both the current DSM-5 and ICD-10 criteria specify that the individual must experience significant impairment in day-to-day life, and that symptoms are present across a range of settings, however whether researchers or those who diagnose ADHD actually ask or look for these criteria varies considerably. Another key difference between DSM and ICD criteria is that comorbid conditions do not necessarily exclude a diagnosis of ADHD in the DSM, but in the ICD co-occurring pervasive developmental disorder, mania, depressive or anxiety disorders exclude a diagnosis of HKD (Moffitt and Melchior, 2007). ADHD/HKD (both henceforth referred to as ADHD) is known however to have high levels of comorbidity with a wide array of mental disorders (Rohde et al., 2005), which suggests that the more stringent ICD criteria may in fact underestimate the true prevalence of the disorder. Diagnostic criteria for ADHD are culturally and historically bound, and so diagnostic definitions and prevalence rates may change over time. An important finding from studies comparing diagnostic criteria is that, no matter which criteria are used, ADHD does seem to be a universal disorder that occurs around the world (Moffitt and Melchior, 2007). In the United Kingdom (UK), epidemiological and cohort studies find an estimated prevalence of between 1.4-2.2% for ADHD: the widely cited 2-5% worldwide estimate is accepted to be accurate for the UK population (Ford, Goodman and Meltzer, 2003, Russell et al., 2014, Faraone et al., 2015).

Disorder or personality trait?

In spite of categorical diagnostic instruments and criteria being available, there has been an increasing argument that ADHD should be considered as an extreme end of normal variation in traits of hyperactivity, inattention and impulsivity (Larsson et al., 2012). One recent review found evidence to support a spectrum model of ADHD, much like that used for Autism Spectrum Disorders (ASD) (Heidbreder, 2015). Others conceptualise ADHD as a risk factor, with those who have the traits being more susceptible to negative outcomes (Shah and Morton, 2013). Whilst it is likely that this is indeed the case, it is rarely contested that those who have this constellation of traits do indeed suffer from clinically significant impairment and so there is often need for recognition and/or intervention, be it in the form of preventative, symptom management or treatment strategies. Indeed, it is now common for researchers to use both categorical and dimensional instruments when assessing ADHD.

One relatively recent advance in developing a classification for psychiatric disorders which has a focus on understanding the dimensional constructs underlying the expression of disorders is the National Institute of Mental Health's Research Domain Criteria (RDoC) (Faraone et al., 2015). The aim of this system is to relate behavioural functioning domains to underlying neurological circuits that may cause disorders (Levy, 2014). Levy (2014) suggests that categorical and dimensional measures of ADHD should not oppose each other, but can each contribute to enhancing understanding of ADHD and in particular its relationships with comorbid disorders. ADHD does not directly correspond to one domain in the RDoC criteria: a study utilising a community cohort of 247 children with ADHD found evidence for three "types" of ADHD using measures of temperament closely resembling the RDoC domains (Karalunas et al., 2014). The types were labelled as "mild", "surgent" and "irritable" and do not map on to the clinical subtypes described in the DSM-5 or ICD-10.

A large number of validated instruments exist that can be used to assess the symptoms of ADHD, and dimensional scales are often employed in assessment and diagnosis in both research and clinical practice. Along with structured interviews conforming to DSM or ICD criteria (e.g. the Diagnostic Interview Schedule for Children (DISC)), there are dimensional measures often used to gather information regarding a diagnosis from informants: commonly parents and teachers. These include, but are not limited to;

- Strengths and Difficulties Questionnaire (SDQ) (Goodman, Renfrew and Mullick, 2000)
- Conners comprehensive behaviour rating scales (CBRS or Conners) (Conners et al., 1998a, Conners et al., 1998b)
- The Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000)
- Achenbach's child behaviour checklist, along with teacher and youth self-report scales (Achenbach and Rescorla, 2000).

Descriptions of these can be seen in Table 4.

Table 4: An overview of scales commonly used to assess ADHD symptoms and contribute to diagnosis

Name	Measures	Subscales	Informants
Strengths and Difficulties Questionnaire (SDQ)	25 items, positively and negatively scored, rated from 0-2 based on whether statement is "not true" "somewhat true" or "certainly true" of the child over the past six months	Emotional symptoms, conduct problems, hyperactivity and inattention (ADHD symptoms), peer relationship problems, prosocial behaviour. Impact supplement optional	Parent, teacher and child self-report (age 11+) versions. Different versions for ages 2-4, 4-17
Conner's comprehensive behaviour rating scales (CBRS)	Range of scales available corresponding to DSM diagnostic criteria	Assesses behavioural, social, academic and emotional problems	Parent and teacher report versions (age 6-18) and self-report version (age 8-18)
Development and Wellbeing Assessment (DAWBA)	Interview (can be computer administered) and questionnaire combining open-ended and closed questions	Assesses emotional, behavioural and hyperactivity disorders as well as less common disorders	A clinical decision is made regarding a diagnosis based on parent interview and teacher questionnaires for age 5-17, as well as child interview (age 11-17). Diagnostic algorithms also available that categorise likely probability of diagnoses
Child Behaviour Checklist (CBCL), Teacher Report Form (TRF) and Youth Self-Report scales (YSR)	Report on list of symptoms in last six months as either “not true” “somewhat true” or “certainly true” of child.	Empirically-based syndromes including attention problems, and DSM-5 oriented scales including ADHD problems. Other internalising and externalising problems also assessed.	Preschool (child aged 1 ½ - 5) and school-aged versions (child age 6-18). Parents (CBCL), teachers (TRF) and young people aged over 11 (YSR). From the Achenbach System of Empirically Based Assessment.

What is the purpose of a diagnosis?

Defining and diagnosing has long been a contentious issue when it comes to mental illness. Comparisons are often drawn between physical and mental diseases as if they are different. Historically this is because these were seen to be either of the body or the mind respectively, and were thought to be "better treated by philosophers than physicians" (Kendell, 2001). The belief that physical and mental illness are separate entities remains widely accepted due to this assumption and also the misbelief that there is a fundamental difference between the causes of mental and physical illnesses (Kendell, 2001). Scientific thinking has moved forward however, as evidenced by the ICD-10 having no distinction in categories between mental and physical diseases (World Health Organization, 2004).

Are mental and physical illness comparable, compatible or completely separate things? The first issue to consider is the idea of disease of any kind being either present or absent. In mental health or illness this is often not considered the case; depression is often measured on a scale, from not present through to mild, moderate, severe and suicidal. It can also be chronic or acute: many of these aspects are currently conceptualised as different diagnoses in the DSM-5; dysthymic disorder is chronic relatively mild depression, cyclothymic disorder is similar but includes periods where the individual feels hypo-manic and periods of depression (American Psychiatric Association, 2013). It is however recognised that all these subtypes of depression include varying levels of several core symptoms; pervasive low mood, lack of self-worth and some associated physical symptoms such as alterations in sleeping patterns. Similarly, there are core symptom clusters in ADHD subtypes.

Mental health conditions are not easy to dichotomise. In the case of physical health and illness, intuition suggests that disease is present or absent; you don't have 'a bit of TB' for instance. Or do you? In actuality many physical illnesses can be present in degrees of severity, with what we label "disease" simply being the other side of a predetermined threshold, for example in hypertension, cancer or diabetes. Geoffrey Rose influentially argued that almost all medical conditions are in fact distributions: "nature presents us with a process or continuum, not a dichotomy" (World Health Organization, 2002). Therefore illness, both mental and physical, is almost always a continuum between wellness and illness, with symptoms or physiological measures

increasing from wellness towards illness before passing a predetermined threshold where they become ‘disease’ or ‘disorder’. There are many ways to define thresholds for disease or psychiatric disorder: presence or absence, level or severity of symptoms or physiological markers, or having extreme values as compared with the population. Clinical definitions are used to delineate a point at which symptoms are considered severe enough to warrant medical intervention, other definitions are based on the assumption that the measure of interest follows a statistical distribution within the population, and those at extreme ends of the distribution suffer in some way from this lack or excess of the measure. Many diagnostic definitions use a threshold score at which disease is considered present, however how this threshold is determined and to what level clinical knowledge is applied will vary between illnesses. This is much the same in mental illness, with most disorders being defined in the DSM and ICD as presence or absence of a certain number of symptoms, their severity and whether the patient meets any other predetermined criteria (frequency and pervasiveness of symptoms, impairment in day to day life, age of onset) (American Psychiatric Association, 2013, World Health Organization, 2004).

ADHD is considered a contentious example of a mental illness as it is both cognitive and behavioural in nature, and no unique patterns of physiological abnormality have been found to be associated with symptoms. Unlike some mental illnesses, where few genes are known to be involved in the causal process of the disorder, many genes have been implicated in ADHD, and so biomarkers or neuropsychological tests for objective diagnosis of ADHD have not yet been developed (Thapar et al., 2013).

This has prompted a huge volume of research into identifying the causes and aetiological mechanisms of ADHD, in particular genetic and neurological. Theories abound as to neurological deficits that may produce the core symptoms, and where these deficits may physically be based in the brain. The high heritability of ADHD suggests it may be largely genetic, and many studies examining genetic associations and their links to the hypothesised neurological pathways have been published, leading to a wealth of complex information. From this we can draw the conclusion that ADHD is not a homogeneous disorder in either cause or consequence: symptoms can occur in one of two

domains or both, perhaps with each domain reflecting different neurological deficits or genetic mechanisms.

Guidelines for assessing and managing ADHD in the UK

In spite of widespread media attention to ADHD and concerns over medicalising childhood behaviour and disease mongering (Moynihan, Heath and Henry, 2002), the picture of ADHD in the UK is more conservative than some may think, with much of the controversy surrounding ADHD being centred in the United States of America (USA), which has very different healthcare systems to the UK. The National Institute for Health and Care Excellence (NICE) guidelines for diagnosis and management of ADHD require that either DSM or ICD symptom criteria are met: severe ADHD with severe impairment is considered to be synonymous with HKD (NICE, 2008).

The recommended first-line treatment in the UK is non-pharmacological; parent education programs and behavioural interventions are advised for the patient prior to drug treatment, unless the young person is presenting with severe symptoms or impairment, in which case stimulants such as methylphenidate are recommended. The NICE guidelines state the importance of a comprehensive approach to the case regardless of whether pharmacological treatment is utilised, with psychosocial interventions considered an integral part of the treatment plan (NICE, 2008). Whether this is indeed what happens in practice varies between areas of the UK, with some only providing pharmacological treatment and no psychosocial treatment on the NHS (personal communication by teacher, 2015).

NICE advocate multi-disciplinary teams in order to best manage the needs of those with ADHD, and recognise that primary care physicians will not always be the first to recognise the symptoms; schools, special educational needs coordinators (SENCo's) or social services may be the first to flag up a child with possible ADHD (Phillips, 2006). Diagnosis in the UK is usually made in secondary care e.g. in child and adolescent mental health services or community paediatric services, and pharmacological treatment should not to be started by a general practitioner (GP) without the child being seen in secondary care services (NICE, 2008). This hierarchy, whereby GP's are advised not to prescribe pharmacological treatment to the child, unless under a shared-care agreement, reflects cultural differences between the UK and the USA where

prescription rates for ADHD are much higher. In the USA stimulant prescription prevalence was estimated at 2.9% for those up to age 19 in 2002 (Zuvekas, Vitiello and Norquist, 2006), whereas in the UK the estimated prevalence of pharmacologically treated ADHD in 2008 for those aged 6-12 was estimated at 0.92% (95% CI 0.88, 0.96) and for 13-17 year olds 0.74% (95% CI 0.70, 0.78%) (McCarthy et al., 2012).

Treatments

The NICE clinical guidelines for diagnosis and management of ADHD (NICE, 2008) state the importance of any ADHD symptoms being associated with functional impairment, as well as taking into consideration the severity of symptoms. A global approach is advised when assessing a patient with possible ADHD: assessment around various settings should take place as well as ensuring that the level of impairment the patient displays is taken into account (Hudson, 2005).

As detailed above, current UK advice is for psychosocial and educational interventions to be at the forefront of available treatments for ADHD: Table 5 summarises treatment guidelines by age group (NICE, 2008). The main debates surrounding treatment regard pharmacological interventions with methylphenidate or another stimulant: dexamfetamine. There is also one licensed non-stimulant medication: atomoxetine (Baldwin and Cooper, 2000, McCarthy et al., 2012). The most commonly used medication for ADHD in the UK is methylphenidate, with 88.6% of ADHD prescriptions in 2008 being for methylphenidate, 2.2% for dexamfetamine and 9.6% for atomoxetine (McCarthy et al., 2012). Much of the debate around the appropriateness and level of medication for children with ADHD concerns the complex relationship between pharmacological treatment of symptoms and the aetiology of ADHD. Most scientists now regard ADHD as a complex disorder which, although heavily genetically influenced, has no discrete biological or neurological cause (Richards, 2012). It is clear that pharmacological treatments are used to ameliorate ADHD symptoms without addressing the underlying cause, something that is considered a controversy in debates around the validity of behavioural disorders such as ADHD. Some argue that medication for ADHD is focussed on treating the child when the focus should in fact be on changing the environment around the child. There is clear evidence that pharmacological

treatment for ADHD leads to improvement in symptoms and impairment in the short to medium term (Tarver, Daley and Sayal, 2014).

Table 5: Recommended treatment for ADHD in UK by age group (NICE, 2008)

Age-range	**Treatment**	
Pre-school children	Parent training (either individual or group based) Education programmes	
School-age children (moderate impairment)	**First line treatment** Group based parent training Education programmes Cognitive behavioural therapy Social skills training	**Second line treatment** Pharmacological treatment
School-age children (severe impairment)	**First line treatment** Pharmacological treatment	**Second line treatment** Group based parent training Education programmes Cognitive behavioural therapy Social skills training
Adults	**First line treatment** Treatment with methylphenidate	**Second line treatment** Cognitive behavioural therapy Social skills training

1.3 Aetiological Theories of ADHD

Biological theories

Since the publication of the DSM-III in 1980 researchers have theorised about and investigated the causes of ADHD from a wide variety of perspectives. Biological theories are often supported or given weight to because they remove the cause or blame from the child or family. However, unlike some disorders, there is no clear evidence for a solely biological cause for ADHD (Faraone et al., 2015). In spite of its high heritability, often estimated at around 76% from behavioural genetics studies (Faraone et al., 2005), higher than for most other diseases or disorders (Cross-Disorder Group of the Psychiatric Genetics Consortium, 2013) there has been no evidence for simple biological explanations, either genetic, neurological or epigenetic.

Candidate gene studies have identified a variety of genes across the genome that may contribute to symptoms of ADHD, but findings are often not replicated or are weak due to small sample sizes (Thapar et al., 2013). Indeed, in a recent review Thapar et al. (2013) discuss the risks of using relatively common genetic variations to try to 'detect' ADHD as this may well be representing an arbitrary cut-off in population level gene-variance. Other studies have focussed on genes whose function is known to relate to the neurotransmitters serotonin or dopamine, hypothesising dysregulation of these neurotransmitters as underlying the symptom profile of ADHD (Faraone et al., 2005). Although there is little evidence for this, the theoretical standing is that effective pharmacological treatments for ADHD act on these neurotransmitters. Some authors suggest that lack of significant genetic findings is due to low statistical power (Doyle and Faraone, 2002) and that an effect may be found in studies that have sufficient sample sizes. Current theory is that multiple small genetic effects may contribute to the onset, persistence and remission of ADHD, and there is recent evidence of interactions between genotypes and environmental factors that can exacerbate the risk of ADHD symptoms (Faraone et al., 2015, Nikolas, Klump and Burt, 2015).

Neurological and neuropsychological theories of ADHD hypothesise specific processing deficits that result in the ADHD phenotype. Theories of a core deficit in inhibitory control or executive processes have been put forward, as well as those that suggest a singular deficit in processes associated with response inhibition (Sonuga-Barke, 2005). Experts in the field now consider

executive dysfunction to be a common co-occurring deficit and not central to the mechanisms of ADHD, even arguing that the last two decades of research on ADHD aetiology (since the publication of Barkley's work in 1997), have been wasted due to this focus on the theory of executive dysfunction (Duff and Sulla, 2014). The reality is that ADHD is not a disorder that can be simply defined.

In line with limited scientific understanding of the neurological mechanisms of ADHD, there is no definitive neuropsychological 'test' for the disorder: when existing assessment instruments are applied to children with ADHD they do not reveal a uniform deficit with any one or two particular processes (Sjöwall et al., 2013, Frazier, Demaree and Youngstrom, 2004). . However, research into differential neurological mechanisms contributing to heterogeneous presentations of ADHD is supported by resting-state functional neuroimaging evidence which suggests there are unique patterns of atypical connections between children with combined and inattentive subtypes of ADHD, as well as overlapping regions that are atypical in children with ADHD compared with typically developing children (Fair et al., 2012). Emerging research supports the theory that children with ADHD experience a neurodevelopmental delay, lagging behind other children of the same age in the maturation of structural areas of the brain including the cortex (Sripada, Kessler & Angstadt, 2014).

It has also been suggested that this lack of consistent processing deficit may reflect that there are multiple neurological pathways which lead to similar constellations of symptoms, all under the umbrella term of "ADHD" (Sonuga-Barke, 2005). Although this may be a feasible explanation, it has limited utility for understanding the profiles of individuals with ADHD. However, Sonuga-Barke (2005) does suggest that these different processing deficits may result in different ADHD subtypes, each of which could then be targeted by tailored intervention.

Having not found evidence for clear genetic or neurological pathways that contribute substantially to the cause of ADHD, researchers have more recently focussed on epigenetic changes that may explain some of this complex aetiology. Epigenetics is an emerging field, and although there have been studies that link epigenetic differences between individuals with and without ADHD, findings are still somewhat exploratory rather than conclusive (Archer, Oscar-Berman and Blum, 2011, Mill and Petronis, 2008). Epigenetics can

explain links between genes and environment, with genetic risks being either amplified or reduced through epigenetic changes (for example in DNA methylation and therefore gene expression) which themselves arise due to environmental factors, for example poor diet or stress (Archer, Oscar-Berman and Blum, 2011) (see Chapter 3 section 3.5 for a more detailed overview of the study of epigenetics). Epigenetic mechanisms also provide potential explanation for impacts of the environment on very young children's physiology, which has been illustrated by the body of research exploring maternal smoking and its link to an increased risk of ADHD (Thapar et al., 2003).

Whilst biological theories have important strengths both in indicating where research may best reveal causal mechanisms and in reducing blame and stigma on the individual for the disorder, they also have weaknesses. Individuals do not grow up in isolation from the environmental factors that impact on their lives and health, and although biological theorists may look to find a simple causal mechanism for a disorder (such as in Huntington's disease, which in the majority of cases is due to one faulty gene), in reality this is not often the case. ADHD is a particularly complex disorder. It is likened to other complex disorders such as autistic spectrum disorders because of its high heritability. The gender ratio of 4:1 (males: females) in ASD could indicate an underlying biological basis for the disorder, for example through X-chromosome linked risk genes (Russell et al., 2014). It is unclear whether this is the case for ADHD: although it has been shown to be almost identical to ASD in male: female prevalence, this gender bias is argued by some as being due to differing symptom profiles. Indeed, studies with girls only find equivalent prevalence rates to studies using boys (Knopik et al., 2005). Certainly, the evidence is not as clear-cut as it is for gender differences in ASD.

Developmental and Psychological theories

Other theoretical models consider ADHD in an individual as being causally influenced by their surroundings. These models vary from traditional psychological behaviourist models which put forward that behaviour is learned in response to reinforcement (Skinner, 1965), to sociological theories which emphasise the responsibility of those around the individual in the creation and maintenance of symptoms (Stolzer, 2009). Research and understanding of

ADHD is commonly framed using a developmental psychopathological approach, whereby ADHD and other developmental disorders are caused by disruption of the normal developmental processes in an individual. This particularly applies to ADHD as it is clinically characterised by hyperactive and inattentive behaviours that are inappropriate for the child's age, and it is often noted that these behaviours are considered developmentally normal in younger children (Rowland, Lesesne and Abramowitz, 2002). Some studies have found that children who are young within their school year are more likely to be diagnosed with ADHD than their relatively older peers (Schneider and Eisenberg, 2006). Within this framework, ADHD is therefore seen as the child displaying an immaturity rather than a deviation in the development of their attentional and behavioural regulatory skills.

Not all children with ADHD will continue to display symptoms in adulthood or through the life course (Döpfner et al., 2015, Moffitt et al., 2015), suggesting that this lag in age-normed development may correct itself over time. The neurodevelopmental delay theory is supported by evidence that cortical maturation in children with ADHD happens in the same trajectory but at a later age than in children without ADHD (Shaw et al., 2007, Sripada, Kessler and Angstadt, 2014). Those who do experience symptoms into adulthood may perhaps have a more pervasive form of ADHD (Able et al., 2007), with a longer developmental delay, or never fully catch up with their typically-developing peers. A contrasting theory recently put forward is that adults meeting criteria for ADHD do not necessarily have childhood onset of symptoms, and persistent ADHD from childhood is not as common as previously thought (Moffitt et al., 2015). Prospective studies following children with ADHD into adulthood are needed in order to disentangle this.

Developmental psychopathological approaches do not define the exact processes that cause disorders and the framework has strengths in that it is flexible and allows for multiple complex processes to contribute to the cause of a disorder (Deault, 2010). They are therefore much utilised within the ADHD literature (Johnston and Mash, 2001) as well as being open to evidence from across academic fields. An influential factor with regards to ADHD within this framework is parenting and the early environment of the child. Indeed, Taylor and Rogers (2005) combine biological and developmental theories when exploring how adversity early in a child's life could lead to developmental

disorders. This is a recurring theme throughout the ADHD literature, with researchers often combining theoretical approaches in order to best explain potential causal models for ADHD, with no one theory or field able to cover all that is known. Methodologically this approach works well, as within the body of literature surrounding the aetiology of ADHD it is now quite rare to find authors who adopt a purist approach within their domain: blending theories and disciplines may indeed allow for the best possible and most realistic understanding of this complex disorder (Richards, 2012).

Sociological theories

Although it is now widely accepted that ADHD is at least partly, if not mostly, biologically influenced, some still argue that ADHD is purely a social construct (Timimi, 2005b). These theorists contend that ADHD is a label created in order to medicalise a societal-level problem of dealing with unruly or naughty children (Stolzer, 2009). Although there is a valid debate surrounding the safety and efficacy of prescription of stimulants for young children, studies around the world suggest that rather than being a purely Western cultural construct, ADHD is a valid clinical disorder that is found in many countries (Rohde et al., 2005, Polanczyk et al., 2007, Polanczyk et al., 2014). Sociological theories are useful for understanding the context of ADHD and conceptualising knowledge around its causes. Relationships between child and parents, as well as their culture and surroundings are known to be important in the development of ADHD, and the argument has been made that a multi-faceted, bio-psycho-social theoretical approach should now be adopted when studying the topic (Richards, 2012).

When exploring social and environmental associations with ADHD, two sociological theories are of importance. One is social selection, and the other social causation (Miech et al., 1999, Hudson, 2005). These theories comment on the supposed directionality of the environment-ADHD association. Social causation theory suggests that having a disorder such as ADHD is caused by poor environmental conditions, and social selection theory hypothesises that ADHD causes the individual to ‘select’ into more disadvantaged groups due to impairing ADHD symptoms. Within the case of ADHD it is difficult to imagine how a child could select themselves to be in a deprived environment, however if the child’s parents have ADHD traits (one study found parental ADHD is 2-8 times more common in families of children with ADHD than families with

children without ADHD (Karakaş et al., 2015)), this could have led to the family's downslide into lower socioeconomic strata.

Ecological theories

Ecological theories emphasise the context surrounding an individual. One such theory often cited within developmental psychology is Bronfenbrenner's bioecological model of human development (Bronfenbrenner and Bronfenbrenner, 2009, Bronfenbrenner and Morris, 2006). This theoretical model is most often shown as a series of concentric circles with the individual in the centre. The model demonstrates how the internal state of the child interacts reciprocally, not just with the child's immediate surroundings, but also within the larger context of the child's society and culture.

The bioecological model is especially useful when exploring disorders such as ADHD, as research has shown complex and potentially causal influences coming from the many levels surrounding the individual (Cooper, 2001, Rutter et al., 1997). Hence this thesis will be based upon this framework, which is outlined further in Chapter 2, whilst also drawing on a developmental psychopathological perspective.

Chapter summary

In this chapter I have provided a brief overview of ADHD, how it is diagnosed and the theoretical stances that are taken around its aetiology and mechanisms. In the following chapter I will introduce the field of health inequalities in relation to child mental health and ADHD in particular.

Chapter Two: Socioeconomic disadvantage, child mental health and the bioecological model of human development (Introduction part 2/2)

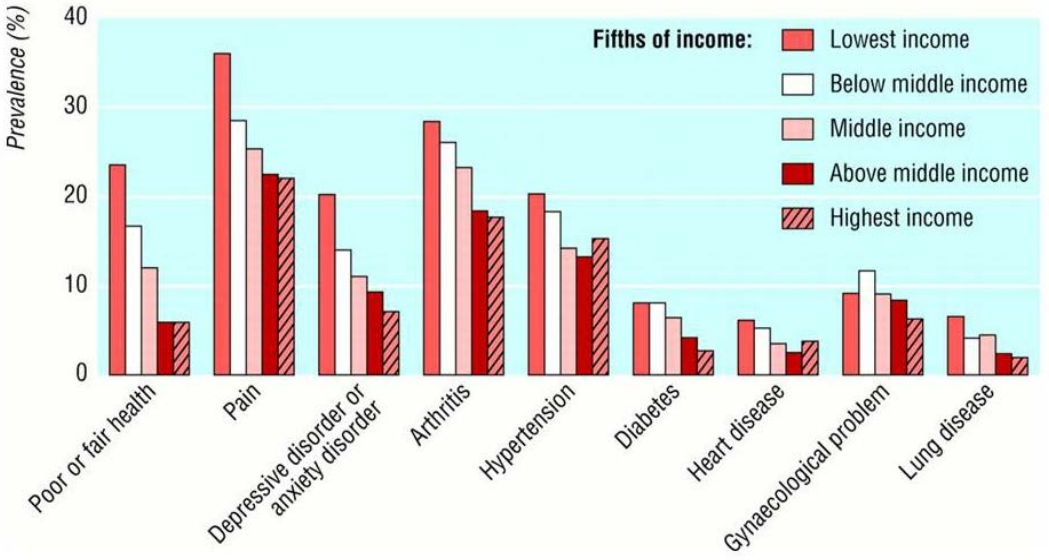
2.0 Chapter Overview

In this chapter I will review literature on health inequalities, as well as explore existing research linking socioeconomic status (SES) to child mental health problems and ADHD in particular. Mechanisms that could explain this association will be briefly introduced, within the context of a bioecological model of child development.

2.1 Socioeconomic disadvantage

There are long-established links between low SES and poor health outcomes (Mackenbach, 2005), with there being overwhelming evidence that the most disadvantaged socioeconomic groups of society are at an increased risk of a vast range of negative health, social and economic outcomes compared with those in higher SES groups. Figure 1 illustrates the prevalence of chronic health conditions by income quintiles in the USA. Researchers have focussed on the importance of the link between low SES and poor child outcomes as a mechanism by which risk of disease can be transmitted between generations (Bradley and Corwyn, 2002).

Figure 1: Prevalence of chronic conditions by income quintiles (USA) (from Sturm and Gresenz, 2002)



What is socioeconomic status?

The term “socioeconomic status” has been used widely across disciplines to refer to a person’s standing within society, often based on material measures of income, education or occupational status (Bradley and Corwyn, 2002). There is, however, a lack of consensus on how best to capture the SES of an individual or group, and researchers measure it in many ways (Bradley and Corwyn, 2002). There is also the additional complication that different measures or facets of SES may represent aspects of SES that range in stability over time. For individual-level SES, measures used include occupational category (e.g. manual/non-manual/professional), income, employment status (e.g. employed full/part time/unemployed), level of education (highest qualification completed), marital status and housing tenure. Some researchers compile indices of SES, whereby a combination of these variables are aggregated to give a score or place an individual in the ‘low’, ‘medium’ or ‘high’ category. One of the most commonly used SES indices is the Hollingshead Scale, a four-factor scale of SES developed by August Hollingshead in the 1970s (Hollingshead, 1975). Hollingshead based his scale on observations of social structure in varying areas of the USA, and had three core assumptions:

“(1) A differentiated, unequal status structure exists in our society. (2) The primary factors indicative of status are the occupation an individual engages in and the years of schooling he or she has completed; other salient factors are sex and marital status. (3) These factors may be combined so that a researcher can quickly, reliably, and meaningfully estimate the status positions individuals and members of nuclear families occupy in our society.” (Hodge and Treiman, 1968)

The four factors used by Hollingshead were education (years of schooling), marital status (which included employment status of the family unit, or “gainful employment”), occupation (based on a scale used by the US Census), and gender. This index was based on theory rather than a factor-analytic method, and is now culturally dated although still widely used and broadly applicable (Hollingshead, 1975). White (1982) suggested that a combination of measures of income, education and occupation better represented an individual’s SES than either measure alone (Bradley and Corwyn, 2002), and more recently Najman et al. (2004) used a combination of maternal age, family income, marital status and the occupational status of the

maternal grandfather to measure SES in a cohort of pregnant women. As illustrated, there is still no consensus on the best way to combine socioeconomic factors in order to measure an individual's status.

Geographical or neighbourhood-level SES or deprivation is also commonly measured. In the UK, census data are used to calculate a postcode-based "Index of Multiple Deprivation" (IMD) which takes into account levels of deprivation of income, education, employment, health and disability, geographical access to services and housing (Noble et al., 2006). Researchers in other countries use census-level methods of classifying areas, with median income, perceived safety and other measures being used to categorise neighbourhoods (Schneiders et al., 2003, Getahun et al., 2013, Albor et al., 2014). Other methods of classifying neighbourhood-level SES include the proportion of council or social housing, and the proportion of people in the neighbourhood living below the poverty line (Jackson et al., 2009).

2.2 How does low SES impact on child development? (Review of studies)

The importance of health inequalities in the UK was initially emphasised in 1980 with the Black Report, where the gap in both income and health outcomes between the wealthy and the poor was highlighted (Black et al., 1980). Since then, a large body of literature has examined how parental socioeconomic status can impact on a child's health outcomes, both of physical and mental health (Bradley and Corwyn, 2002, Najman et al., 2004, Reiss, 2013, Schneiders et al., 2003). Indeed, although research has traditionally considered SES to be a distal factor in that it impacts on child health indirectly, recently an argument has been put forward to consider SES a proximal determinant of health (Kelly, Kelly and Russo, 2014).

SES and mental health in children

Reiss (2013) conducted a systematic review exploring the association between socioeconomic inequalities and mental health outcomes in children and adolescents. In the review Reiss explores theories of social selection ("assumes that people with mental health problems drift down in socioeconomic position because of their psychopathology and inability to fulfill expected role obligations") and social causation ("posits that mental health problems are a result of socioeconomic deprivation"), with the caveat that the two theories are

not mutually exclusive (Reiss, 2013). Of the 55 studies she included, 52 had results indicating an inverse relationship between SES and mental health, concluding that those of low SES are two to three times more likely to develop mental health problems in childhood or adolescence than their higher SES peers. The review has many strengths; a comprehensive search included research from 23 countries with a mixture of cross-sectional and longitudinal/cohort designs. The author also includes many measures of SES in the review, and indeed identifies the need for clearly defined definitions of SES due to the heterogeneity of measures and concepts included in the reviewed studies. Reiss found that the SES measures most associated with poor mental health outcomes were parental income and education, as opposed to occupation or employment status.

Reiss (2013) describes the relationship between mental health problems and SES as a cycle that operates across generations. The obvious flaw with applying the social selection hypothesis to cases of child mental illness is that it is parental SES which is associated with this, and children are rarely able to influence their socioeconomic position themselves, except in exceptional circumstances such as children who became famous and wealthy after successful acting roles. Reiss (2013) highlights how social selection may work in the case of ADHD: assuming the parent has genetic traits for ADHD themselves they may then experience downward social mobility because of their ADHD, and these traits are transmitted to the child who is subsequently diagnosed with ADHD.

Hudson (2005) also explored theories of social selection and social causation with regards to mental illness by examining both census data and data for acute psychiatric hospitalisation of 109,437 individuals over a six year period. Hudson found that social causation theory was more strongly supported by the data than social selection as they found no evidence of downward drift in SES of hospitalised individuals, yet they did find an association between low SES and mental illness. This research in adults supports theories of social causation, yet the relationship across generations is in need of clarification.

SES and child emotional and cognitive development

Najman et al. (2004) explored the intergenerational transmission of socioeconomic inequalities using emotional health and cognitive development

of children as their outcome, due to the strong links between these domains in childhood and health-related behaviours in adulthood. The authors suggest that being born to parents of low SES means that a child begins life with a “poorer platform of health” and has less capability than their peers to benefit from potential advances in economic and social resources. Najman et al. (2004) followed up a cohort of 8,556 pregnant women until their child was age 14 (n= ~4,600). The authors not only looked at parental SES but also that of the maternal grandfather. They found that externalising problems in the child at age 14 were associated with their having a teenage mother, being in a low income family, living in a single parent household and also having a grandfather who was in the lowest SES group based on their occupation. Internalising problems were associated with having a younger mother and being in a low income family. The authors conclude that some health inequalities may be transmitted across generations. Unfortunately the authors did not examine the impact of change in SES of the family on child outcomes, which may have further informed the debate.

SES and resilience in child development

Having established links between socioeconomic disadvantage and behavioural problems in childhood, both internalising and externalising, Flouri, Midouhas and Joshi (2014) examined factors that predicted resilience to emotional and behavioural problems in children from families of low SES. The authors theorise that the pathway between parental low SES and child internalising and externalising problems is due to the increased stress on the parents because of lack of social and economic resources, which may lead to poor parent mental health. Poor mental health may then increase the likelihood of poor parenting practices and so increase the risk of the development of emotional and behavioural problems in the child. The concept of resilience is of importance because it is known that not every disadvantaged child goes on to experience mental health problems, and as such there must be individual differences in resilience as well as risk factors.

Flouri, Midouhas and Joshi (2014) investigated interacting characteristics that influence resilience. The authors found that high self-regulation abilities in the child in a sample of 16,916 families acted as a protective factor by moderating the relationship between low SES and emotional and behavioural

problems. Children of low SES who had high self-regulation abilities were less likely to develop emotional/behavioural problems than their peers of middle SES with poor self-regulating abilities. The authors suggest that both high self-regulation and good verbal cognitive abilities were protective factors in the study, but highlight the role of parents in mediating these effects. It may be that the detrimental effects of SES are lesser in magnitude than positive effects of child resilience, especially with regard to self-regulation.

In the case of ADHD, one of the prominent aetiological theories is that there are deficits in the child's ability to self-regulate their responses and behaviours. If this is indeed the case, children with ADHD are highly unlikely to have high self-regulation abilities, thus limiting the potential protective power of this trait. In the sample used by Flouri, Midouhas and Joshi (2014), the Millennium Cohort Study (MCS), it would have been of interest to know if any of the children with high self-regulation abilities were diagnosed with ADHD or had attention problems. This illustrates that mechanisms between SES and ADHD are likely to be complex and involve both risk and protective factors. If children from low SES households are more likely to have poor self-regulation abilities, this ADHD-related trait potentially exposes them to an increased risk of ADHD through lack of resilience. Circular risks and exposure relationships like this illustrate how complex the relationship between SES and ADHD is likely to be: more studies focussing on specific characteristics of the SES-ADHD relationship are needed.

Mechanisms of links between SES and child development: parental well-being

Utilising the MCS, Kiernan and Mensah (2009) found that 18% of the children in persistently poor families had behavioural problems as compared with 4% of children in non-poor families. Children of poor families were also more likely to have cognitive delay. The authors also investigated maternal depression as a putative mechanism that may explain the findings and found that it was associated with behavioural problems in three year old children, in fact they found that maternal depression was a stronger predictor for behavioural problems than poverty (defined as an income of 60% below the median before housing costs were taken into account), and poverty was a stronger predictor for cognitive delay. This study lends support for the

theoretical mechanism proposed by Flouri, Midouhas and Joshi (2014), and with regards to ADHD this could mean that children who are in a socioeconomically disadvantaged family where the mother has experienced mental health problems could be particularly at risk for ADHD. Alternately, SES may be a confounder in the relationship between maternal and child mental health problems.

Boe et al. (2013) also examine the role of emotional well-being of parents and parenting practices in the association between SES and child mental health. The authors explore Conger and Elder's Family Process Model (Conger and Elder, 1994), which puts forward the theory that parenting is a key mechanism through which the SES-child wellbeing relationship operates. There is supporting evidence for this mechanism described above, and the association has been established using measures of income for SES (Benner and Kim, 2010, Parke et al., 2004, Mistry et al., 2002). Boe et al. (2013) expand on this by using multiple measures of SES, in particular maternal education, as it has been suggested that mothers of higher educational level will have more knowledge about child rearing and thus have more supportive parenting strategies than lesser educated mothers (Morawska, Winter and Sanders, 2009, Waylen and Stewart-Brown, 2010). The authors hypothesise that because of this education may have a direct effect on child mental health and income an indirect effect through parental well-being. This hypothesis was supported by their analysis. Additionally, the authors found that the effect of maternal education operated through negative discipline (factors related to child punishment). This however may be an oversimplified conclusion, as paternal education was found to be associated with child externalising problems but not mediated by any measured parenting factor (Boe et al., 2013).

The above studies examine parent mental health and well-being mainly in a cross-sectional manner or during the lifetime of the study child. Van Batenburg-Eddes et al. (2013) bring consideration of timing to the forefront in their examination of parental depression and anxiety during pregnancy and attention problems in children at age three or four. Although the authors found an association between maternal symptoms of anxiety or depression in pregnancy and subsequent attention problems, they found that this was no longer significant when they adjusted for mental health problems after birth. They also found similar associations between maternal and paternal mental

health problems during pregnancy, suggesting that intrauterine effects are not the cause of this association (Batenburg-Eddes et al., 2013). If the timing of exposure to parental mental health problems during pregnancy is not key to the development of ADHD, research that investigates exposures during childhood is well positioned to further explore these mechanisms.

Mechanisms of links between SES and child development: home learning environment

Mulligan et al. (2013) explored the home environment in terms of enrichment, learning materials and opportunities, family factors, physical environment quality and other dimensions, and found that children under the age of ten who had a poor quality home environment or fewer opportunities for learning at home were rated as having more hyperactive and inattentive symptoms by their teachers. SES was measured in this study as the type of occupation held by the parent and was found to have a relatively low contribution to ADHD symptoms. This may reflect the choice of SES measure.

Schmiedeler, Niklas and Schneider (2013) also examined the home environment with regard to development of ADHD, with their definition and measure of home environment encompassing the provision of intellectual stimulation for the child, measured by parent report of what was present in the home and what activities parents engaged in with their child (e.g. reading books). The authors also considered family SES, and hypothesise that because parents of higher SES are more likely to engage in development-enhancing activities with their children than their lower SES counterparts, the link between low SES and ADHD could be explained by these parenting practices. They found that both low SES and poor home learning environment were associated with increased symptoms of ADHD in a sample of 924 children (although the SES-ADHD association was not statistically significant at $p<0.05$), and that home learning environment mediated the association between SES and ADHD (which was statistically significant at $p<0.05$). The authors used a measure of occupational prestige for SES and utilised a community sample (Schmiedeler, Niklas and Schneider, 2013).

2.3 Research exploring associations between SES and ADHD

In this subsection I will describe studies that have examined the association between SES and childhood ADHD specifically, with a focus on the role of family life.

A recent study in the UK explored the link between SES and incidence of ADHD. The authors utilised GP records through the Clinical Practice Research Datalink, which holds routine data for around 13.5 million individuals. The authors used the IMD of the GP surgery as their SES measure, and Read codes for ADHD diagnosis and treatments as their outcome. They found that those attending GP surgeries in the most deprived IMD quintile had a significantly higher incidence rate of ADHD cases than the other four quintiles: 13.84 cases per 10,000. Similarly, those in the least deprived quintile had a significantly lower incidence rate than the other four quintiles (9.24 cases per 10,000) (Hire et al., 2015): a relative risk of ADHD of 1.50 (95% CI 1.38, 1.63) for those in the most deprived quintile compared with the least deprived. In order to establish whether practice-level IMD is a relevant measure of SES for individuals, the authors further reported that individual IMD data were available for 80% of patients with ADHD, and in 70% of instances, patients were either living in areas of equal or higher deprivation than their GP surgery IMD (Hire et al., 2015). This study provides initial evidence that there is indeed an association between SES and incidence of ADHD in the UK.

A study by Larsson et al. (2013) examined in detail the association between family income in early childhood and ADHD in a cohort of 811,803 children, with low income considered by the authors as a marker of causal factors for ADHD. Utilising data from Swedish national registers, the authors used information from cousins and siblings of children with an ADHD diagnosis (or prescription for stimulants) in order to reduce confounding from genetic and shared environmental effects. They found that those in the lowest income quartile had a hazard ratio of 1.61 for ADHD as compared with the highest quartile, and the rising risk was incremental in line with lowering income quartiles (Larsson et al., 2013). One aspect that is apparent from the study is that many factors that are modelled in the causal pathway have relatively small effects on ADHD as an outcome. The authors found that the impact of low income on ADHD risk was similar in magnitude to that of low birth weight or

preterm birth: both universally acknowledged to be robust predictors of poor health throughout life (Hack, Klein and Taylor, 1995).

In line with the above, an earlier study examined the impact of low income and child health (measured by mother reports of physical symptoms and child's general health status), and found that this association in the Avon Longitudinal Study of Parents and Children (ALSPAC)is almost completely eliminated when taking into account maternal behaviour and mental health (Burgess, Propper and Rigg, 2004). The authors also examined the timings and duration of these impacts, and found that persistent low income seems to be more detrimental for child outcomes than being of low income at one time point in the study. These findings drive the conversation back to the potential of there being a direct impact of low income on the aetiology of ADHD, and whether material resources are of crucial importance in this (Burgess, Propper and Rigg, 2004). From the above evidence it could be considered that this may be because of the lack of resources to provide a stimulating environment for the child during early development.

I have briefly mentioned that the impact of parental ADHD (and thus low SES) on a child's outcome of ADHD may be due to genetic selection. The impact of a parent having ADHD may however exert effects on the child's outcome in other ways. One Canadian study explored parenting behaviour in a sample recruited from the local community of 80 mothers with differing levels of ADHD symptoms. Those mothers with higher levels of ADHD symptoms reported having lower parenting self-esteem than the low ADHD symptom group, as well as reporting lax parenting and using more ineffective disciplinary styles (Banks et al., 2008). ADHD symptoms were also related to comorbid disorders: this is not surprising as a high percentage of children with ADHD will also have other mental health disorders such as conduct disorder (CD) or anxiety (Banks et al., 2008). Of these comorbidities, the authors found no link between ADHD and co-existing depression in their sample of mothers, which is of interest as I have discussed parent mental health as a potential causal process and findings have been reported linking maternal mental health and child ADHD. However this may be because a convenience, non-clinical sample was used by Banks et al., and as there is a low base-rate of problems in these samples, a much larger sample of mothers would be needed to detect whether ADHD and depression do co-occur.

Also exploring parenting and ADHD, Harvey et al. (2003) recruited a sample of parents with ADHD whose children were also diagnosed with ADHD, and examined different aspects of parenting. The authors found that mothers who reported inattentive symptoms were more likely to report lax parenting and also negative parent-child interactions (the latter especially if the mother reported moderate levels of inattentive symptoms). For fathers, lax parenting was associated with inattention and impulsivity, and arguing during the parent-child interaction may be a risk factor for impulsive symptoms. During the course of the study a parent training programme was conducted: the authors found that after parent training the impulsivity-arguing association in fathers decreased, however the parent training had little effect on parent ADHD symptoms or the quality of the parent-child interactions. The authors also discussed the role that comorbid disorders may play in parental ADHD and the impacts these may have on parenting skills (Harvey et al., 2003).

Furthering the discussion on parental ADHD when the child also has ADHD symptoms, Psychogiou et al. (2008) take a different perspective from that considered above. The authors discuss the negative effects of child ADHD on parenting, acknowledging that parents who have a child with ADHD find their child's behaviour to be both stressful and challenging, which leads to negative impacts on parenting. This cycle between parent and child influence on parenting strategies is teased apart by the authors when exploring whether the mothers' own ADHD symptoms may result in different parenting skills. They found that parenting of children with high levels of ADHD symptoms was more critical, directive, negative and less socially engaged than parenting of children with low ADHD symptoms. However when the mother and child both had high levels of ADHD symptoms, parental responses to the child were more positive and affectionate than when the mother did not also have ADHD symptoms. The authors also found that the negative impacts of child ADHD symptoms on parenting were much lower when mothers had high levels of ADHD symptoms, because of higher levels of positive parenting (rather than less negative parenting) (Psychogiou et al., 2008).

Whilst Psychogiou et al. (2008) consider ADHD in mothers of children with ADHD, Romirowsky and Chronis-Tuscano (2013) consider the role of fathers' ADHD symptoms on conduct problems in children with ADHD. The authors found a differential effect due to involvement: if a father had low

involvement in parenting, his ADHD symptoms were not related to child conduct problems. However, if the father reported being highly involved with parenting then his ADHD symptoms were positively related to the child's conduct problems. Also of interest was the interaction found with SES: low SES fathers were less likely to be highly involved with parenting than high SES fathers. The authors concluded that paternal involvement moderates the relationship between paternal ADHD symptoms and conduct problems in the child with ADHD. This study highlights the complex interaction between how a parent's own ADHD symptoms may relate to a child with ADHD; pathways include genetic effects, effects of parenting involvement, susceptibility to other mental health problems and parenting skills. It has also been discussed how across all of these factors the impact of low SES on a family increases the chances of negative outcomes for all involved (Romirowsky and Chronis-Tuscano, 2013).

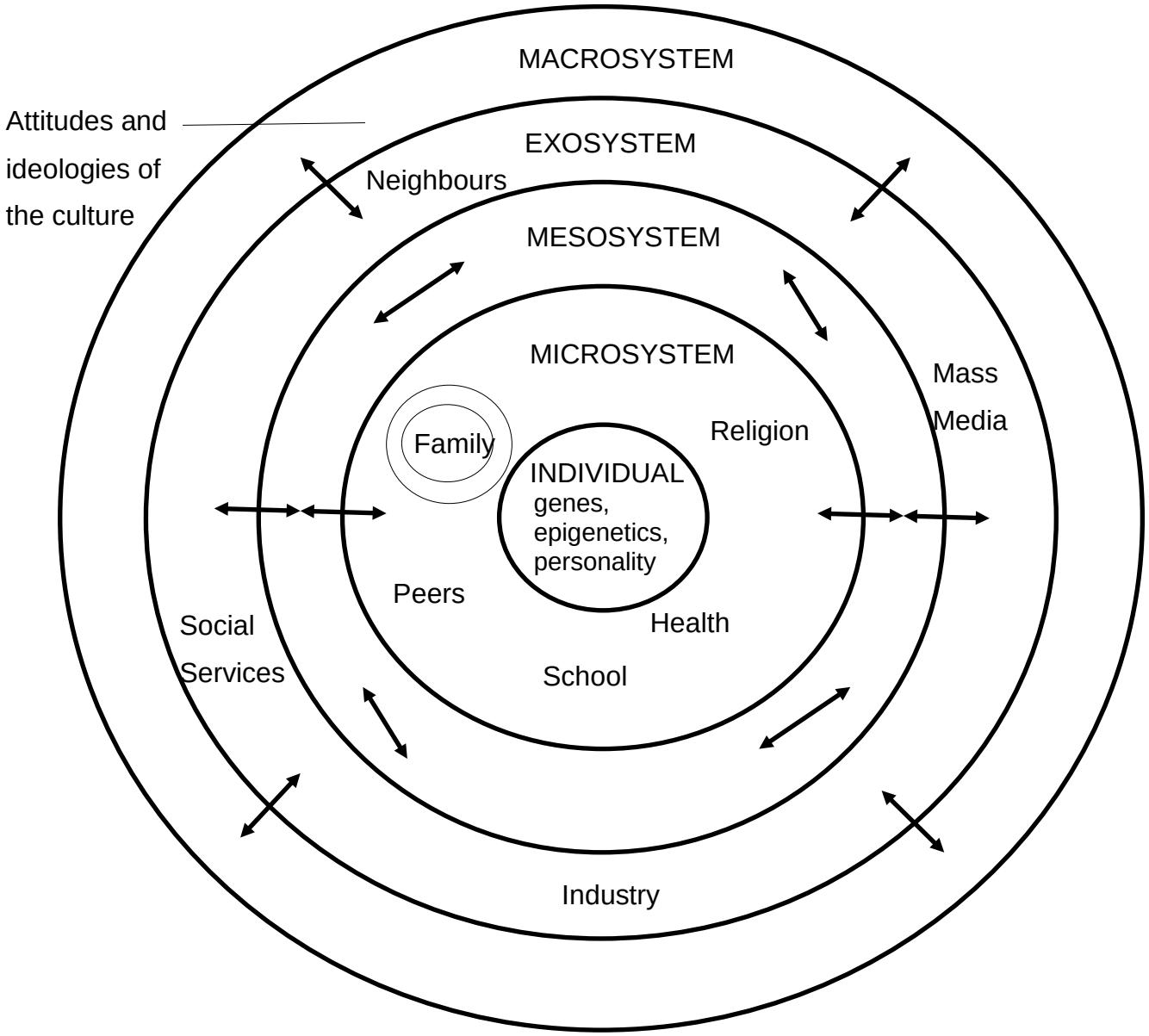
2.4 ADHD and SES within an ecological framework

Current evidence shows associations between a variety of socioeconomic factors and ADHD. Both social causation and social selection theories have been put forward to explain this association. It could be that ADHD is associated with low SES through social causation (low SES has causal influence on ADHD) due to direct impacts of SES factors on the child, or it could be due to other variables which themselves are associated with a disadvantaged socioeconomic living situation (for example poor diet, living within a dangerous neighbourhood or suboptimal parenting strategies). This is often referred to as proximal or distal influences, although more recently researchers have argued that factors that appear distal may actually exert proximal effects. In the case of SES, Kelly, Kelly and Russo, (2014) argue that SES is a proximal risk factor if it is directly related to the immediate environment that plays a role in pathogenesis. Evidence for this does not exclude that there may be social or genetic selection effects at play.

Within Bronfenbrenner's bioecological framework it is easy to see how the different facets of a child's life may contribute to, or reduce, their ADHD symptoms over the course of development (see Figure 2). The framework also allows for interactions between areas, for example parenting practices may be influenced by parents' own genetic makeup, their religion or culture, and attributions for behaviours the child displays may be influenced by media, or

within the more immediate environment, neighbours or schools. This complex profile of factors is theoretically appealing because it represents a more 'real-life' or ecologically valid model of how a child grows up and develops, and details some of the major influences within their development (Bronfenbrenner and Morris, 2006, Bronfenbrenner and Bronfenbrenner, 2009).

Figure 2: Bronfenbrenner's bioecological model of human development (adapted from Bronfenbrenner and Bronfenbrenner (2009)



One aspect of the model that Bronfenbrenner does not expand upon is that those closest to the child will also have their own ecological system, which will impact on how they interact with the child. Parents' genetics will impact on their own life experiences and influence the child both by inheritance of these genes and the impact of parents' behaviour on the child's upbringing. This is alluded to in Figure 2 by the circles around those within the child's mesosystem. This also applies to teachers and other individuals close to the child; although they will not share genes unless related by blood, the experiences and innate individual characteristics of teachers will influence how they perceive the child and whether they see the child as experiencing symptoms of ADHD.

As mentioned, researchers now call for integrated approaches when relating aetiological theory to ADHD. This takes into account the traditional gene-environment debate by suggesting that strict uni-disciplinarian theory does not reflect the clinical picture of causal influences on ADHD within a child. However, it is still commonplace for authors to state their theoretical approach to ADHD when publishing an article on the subject. For example Deault (2010) takes a developmental psychopathology approach in her review on parenting, comorbidities and ADHD, Taylor and Rogers (2005) consider ADHD a neurodevelopmental disorder, implying that the authors believe ADHD to have biological origins, whilst Timimi and others in the critical-psychiatry movement consider it to be a cultural construct (Timimi, 2005a) and Miech explores both social selection and social causation theories (Miech et al., 1999).

Applying Bronfenbrenner's model to the aetiology of ADHD

Bronfenbrenner's ecological model is often drawn as five concentric circles detailing the individual and their interactions with their surroundings, both those proximal to the individual such as immediate family and those more distal, for example neighbourhoods (Figure 2). Bronfenbrenner comments that defining properties of the model are the proximal processes: reciprocal interactions between the child and the factors in the systems surrounding them (Bronfenbrenner and Morris, 2006). These are thought to impact on development differentially depending on the characteristics of the individual, the environment in which the processes are taking place (both proximal and more remote), and the particular outcome of interest (Bronfenbrenner, 1994), as well

as the time over which the processes take place (Bronfenbrenner and Morris, 2006).

The individual

The centre of the model (when applied to the aetiology of ADHD) is the child. Each child will have unique genes and predispositions as well as a unique early environment, all of which may contribute to their risk of developing ADHD (Taylor and Rogers, 2005). As discussed earlier, genetic influences play a large part in the makeup of ADHD (Rutter et al., 1997), and these innate processes within the child, in interaction with their early environment (proximal processes), would give them a level of risk or resilience for ADHD-like behaviours.

The Microsystem

Immediately surrounding the child are factors such as family, school, peers and health services. Each of these may play a role in the aetiology and/or recognition of ADHD. There is a large body of research detailing family processes, particularly parent-related factors that may play a significant part in exacerbating a child's ADHD symptoms, some of which have been discussed. Parental mental health, parenting styles and parental behaviours have all been shown to be associated with ADHD risk in children (Taylor and Rogers, 2005, Johnston and Mash, 2001, Deault, 2010).

Schools and health services are key in the recognition and treatment of ADHD. In the UK, schools are often the first to recognise potential ADHD within a child, perhaps because of the level of disruption caused to the class. This will often depend on individual teachers' beliefs and knowledge around ADHD (Hillman, 2011). Diagnostic criteria for ADHD state that symptoms must be present across a range of settings, which regularly includes the school, and a host of factors put pressure on teachers to increasingly recognise and evaluate children who are struggling, either to provide additional support to the child or in order to be able to access extra resources for them (Moore et al., 2015).

The role of peers is perhaps not considered to be central in the development of ADHD, but more linked to awareness of the disorder and exacerbation and course of symptoms. A recent study (Singh, 2011) interviewed over 150 UK-based children diagnosed with ADHD about their experiences at school. The data highlighted the interplay between ADHD

symptoms and aggressive behaviour. Children reported that when their peers acted negatively towards them they were likely to behave unpredictably and potentially lash out, exacerbating behaviours which make school life challenging. Children also reported using their ADHD diagnosis as an excuse or reason for behaving badly, and some commented that their friends also told teachers that they (the friend) had ADHD, even if this was not necessarily true. Peer relationships are important for social development, and the nature of these relationships can impact on a child's hyperactive or impulsive behaviours. Studies have found that children with ADHD are both more likely to experience bullying as well as bully other children (Holmberg and Hjern, 2008), and symptoms can also be exacerbated by the loss of a close friendship (Ford et al., 2007a).

Health services are of importance, not in the cause of ADHD, but in recognition, maintenance and treatment of the child. Early recognition and appropriate treatment (be it psychosocial, behavioural or pharmacological) may improve a child's ability to cope with their symptoms and the impairments they may face because of them.

The Mesosystem

The third circle of Bronfenbrenner's model is an interactive one, illustrating links between facets within the microsystem, exosystem and individual, and also the interaction of different variables within one system, for example between health services and school, or neighbours and family. This reflects some of the complex interplay that shapes a child's experiences and behaviours. For example, family-level disadvantage has been shown to be associated with ADHD risk (Graetz et al., 2001, Boe et al., 2012), but studies have shown that this may be at least partially due to neighbourhood-level deprivation (Schneiders et al., 2003). There are also reciprocal influences between school level policy and local politics, as well as the media and a family's perception of what ADHD is.

The Exosystem and Macrosystem

The exosystem is the fourth level of Bronfenbrenner's model. It includes higher-level services such as social services, local politics and the media. The main role of the exosystem in ADHD aetiology is its influence on lower-level

perceptions of the disorder. This is also linked with the outer layer of the model, the macrosystem, which includes the attitudes and the ideologies of a culture. ADHD, although shown to be more than a purely cultural construct (Rohde et al., 2005), is certainly experienced within a larger cultural context in terms of recognition, treatment, prevention and aetiological beliefs. One example of this is the large amount of attention given to ADHD as a medical disorder in the USA. From media attention, such as Louis Theroux's TV episode entitled "America's medicated kids", to concerns about disease mongering and the role of pharmaceutical companies in promoting stimulant treatment through funding patient information groups (Moynihan, Heath and Henry, 2002), alongside differing healthcare availability due to a privatised medical system, the USA's version of ADHD is qualitatively different than that in, for example, the UK. The UK has free healthcare, conservative prescription guidelines for ADHD (NICE, 2008), and differing attitudes towards medicalisation of the disorder, which appears to be reflected in the reluctance of many teachers to suggest stimulant treatment for children with ADHD symptoms (Moldavsky, Pass and Sayal, 2013).

ADHD research has spanned many countries across the world, and although reported prevalence does differ between countries this is thought to reflect methodological differences in studies as opposed to true variation of prevalence (Polanczyk et al., 2007). Nevertheless, cultures and countries differ both in their policy for recognition of ADHD as a disorder, and in the need for and manner of intervention.

2.5 Chapter Summary

I have introduced the field of health inequalities, as well as explored the literature linking SES to child mental health problems and ADHD in particular. Mechanisms that could explain this association have also been briefly introduced along with Bronfenbrenner's bioecological model of child development. In Chapter three I will provide an overview of each of the studies that comprise this PhD thesis, and explore the rationale for each.

Chapter Three: An overview of the thesis

3.0 Chapter Overview

This chapter provides a brief overview of the studies that comprise my thesis, outlines the rationale for each, links between studies and discusses in broad detail the methodologies used. The original research described in my thesis consists of three published journal articles, two articles submitted for publication and one chapter written in collaboration with a researcher at the University of Bristol that we plan to submit to a journal. All are presented in Microsoft Word format.

3.1 Overview of the thesis

This thesis builds on a recent paper describing potential explanations for associations between socioeconomic disadvantage in families and ADHD in children (Russell et al., 2013). In the study, several pathways that could explain this association are listed: mediation by risk factor (pre or perinatal, or during childhood), genetic confounding (social selection), reverse causality, identification bias (by clinicians) and reporting bias (by parents/teachers) (see Figure 1). This study was informative but does not provide information on whether the association between SES and ADHD is generalisable and consistent. It raised a number of unanswered questions about the nature of the SES-ADHD association in childhood that my thesis aimed to partially disentangle. The studies in my thesis first consolidate published evidence for the SES-ADHD association, and then explore one of the above pathways across childhood: that of social causation (socioeconomic disadvantage causing ADHD) and its mediation by other early life exposures.

My thesis addresses two overarching research questions assessing the evidence around social causation of ADHD through socioeconomic disadvantage: firstly, is there evidence for an association between socioeconomic disadvantage and childhood ADHD? Secondly, how does this association vary throughout childhood and what implications does this have for understanding the relationship between socioeconomic disadvantage and ADHD?

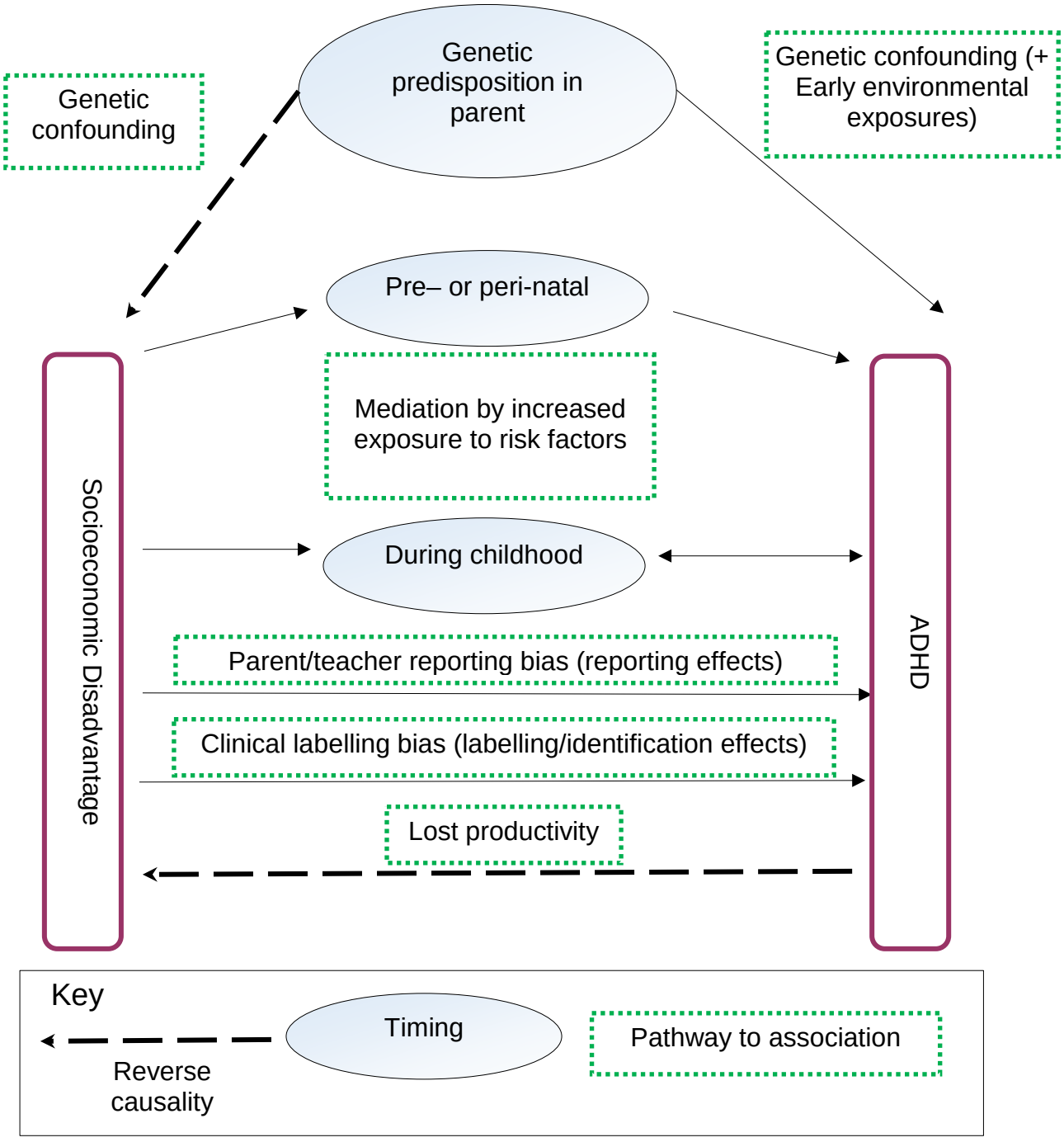
The first study in the thesis is a systematic review that evaluates whether an association between SES and ADHD has been previously reported in the literature, and whether there was evidence that the association was robust

across countries and study populations. This was necessary to establish the scope of existing evidence as groundwork for my other studies. I then go on to describe study two, a qualitative study that investigates whether those involved in the identification and management of children with ADHD (teachers and other educational practitioners) believe there to be a causal link between SES and ADHD, and investigate how educational practitioners conceptualise the causes of ADHD.

The qualitative study is followed by three analyses of existing data that provide evidence of the mechanisms of the association and elucidate knowledge on the relevance of different timing and trajectory of SES across childhood. Study three (chapter 6) explores how different measures of SES are related to diagnoses of ADHD, as well as exploring evidence for early life home and family factors that may mediate the association. Following this, study four (chapter seven) describes an analysis of existing data that focuses on disaggregating the association between SES and ADHD over the course of childhood, and explores whether the timing of exposure to low SES or the duration of exposure is related to symptoms of ADHD across childhood. Study five (chapter eight) explores whether there are different levels of ADHD symptoms in children who experience different patterns of exposure to financial difficulty across childhood. As my aims were to elucidate evidence for how the association between SES and ADHD operates, if these studies find differential patterns of ADHD symptoms due to different SES exposures or timing, inferences can be drawn about whether there is likely to be a causal relationship from SES to ADHD, and whether theories of social causation are supported.

Finally, I report on study six: a collaborative study with the University of Bristol where we explore if low SES is associated with epigenetic differences across childhood, as this could be a potential explanation for how the environment, namely SES, exerts its effects on health and could lead to disruption of normal development. The following sections will provide a brief overview of the rationale for the studies I report, how the studies inform one another and address gaps in existing literature along with some detail on methodologies.

Figure 1: Schematic diagram illustrating explanations for the association between socioeconomic disadvantage and ADHD, from Russell et al. (2013)



3.2 Rationale for systematic review (study 1). This study is reported in chapter four (page 67)

Rationale

My first study aims to assess whether there is an evidence base for an association between SES and ADHD in the academic literature using a systematic review and meta-analysis. The review aims to specifically address if there is evidence for an independent association between a diagnosis of ADHD in children and low family SES, as well as explore the size of the association if it is present. I identified this as a core question that underpinned the rest of my thesis: to inform further studies I needed to establish where there was evidence that the association between SES and ADHD occurred, and whether this was found across contexts and across childhood.

Methodology

I use a systematic review to answer these questions as this is seen as the gold standard for synthesising data on a research topic. The strengths of systematic reviews come from the transparent methodology and rigorous inclusion and exclusion criteria used to select studies (Egger, Davey-Smith and Altman, 2008). Although systematic reviews are often conducted in order to collate evidence on treatment efficacy, they are also a useful tool for collating existing evidence for any research question. Meta-analysis, a statistical supplement to a narrative synthesis of literature, is another useful tool and statistically combines individual study results in order to aid the conclusion of a review. My systematic review concludes that there are widely reported associations between low SES and ADHD, however determining the strength of the association is difficult due to the heterogeneous measures authors use for both SES and ADHD.

My systematic review identifies that there are a host of measures of SES that may each have a different relationship with ADHD. The review reveals the limitations of SES as a conceptual measure that is measured in multiple ways. This led me to question which aspects of SES are the most salient to the relationship. It could be that the association between ADHD and SES is specific to one facet of the heterogeneous construct of SES, for example maternal education, family structure or low income: finding this could shed light on the causal mechanism by which it operates. This question raised by the findings of my systematic review is one I was able to explore further in study 3, described

in chapter six. My systematic review found evidence for the SES-ADHD association across countries.

As described in chapter one, the conceptualisation of ADHD varies by country and across time. As I intended to design further studies using a UK based cohort, I thought it important to gain further understanding of the way that cultural context influences how ADHD is conceptualised in the UK. It became important to understand lay conceptualisation of the causes of childhood ADHD and whether these are described in terms of factors linked to family SES. I found there was a gap in the literature on teachers' experiences of working with children with ADHD. The finding of a fairly robust link between ADHD and SES in the systematic review raised the question of whether teachers who work with ADHD children know about the relationship between ADHD and SES, and if so, whether they see SES as causal factor. I therefore set about answering this through conducting a qualitative research study (study 2), described below.

3.3 Rationale for qualitative research (study 2). This study is reported in chapter five (page 102)

Rationale

I conduct this study to gain an in-depth understanding of the beliefs and conceptualisations of ADHD among those who commonly work with children with ADHD: educational practitioners. My initial systematic review led me to question whether the SES-ADHD association is understood as causal in an educational context, given that educational practitioners work directly with affected children. I also aimed to begin to untangle how such understandings might modify what is considered to be ADHD by those frequently asked to inform on a diagnosis. Investigating how educational practitioners conceptualise the causes of ADHD can be used to aid understanding of whether empirical research findings are reflected in commonly-held beliefs, as well as informing discussion on the nosology of ADHD. My qualitative study aims to explore what educational practitioners believe are the causes of ADHD and how they conceptualise these.

Methodology

I conduct this study with the aim of exploring educational practitioners' (e.g. teachers, teaching assistants (TA's), Special Educational Needs Co-ordinators (SENCo's)) experiences and beliefs about working with young people

with ADHD. This study not only addresses a gap in the research literature (Moore et al., 2015) but highlights the significance of the role of educators when researching and understanding a childhood condition such as ADHD. A series of systematic reviews undertaken to explore the evidence for non-pharmacological interventions for ADHD in school settings found that there is a knowledge gap in research into the qualitative experience of educators working with children with ADHD in the UK (Moore et al., 2015).

Teachers and other school staff are often the first to recognise that a child may be displaying symptoms of ADHD, and their views are crucial in making an informed clinical decision on a diagnosis (Phillips, 2006). As educational practitioners play an important role in the recognition, referral and treatment of children with ADHD, an understanding of the views they hold about how ADHD is caused and the role that social and environmental factors play in expression of ADHD symptoms is necessary in order to determine whether this may impact on how they rate behaviour when asked to provide information to inform a clinical diagnosis of ADHD (Vereb and DiPerna, 2004). This topic is also of personal interest to me given my background working in schools for children with special educational needs.

My qualitative study utilises focus groups and individual interviews across ten schools in the South West of England and includes 41 educational practitioners with varied experience and job roles. The data are analysed using thematic analysis (Braun and Clarke, 2006).

I explore what practitioners believe to be the cause of ADHD and how this relates to their experience working with young people with ADHD or symptoms of ADHD. I also construct a model illustrating the four causal theories that practitioners advocated, and discuss these conceptualisations relative to scientific research findings.

Although the qualitative study is not investigating the topic of my thesis in the same manner as the analyses of existing data, the findings are relevant and important to the subject as a whole. My findings raise further questions about the association between ADHD and SES, and have implications for nosology: for example whether ADHD should only be diagnosed where its cause is not thought to be heavily environmentally influenced.

3.4 Rationale for analyses utilising ALSPAC data (studies 3, 4 and 5). These studies are reported in chapters six (page 124), seven (page 152) and eight (page 176)

Rationale

As my systematic review reveals that the facet of SES measured may be key in determining the relationship between SES and ADHD, this raised a question as to whether the specific facets of SES associated with ADHD could provide clues to the mechanism by which the association operates. I therefore conduct an investigation of which facets of SES are most strongly associated with ADHD in a longitudinal UK birth cohort. My systematic review also finds that there are gaps in the published literature that could aid a deeper understanding of the relationship between SES and ADHD. The impact of different timings and duration of exposures to SES on the association with symptoms of ADHD is currently unknown, as is whether experiencing a change in family SES affects the association. In the following section I describe the ALSPAC and brief methodology of these studies.

Methodology

I answer these questions in three separate studies using data from the ALSPAC. This longitudinal birth cohort is the most appropriate dataset available to answer these research questions as it is population-based and the findings are therefore more likely to be generalisable, particularly if they support previously reported associations. Longitudinal studies allow for detailed examination of the course of both family SES and ADHD symptoms, and ALSPAC has recorded several measures indicative of ADHD at different timepoints, including research (DAWBA) diagnoses and SDQ scores. They allow exploration of whether there are specific developmental periods that are important in the SES-ADHD association or whether changes in SES are followed by changes in ADHD symptoms. A wide range of socioeconomic data are available, some measures are repeated across the course of childhood, and there are both categorical and dimensional measures of ADHD. ALSPAC data does impose limitations on the studies in my thesis: there is no measure of parental ADHD traits or diagnoses meaning that it is not possible to control for inherited influences, and many of the measures are self-report questionnaires, leading to the possibility of reporter bias in the data.

ALSPAC is one of several longitudinal birth cohort studies set up in Europe in the late 20th century that aimed to extend research examining modifiable influences on child health and development. It was originally funded by the World Health Organisation Europe (Boyd et al., 2013). Existing cohort studies in the UK were established in the mid-20th Century, such the Aberdeen Children of the 1950's cohort (von Stumm et al., 2011), and ALSPAC was designed to update and progress the understanding of how genetic and environmental characteristics influence health and development in parents and children (Fraser et al., 2013). ALSPAC began by recruiting pregnant mothers due to give birth between 1st April 1991 and 31st December 1992, in the county of Avon in the South West of England (Fraser et al., 2013) and had an original cohort of 14,541 pregnancies (Boyd et al., 2013). The number of individuals with available data varies by individual study and measures used, with some variables (particularly those measured in the first few years of the study) having more complete data than others. This is due to attrition and supplementary recruitment, however sample sizes are generally substantial.

Data from the ALSPAC are utilised by and are available to accredited researchers from a wide range of disciplines, encompassing health, social science and education. Up to the age of 18 participants and their families completed 59 questionnaires and nine clinical assessments, as well as over 11,000 children providing DNA samples (Boyd et al., 2013, Fraser et al., 2013).

The three studies described in my thesis that I conduct with the full ALSPAC population are designed as follows: study three takes advantage of the longitudinal nature of the cohort and uses predictors at birth, mediating factors from ages two to six and a research outcome of ADHD at age seven to examine whether home and family environment factors mediate the association between SES and ADHD. In study four, I use multilevel modelling to capture SES and symptoms of ADHD across childhood in order to assess the impact of timing and duration of low SES on symptoms of ADHD: in this study I am assisted in the analysis by two statisticians: William Henley and Justin Matthews. I complement this with study five, that uses multilevel mixed effects regression models to assess whether changing SES is associated with symptoms of ADHD.

Finding evidence that there are complex relationships between SES and ADHD across childhood, I move on to examine a mechanism by which

environmental factors such as SES may potentially influence human biology and disease: epigenetic variation.

3.5 Rationale for epigenome-wide association study (study 6). This study is reported in chapter nine (page 201)

Rationale

Having explored family and environmental factors that may mediate the SES-ADHD association and finding evidence that the association operates early in childhood, I decided to explore a feasible biological mechanism through which exposure to low SES may result in biological changes in humans. One viable explanation is that low SES exposures alter an individual's epigenome. These alterations then lead to biochemical differences in exposed individuals that may contribute to disease pathways. In study six I investigate whether exposure to socioeconomic disadvantage is associated with characteristic epigenetic profiles (measured by DNA methylation) in children in the Accessible Resource for Integrated Epigenomic Studies (ARIES) subsample of the ALSPAC. If this study were to find distinct epigenetic signatures reflecting exposure to socioeconomic disadvantage, further research could explore whether these epigenetic differences are also associated with ADHD, or whether their position implicates involvement in biological pathways that could underpin expression of ADHD symptoms.

Methodology

The epigenome consists of molecular markers that alter the structure of DNA and thereby regulate gene activity and expression (Rozek et al., 2014). These markers are crucial because the way in which DNA is physically coiled in space alters the access of enzymes, which can lead to transcription or silencing of genes (Szyf and Bick, 2013). The discovery and improvements in understanding of epigenetics was exciting to scientists as it was an obvious mechanism, beyond genetic mutation, by which differential development might occur. The crucial aspect of epigenetics that makes it different from traditional genetics is that epigenetic markers can change over the lifespan, and are modifiable by environmental exposures. Therefore, although your DNA is fixed, epigenetic changes can alter DNA expression across the lifespan. This has implications in understanding that the genetic predisposition for ADHD may be

mediated by environmental influences that themselves lead to altered gene expression, and raises the possibility that epigenetic profiles can be used as biomarkers for future risk of ADHD, in addition to the possibility that environmental exposures could have a causal influence on ADHD independent of genetic risk (Rozek et al., 2014).

Epigenetic markers include DNA methylation, histone modifications and non-coding ribonucleic acids. DNA methylation refers to when a methyl group attaches to a cytosine-guanine nucleotide pair (a CpG site) (Rozek et al., 2014). These methyl groups populate DNA in varying patterns according to cell type (Szyf and Bick, 2013), and epigenetic changes are when these bases become hyper- (proportionately more) or hypo- (proportionately less) methylated compared to the sample average. Technology now exists where the proportion of DNA methylation of ~480,000 CpG sites can be measured simultaneously in epigenome wide association studies (EWAS).

It is already known that some exposures, for example smoking, cause detectable epigenetic profiles (Mill and Heijmans, 2013), such that you can tell from an epigenetic profile whether an individual is a current smoker or not (Shenker et al., 2013). There is also promising research into the epigenetic markers of dementia and schizophrenia among other disorders. However the role that epigenetic processes may play in susceptibility to behavioural disorders such as ADHD is still in its infancy (Mill and Petronis, 2008). Theory is abundant as to how environmental exposures may impact on the epigenome and thus on the individual, but research in the field is relatively young and there are few well-substantiated epigenetic-exposure links (Mill and Heijmans, 2013). Studies exploring epigenetic associations with social exposures such as SES are novel and are an emerging field of interest (Borghol et al., 2012).

There are limitations in epigenetic studies: epigenetic profiles are tissue-specific so there is a possibility that unless you have access to the tissue of interest, you will not find similar effects in blood, brain or peripheral tissues (Mill and Heijmans, 2013). Studying childhood disorders and exposures are difficult as there are ethical considerations around tissues that can be sampled from healthy participants. Easily obtained peripheral tissues such as blood are often used as a proxy for other tissues. However, even different cell types within a tissue have different epigenetic profiles so when analysing whole blood, algorithms have to be used to adjust for cell counts (Mill and Heijmans, 2013).

As a result of this tissue and cell-specificity and our current ability to evaluate only a few of the many molecules that comprise the epigenome, there are huge advances still to be made in the field.

The ALSPAC has a sub-cohort, ARIES, of 1,000 mother-child pairs who had blood samples taken at three time points over the course of the study: at birth (cord blood for the baby's sample), when the child was aged seven and when they were aged 15-17. I used the ARIES cohort for my study.

In order to conduct the analysis for study six, I work in collaboration with a bioinformatics researcher (Matthew Suderman at the University of Bristol) who has access to the data and runs the analysis. We use rigorous regression models in order to identify epigenetic profiles associated with early life socioeconomic disadvantage. These models give confidence that any associations we do find are robust, not least because of the high risk of finding spurious associations. Conversely this rigour also has limitations as small-magnitude but consistent differences in individual sites can be overlooked because they do not meet adjusted significance thresholds. We conduct an EWAS to explore associations of different SES measures across the epigenome, then using our strongest associations (CpG sites with strong evidence they were associated with at least one measure of SES) explore their association with other SES measures, allowing for a sensitive analysis of these key CpG sites to understand whether different SES facets had common epigenetic signatures.

3.6 Chapter summary

My thesis addresses two overarching research questions exploring the evidence around social causation of ADHD through socioeconomic disadvantage: firstly is there evidence for an association between socioeconomic disadvantage and childhood ADHD? Secondly, how does this association vary throughout childhood and what implications does this have for understanding the relationship between socioeconomic disadvantage and ADHD? Each study is presented as a manuscript from papers either published (studies 1, 2 and 3) or submitted to a journal for publication (studies 4 and 5) and one chapter written with input from Matt Suderman who collaborates on the epigenetics study (study 6). The discussion chapter draws together findings from these studies and discusses the answers to the research questions as well as implications for future research, strengths and limitations.

Chapter Four: The association between socioeconomic disadvantage and attention deficit/hyperactivity disorder (ADHD): A systematic review (study 1)

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Abstract

This systematic review examines associations between parental socioeconomic disadvantage and childhood attention deficit/hyperactivity disorder (ADHD). Socioeconomic status (SES) was measured by parental income, education, occupation and marital status. Results were mixed by measure of SES with no one aspect being differentially related to ADHD. 42 studies were included in the review, of which 35 found a significant univariate association between socioeconomic disadvantage and ADHD. Meta-analyses of dimensions of SES and their association with ADHD indicate that children in families of low SES are on average 1.85-2.21 times more likely to have ADHD than their peers in high SES families. In spite of substantial between-study heterogeneity, there is evidence for an association between socioeconomic disadvantage and risk of ADHD measured in different ways. This is likely mediated by factors linked to low SES such as parental mental health and maternal smoking during pregnancy.

Keywords: attention deficit/hyperactivity disorder, ADHD, socioeconomic disadvantage, socioeconomic status, SES, health inequalities

Abbreviations: ADHD: attention deficit/hyperactivity disorder. SES: socioeconomic status

Introduction

ADHD

Attention-deficit/hyperactivity disorder or hyperkinetic disorder (both referred to henceforth as ADHD) affects between 1 and 5% of children and adolescents worldwide (Polanczyk et al., 2007). ADHD is characterised by impairing levels of inattentive, hyperactive and impulsive behaviours that are both inappropriate for the child's age and are present across a range of settings (American Psychiatric Association, 1994). ADHD is a debilitating and impairing condition for children (Cooper, 2001) and is known to increase the risk of poor outcomes throughout stages of life including poor educational attainment, lower occupational status, being more likely to divorce and have poorer social outcomes (as measured by self-report scales) (Galera et al., 2012, Sacker, Schoon and Bartley, 2002, Klein et al., 2012). The economic impact of ADHD is estimated to be substantial, both in terms of consumption of healthcare resources by those with ADHD as well as the costs indirectly incurred through loss of productivity and risky behaviour and criminality, although the societal costs of ADHD are yet to be thoroughly researched (Bernfort, Nordfeldt and Persson, 2008). In addition, between 30 and 70% of those with a childhood diagnosis of ADHD will continue to experience clinically significant symptoms into adulthood, and risk of other psychiatric disorder is elevated in those with ADHD (Bernfort, Nordfeldt and Persson, 2008, Cooper, 2001).

ADHD has a much-debated aetiology, with theories that range from culturally constructed medicalisation of behaviour (Timimi, 2005b) to those who believe ADHD is a neurobiological disorder with outcomes determined before birth or early in life (Rowland, Lesesne and Abramowitz, 2002, Cooper, 2001, Moffitt and Melchior, 2007).

Evidence suggests that ADHD is highly heritable: one figure calculated with data from 20 twin studies worldwide found the mean heritability of ADHD to be around 76%. Biopsychosocial models of ADHD posit both genetic and environmental interactions leading to increased risk of ADHD, however it has become clear that there is no simple causal explanation (Russell et al., 2013). In line with this complex aetiological picture of ADHD, researchers have examined a wide variety of potential and inter-related risk factors or causal mechanisms, including maternal smoking during pregnancy (Linnet et al., 2003, Thapar et al., 2003), social adversity, severe early childhood deprivation

(Pheula, Rohde and Schmitz, 2011, Kreppner, O'Connor and Rutter, 2001), home environment, parenting (Mulligan et al., 2013), diet (McCann et al., 2007), genetic predispositions or rare genetic events (Williams et al., 2010, Kahn et al., 2003) and low parental socioeconomic status (SES) (Boe et al., 2012, Froehlich et al., 2007, Russell et al., 2014).

Health Inequalities

SES refers to an individual's social and economic position, and has been defined as "A broad concept that refers to the placement of persons, families…with respect to the capacity to create or consume goods that are valued in our society" (Miech and Hauser, 2001). Socioeconomic disadvantage has been linked to a range of poor health outcomes throughout the lifespan. There is a large body of literature that highlights the gap in health between the most wealthy and poorest families that has been detected almost universally across societies (Mackenbach, 2012, Reiss, 2013, Graham, 2002).

Children, like adults from disadvantaged backgrounds, are at increased risk of a range of poor outcomes due to socioeconomic disadvantage, including childhood and adolescent mental health disorders (Reiss, 2013, Taylor and Rogers, 2005) as well as increased mortality and a range of other illnesses (Bradley and Corwyn, 2002). Poor mental health in childhood is itself associated with a range of negative consequences in adulthood, including premature mortality (von Stumm et al., 2011) and continued mental health problems (Reiss, 2013). These children are more likely to have lower educational achievement than their peers (Sacker, Schoon and Bartley, 2002), problems with cognitive and behavioural development (Kiernan and Mensah, 2009) and an increased risk of comorbid mental health conditions (Reiss, 2013).

The current review systematically evaluates whether a socioeconomically disadvantaged background is associated with a diagnosis of (or risk of) ADHD. This review aims to clarify the strength of the association between ADHD and socioeconomic disadvantage, and to see whether this link, if it exists, is robust across the multidimensional concept of SES.

Aims of the current study

The systematic review aims to address the following questions:

- Is there evidence for an independent association between ADHD (or hyperactive/inattentive profiles) and low SES?
- What size is this association by dimension of SES?
- Does this association exist independently of between-study variables (e.g. continent, diagnostic instrument used, dimension of SES)?

Methods

Protocol and Registration

The protocol for this review was registered with Prospero (CRD42013006160, see Appendix 1), a database for registration of systematic review protocols.

Eligibility criteria (inclusion/exclusion)

The population to be studied was not initially restricted by age or setting. This enabled screening to take place for any studies of children and adults with ADHD as long as SES during their childhood was reported, and for studies set within both community and clinical populations to be included. Included study designs were population surveys, and included cross-sectional, longitudinal and cohort studies. Case studies, editorials, reviews and opinions were excluded from the review. Dissertations and conference abstracts were also excluded. To be included, publications had to report on an association between ADHD/hyperkinetic disorder and SES in the family during the person's childhood. A validated diagnostic or dimensional measure of ADHD was required, for example Conners' Ratings scales, the Child Behaviour Checklist, a structured clinical interview (e.g. K-SADS-E or DISC), or parent report of a clinical diagnosis by a health professional. Studies where prescriptions were used as proxy for a diagnosis of ADHD were excluded, as medication for ADHD behaviours does not necessarily mean a clinical diagnosis has been given to the child, and due to differing healthcare systems and policies in different countries, medications are offered to or accepted by different subgroups of children who may have been diagnosed with ADHD.

Accepted measures of individual-level SES included parental education, occupation, income and marital status. Studies were also included if the authors measured geographical or school-level SES, and provided sufficient information about the SES of the area was available. SES indices and measures were only included if details were available on the information that was used to calculate the index (e.g. the Hollingshead index is calculated using marital status, occupational prestige, educational attainment and employment /retirement status). Studies that compared 'urban' and 'rural' populations were not included unless more detailed socioeconomic information was also available. Non-English language articles were included in the review, and translations were obtained for those studies based on their perceived relevance from an English language abstract. Publications from all countries were included on the condition that they had been published in a peer-reviewed journal or book.

Studies were included if they had been published during or from 1994, as this was the year of publication of the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) (American Psychiatric Association, 1994), which includes the widely used ADHD diagnostic criteria.

After initial screening, the authors decided to remove studies that had a majority of participants under the age of five, given that hyperactive behaviours are extremely common among very young children as a normal stage of development, and although some overactive toddlers will go on to be diagnosed with ADHD, the majority will not. Articles which used overlapping study samples were also excluded, for example different studies using data from the same cohort. In these cases, the study with the most reported detail on SES was included in the review, if this was comparable across studies the study with the largest sample size was included.

Information sources

Eight electronic databases were searched for relevant articles in October 2013. These were selected to cover several relevant disciplines such as education, health and psychology. The databases searched were ERIC (via ProQuest); Assia (via Proquest); CINAHL (via EBSCOhost); MEDLINE (via Ovid); PsycINFO (via EBSCOhost); Embase (via OvidSP); Social Policy and Practice (via Ovid) and PubMed. Forward and back-citation screening of

included studies was conducted between December 2013 and February 2014 by two reviewers to identify additional articles to include in the review.

Search

The search strategy was empirically derived, based on principles developed by Hausner et al. (2012). The purpose of this strategy was to reduce subjectivity in development of the search. In brief, 38 directly relevant publications were selected based on one key paper which contained a selective review on the topic (Russell et al., 2013). These were randomly divided into two sets; a development set (n=25) and a validation set (n=13). The development set was entered into a text frequency software package (PubReMiner (Koster, 2004)), and based upon the frequency of emerging key words a search strategy was developed using PubMed. Once this search was as streamlined as possible and yet correctly identified 24 out of 25 articles in the test set, it was tested against the validation set. The final search strategy (see Table 1) could identify 37 out of the 38 relevant articles, and was then adapted for each database.

Study selection

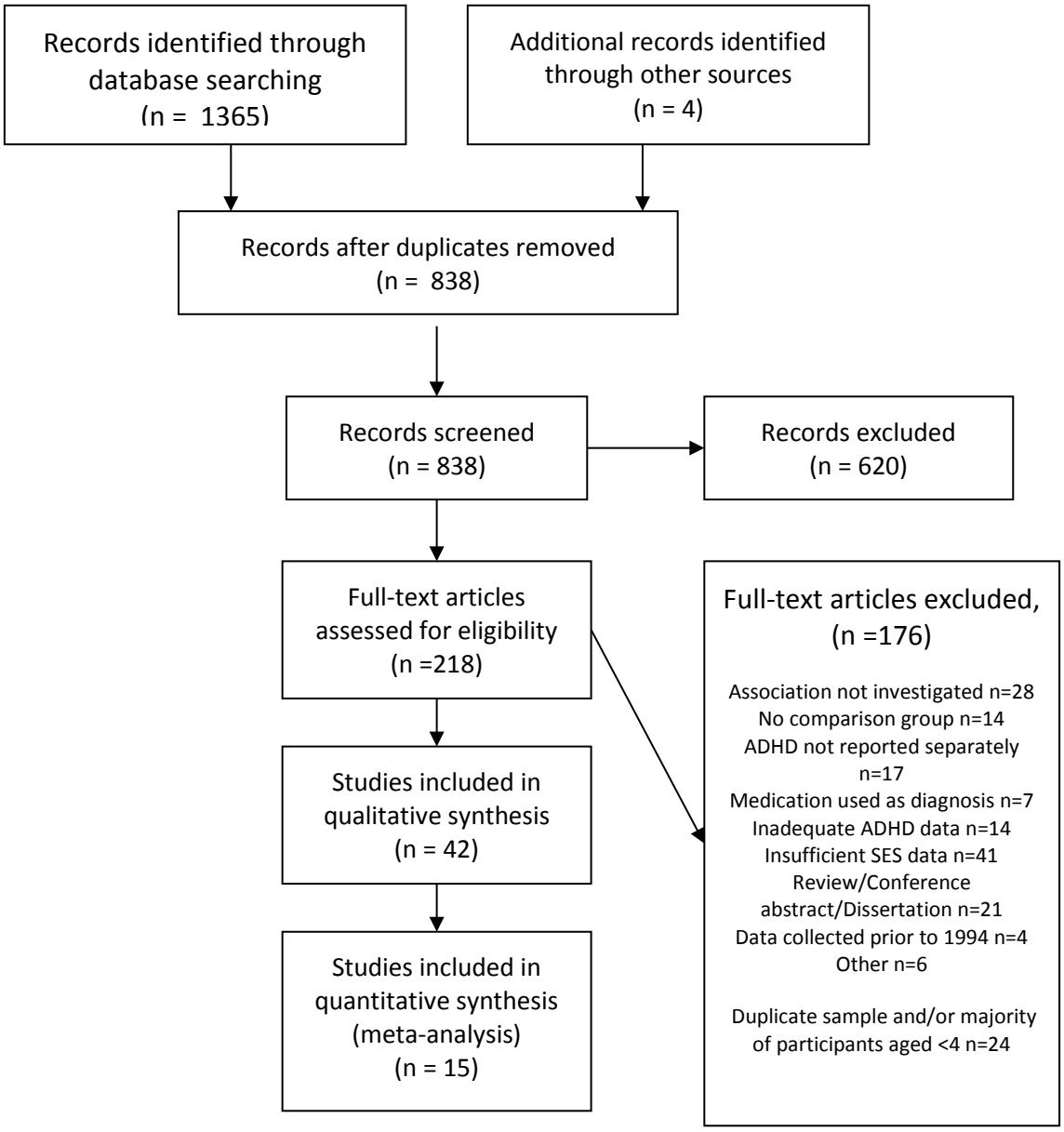
Included studies were selected in a three-stage process. After the initial search and removal of duplicated results, titles and abstracts were screened by two reviewers. Articles were rated for suitability (see Figure 1). Two reviewers then examined the full text of the remaining articles. Translations were obtained for non-English articles, with one reviewer working with translators to determine whether the publication should be included in the final review. Studies were excluded if they did not provide sufficient detail of measures used for both ADHD and SES and if the article met any of the other exclusion criteria. For articles where a consensus could not be reached between the two reviewers, a third reviewer offered a final opinion. EndNote X5 (Reuters, 2011) was used to manage the screening process.

Table 1: Search strategy used in Medline

	PubMed/Medline Search Term	Type of term
	Attention Deficit Disorder with Hyperactivity/diagnosis	MeSH
AND	Socioeconomic Factors	MeSH
AND	ADHD or hyperactive*	title/abstract
AND	Socioeconomic* or advers* or poverty or income	title/abstract
AND	Epidemiology* or prevalen*	title/abstract

Note: MeSH- Medical Subject Heading

Figure 1: PRISMA Flow Diagram



Data collection process

Data were extracted from the included articles by the lead author, and a second reviewer extracted data from a random 10% of the included studies to ensure agreement.

Data Items

The following items were extracted from each publication: study design; population, age range, gender of participants, and country of study; setting; method of ADHD diagnosis and number of informants for the diagnosis; measures of SES (e.g. parental education, income, housing tenure); the level SES was measured at (e.g. family level, school, neighbourhood); and relevant findings. If the authors provided both unadjusted and adjusted analyses, note was taken of the impact this had on findings and the variables authors adjusted for.

Risk of bias

Egger's regression asymmetry test was conducted using studies synthesised in the meta-analyses in order to assess likelihood of publication bias. Quality assessment items were also extracted from included papers. Quality assessment questions were derived from the Newcastle-Ottawa scale, which was specifically adapted for the current study after advice from the Evidence Synthesis Team at the University of Exeter Medical School. The quality items used were:

- Did the authors report psychometric details of the ADHD measure they used?
- Is the cohort representative with minimal potential for selection bias?
- Do the authors report on the number of informants for diagnostic measures and state whether they included impairment/multiple setting criteria in their assessment of ADHD?
- Is detail of drop-outs and missing data provided?
- Do the authors report adjusted analyses regarding SES and ADHD?
- Are the SES measures used robust (do the authors clearly define what was measured and how)?

Synthesis of results

Random effects meta-analyses were carried out where subgroups of studies were suitably comparable, that is studies measured SES in the same way with similar study design and reported results in such a form as to allow calculations of odds ratios (ORs) and 95% confidence intervals for meta-analysis of the data. Meta-analysis results are reported by an overall effect size (OR), with 95% confidence intervals and their significance. I^2, a measure of heterogeneity, and prediction intervals (representing the likely range of odds ratios of studies across different settings) are also reported.

Due to the heterogeneity of included articles, statistical meta-analyses of the majority of studies were not possible. Instead, results were synthesised using a mainly narrative approach, with random-effects meta-analyses conducted in a sub-sample of the included studies, using Stata v13 (StataCorp, 2013).

Results

Study Selection

A total of 1369 electronic records were initially identified (see Figure 1). Screening of titles and abstracts reduced this to 218 publications for full text screening. After screening, 66 publications were found suitable for inclusion in the review. Of these 66 publications, 24 were removed due to overlapping samples, young age of participants or a combination of the above. The final number of studies included in the review was 42, of which 15 provided data for the meta-analyses.

Study characteristics

Characteristics of included studies are summarised in Table 2. Studies were conducted in 22 countries on five continents. Eight studies had samples that were recruited at least in part through a clinical setting, and 34 utilised community samples, which were mainly population-based cohort or cross-sectional studies. Seven case-control studies were included in the review. Sample sizes varied from 53 to 842,830, with 25 of the 42 studies having a total sample of over 1,000 participants.

Table 2: Characteristics of included studies

Continent	First Author	Year	Design	Total Sample	Total with ADHD	Setting	Age	ADHD	SES measures
Europe	Andres	1999	CR	387	23	COM	10	K-SADS	Idx
	Ford	2004	CR	10438	139	COM	5 to 15	DAWBA	I, E, O, SP
	Franz	2003	CR	5178	N/R	COM	5 to 7	CBCL	SP
	Kotimaa	2003	CO	9357	808	COM	8	Rutter B2	O, SP
	Ornoy	2003	CC	160	30-34	COM	6 to 12	Pollack-Tapar and Conners'	Idx
	Khamis	2006	CR	1000	345	COM	12 to 16	DSM interview	I, E, SP
	De Ridder	2007	CC	537	537	CLIN	av 11	Parent report of diagnosis/ belong to ADHD support group	I, E, SP
	Dopfner	2008	CR	2452	123	COM	7 to 17	German ADHD rating scale	Idx
	P'Olak	2009	CR	2230	347	COM	10 to 12	CBCL, YSR, TCP	Idx
	Flouri	2010	CR	801	N/R	COM	11 to 16	SDQ	Idx
	Duric	2011	CR	494	96	CLIN	11.5 (SD 3)	ICD-10, clinician assessment, questionnaires	E, SP
	Boe	2012	CR	5781	N/R	COM	11 to 13	SDQ	I, E
	Apouey	2013	CO	78541	N/R	COM	4 to 17	Parent report of diagnosis	I
	Russell	2013	CO	13305	200	COM	7.2 (SD 0.2)	Parent report of diagnosis	I, E, SP, Idx
	Kvist	2013	CO	172299	2457	COM	4 to 10?	ICD-10 code in psychiatric register	I, E

Continent	First Author	Year	Design	Total Sample	Total with ADHD	Setting	Age	ADHD	SES measures
USA	Scahill	1999	CR	449	89	COM	9.2 (1.78)	DISC and Conners'	I
	Biederman	2002	CC	522	280	COM/CLIN	6 to 17	Screening symptom questionnaire, K-SADS-E	Idx
	St Sauver	2004	CC	5701	305	COM	13 to 19	Clinical diagnosis and supporting questionnaire	E, SP
	Barry	2005	CR	215	N/R	CLIN	9 to 12	CBCL/TRF	Idx
	Counts	2005	CR	206	134	COM/CLIN	7 to 13	DISC and SNAP	Idx
	Schneider	2006	CR	up to 9278	433	COM	~8	Parent report of diagnosis	I, E, SP
	Visser	2007	CR	79264	6183	COM	4 to 17	Parent report of diagnosis	I, E, SP
	Roberts	2009	CR	4175	50	COM	11 to 17	DISC	I
	Wagner	2009	CR	748	N/R	COM	7 to 8	DISC/HBQ/CBQ	I, E
	Lingenini	2012	CR	68634	7137	COM	5 to 17	Parent report of diagnosis	I, E, SP
	Getahun	2013	E	842830	39200	COM	5 to 11	CBCL, clinical interview and ICD criteria	I
	Sagiv	2013	CO	604	~75	COM	8	Conners'	I, E, SP
Australasia	Graetz	2001	CR	3597	268	COM	6 to 17	DISC- not crit D or E	I, E, SP
	Sciberras	2011	CO	3474	64	COM	6 to 7	SDQ, parent report of diagnosis	I, E, SP

Continent	First Author	Year	Design	Total Sample	Total with ADHD	Setting	Age	ADHD	SES measures
Asia	Al Hamed	2008	CR	1287	208	COM	6 to 13	ADDES and parent questionnaire	E, O, Idx
	Bener	2008	CR	1869	208	COM	6 to 12	Conners'	I, E
	Yoshimasu	2009	CC	360	90	COM/CLIN	6 to 15	Clinical diagnosis and questionnaires	I, E, SP
	Li	2009	CR	20152	853	COM	9 (SD 1.5~)	Parent report of diagnosis	I, E, SP
	Siddique	2011	CC	1819	130	COM	9 to 17	DSM-IV criteria and questionnaires	Idx
South America	Cornejo	2005	CR	460	94	COM	4 to 17	Conners', DSM-IV symptom checklist	Idx
	Montiel-Nava	2005	CC	53	29	CLIN	4 to 13	Conners', DISC	Idx
	Bauermeister	2007	CR	1896 & 763	142 and 200	COM/CLIN	4 to 17	DISC	E, SP, Idx
	Pastura	2009	CC	304	26	COM	9 to 14	SNAP and PChIPS	I, E
	Anselmi	2010	CO	4423	880	COM	11	SDQ	I
	de la Barra	2013	CR	1558	156	COM	4 to 18	DISC	SP
	Pires	2013	CR	370	49	COM	6 to 13	CBCL and TRF	E

Notes: Design: CR- cross sectional CO- cohort CC- case control E-Ecological, Setting: COM- community setting CLIN- clinical setting, SES measure: I-income E-education O-occupation SP-single parent Idx- index.

The age range of participants was 5-19 years. No studies that met inclusion criteria examined ADHD in participants over the age of 19 and reported on their SES at birth or during childhood. ADHD was diagnosed with varied clinical measures; information regarding diagnosis was given by parents, teachers, in some cases the child themselves, and clinicians/researchers. Most studies reported using information from one or two informants to make a diagnosis of ADHD, six studies used more than two informants. Seven studies relied on parent report of a clinical diagnosis.

The majority (n=25) of included studies were cross-sectional in design. Seven cohort studies and nine case-control studies were included as well as one ecological (population level) study.

Of the included studies, SES dimensions measured included parental income, occupation, education, and single parent status. There was substantial heterogeneity both in measures of SES used across studies, as well as in the way that studies reported the associations. Twenty seven of the included publications' primary aim was to examine early life or family correlates of ADHD or child mental health problems. Five studies also measured variants of geographical level SES (e.g. SES of residential area, Index of Multiple Deprivation) and two studies measured school-level SES (e.g. private or government school attended) however as the majority measured individual-level SES variables these will be the focus of the results.

Risk of bias

Egger's regression asymmetry test, an indicator of publication bias, was conducted using the data included in meta-analyses of unadjusted study results. Egger's regression conducts a regression of the standardised effect estimates against their precision in order to detect funnel plot asymmetry. If the confidence interval does not include zero this indicates asymmetry (see supplementary Figure 1). The regression was significant at p=0.04 (intercept=1.21, 95% CI 0.06, 2.35), indicating that publication bias is likely to exist (Egger, 1997).

The quality of included studies varied considerably. Table 3 details the quality of each study. Less than half the studies reported psychometric detail for the ADHD measures used, and only five explicitly reported that informants were asked to consider impairment in day-to-day life or across settings. The majority

of studies used a representative sample; however six were open to selection bias i.e. by recruiting through clinical settings, parent support groups or reported minimal detail on recruitment and selection processes. Sample size varied substantially between studies, and several authors failed to report details of participant attrition or evaluate the impact of missing data. Twelve of the 42 papers provided adjusted analyses: often the reason this was not included was because the association of interest to this review was not the primary aim of the individual study. SES measures were generally well reported, in that the measure used and how results were categorised was identified and reported clearly, with parent-reported income, education or marital status being the most frequently used measures. In contrast, one study measured SES by tuition paid to the school as a proxy for parental income. Another is unclear on whether the SES variables were reported by the child to the researchers or by their parent.

Results of individual studies

Due to the heterogeneity of measures used, statistical combination of all study results were not possible. Results of individual studies are presented in Table 4. There was heterogeneity within study results regarding whether an association was found, and what measure of SES this was found for. Syntheses of findings are described according to dimension of SES and overall.

Table 3: Quality of included studies

First Author	Year	Psychometric detail for ADHD measure?	Selection bias? Cohort representative?	Report no of informants?	Impairment/ Impact criteria?	Sample size with ADHD	Details of drop out/missing data provided?	Adjusted analysis provided for SES and ADHD?	Robust SES measure?
Scahill	1999	+	++	+	-	+	++	-	++
Andres	1999	N/R	++	-	-	+	++	-	+
Graetz	2001	++	++	+	+	++	++	-	++
Biederman	2002	N/R	++	+	-	++	-	-	++
Ornoy	2003	N/R	-	+	-	+	-	-	+
Kotimaa	2003	++	++	+	-	+++	++	-	+
Franz	2003	++	++	+	-	N/R	++	-	+
Ford	2004	+	++	+	-	++	++	+	++

First Author	Year	Psychometric detail for ADHD measure?	Selection bias? Cohort representative?	Report no of informants?	Impairment/ Impact criteria?	Sample size with ADHD	Details of drop out/missing data provided?	Adjusted analysis provided for SES and ADHD?	Robust SES measure?
Montiel-Nava	2005	N/R	-	+	-	+	++	-	-
St Sauver	2004	N/R	++	+	-	++	U	+	++
Barry	2005	++	+	+	-	N/R	++	+	++
Counts	2005	N/R	+	+	-	++	++	+	+
Cornejo	2005	N/R	++	+	-	+	U	-	++
Khamis	2006	N/R	++	+	-	++	++	-	++
Schneider	2006	N/R	++	+	-	++	++	-	+
Visser	2007	N/R	++	+	-	++++	-	-	++
Bauermeister	2007	+	++	+	+	++	++	+	++
de Ridder	2007	N/R	-	+	-	+++	++	-	++
Dopfner	2008	N/R	++	+	+	++	++	-	++
Lee	2008	N/R	+	+	-	+	-	-	++
Al Hamed	2008	N/R	++	+	-	+++	++	-	+
P'Olak	2009	++	++	+	-	++	++	-	++
Li	2009	N/R	++	+	-	+++	++	-	++
Wagner	2009	++	++	+	-	N/R	++	+	++
Pastura	2009	++	++	+	-	+	++	-	++
Roberts	2009	N/R	++	+	-	++	++	-	++
Yoshimasu	2009	N/R	-	+	-	+	++	-	++
Bener	2009	N/R	++	+	-	++	++	-	+
Anselmi	2010	++	++	+	-	+++	++	+	++
Flouri	2010	++	++	+	-	N/R	++	-	+
Siddique	2011	N/R	-	+	-	++	++	+	++
Sciberras	2011	+	+	+	+	+	++	+	++
Duric	2011	N/R	-	+	-	+	U	-	++
Apouey	2011	N/R	++	+	-	N/R	-	-	++
Boe	2012	++	++	+	+	N/R	++	+	+
Lingenini	2012	N/R	++	+	-	+++	++	+	+
Russell	2013	N/R	++	+	-	++	++	+	++
Sagiv	2013	++	++	+	-	+	++	+	++
de la Barra	2013	++	++	+	+	++	++	-	++
Kvist	2013	++	++	+	-	++++	N/A	-	+
Pires	2013	N/R	++	+	-	+	++	-	+
Getahun	2013	N/R	+	+	-	++++	N/A	-	+

Notes: ++ good, + adequate, - risk of bias, U unclear, N/R not reported, N/A not applicable.
Sample size (n with ADHD): + <100 ++ 100-500 +++ 500-1000 ++++ >1000

Table 4: Results of Individual Studies

Study Characteristics						Results by SES measure				
First Author	**Year**	**Country**	**Total N**	**Design**	**Setting**	**Income**	**Education**	**Occupation**	**Single Parent**	**Index of SES**
Ornoy	2003	Israel	160	CC	COM					**
De Ridder	2007	Belgium	537	CC	CLIN	-	-			
Biederman	2002	USA	522	CC	COM/ CLIN					**
St Sauver	2004	USA	5701	CC	COM		*		-	
Lee	2008	South Korea	109	CC	COM		-			
Yoshimasu	2009	Japan	360	CC	COM/ CLIN	-	-		**	
Siddique	2011	India	1819	CC	COM					*
Montiel-Nava	2005	Venezuela	53	CC	CLIN					-
Pastura	2009	Brazil	304	CC	COM	-	-			
Kotimaa	2003	Finland	9357	CO	COM			*	**	
Apouey	2013	UK	78541	CO	COM	**				
Russell	2013	UK	13305	CO	COM	*	*		*	*
Kvist	2013	Denmark	172299	CO	COM	**	*		**	
Sagiv	2013	USA	604	CO	COM	*	**		*	

Study Characteristics						Results by SES measure				
First Author	**Year**	**Country**	**Total N**	**Design**	**Setting**	**Income**	**Education**	**Occupation**	**Single Parent**	**Index of SES**
Sciberras	2011	Australia	3474	CO	COM	-	*		*	
Anselmi	2010	Brazil	4423	CO	COM	**				
Andres	1999	Spain	387	CR	COM					**
Ford	2004	UK	10438	CR	COM	-	-	-	-	
Franz	2003	Germany	5178	CR	COM				-	
Khamis	2006	Israel	1000	CR	COM	*	*		*	
Dopfner	2008	Germany	2452	CR	COM					**
P'Olak	2009	Netherlands	2230	CR	COM					**
Flouri	2010	UK	801	CR	COM					-
Duric	2011	Norway	494	CR	CLIN		**		-	
Boe	2012	Norway	5781	CR	COM	**	**			
Scahill	1999	USA	449	CR	COM	**				
Barry	2005	USA	215	CR	CLIN					**
Counts	2005	USA	206	CR	COM/					*
Schneider	2006	USA	up to 9278	CR	COM	**	-		**	
Visser	2007	USA	79264	CR	COM	*	-		**	

Roberts	2009	USA	4175	CR	COM	-				
Wagner	2009	USA	748	CR	COM	**	**			
Lingenini	2012	USA	68634	CR	COM	*	**		**	
Graetz	2001	Australia	3597	CR	COM	*	*	*	*	
Al Hamed	2008	Saudi Arabia	1287	CR	COM		*	*		*
Bener	2008	Qatar	1869	CR	COM	**	-	-	-	
Li	2009	China	20152	CR	COM	**	**		**	
Cornejo	2005	Colombia	460	CR	COM					*
Bauermeister	2007	Puerto Rico	1896 and 763 [a]	CR	COM/ CLIN		-		-	*
de la Barra	2013	Chile	1558	CR	COM				*	-
Pires	2013	Brazil	370	CR	COM		**			
Getahun	2013	USA	842830	E	COM	--				
Number of studies						22	23	5	19	15
total N of all studies by measure of SES						1322062	401501	26548	408458	27351

Notes: Aus= Australia. CR=cross sectional CO= cohort CC= case control COM=community CLIN=clinical E-ecological ** significant in adjusted model at p<0.05, * significant in unadjusted model at p<0.05 ,– not significant, a inattentive subtype b combined subtype c this study found a significant association between increasing income and risk of ADHD d hyperactive/impulsive subtype e ADHD significantly more likely if the child's mother is a housewife rather than employed. Father occupation was non-significant (NS) f significant for those in group whose perception of poverty was "live poorly" as compared with "living well". "Living paycheck-paycheck" was NS

Results of studies by dimension of SES

Mother Education

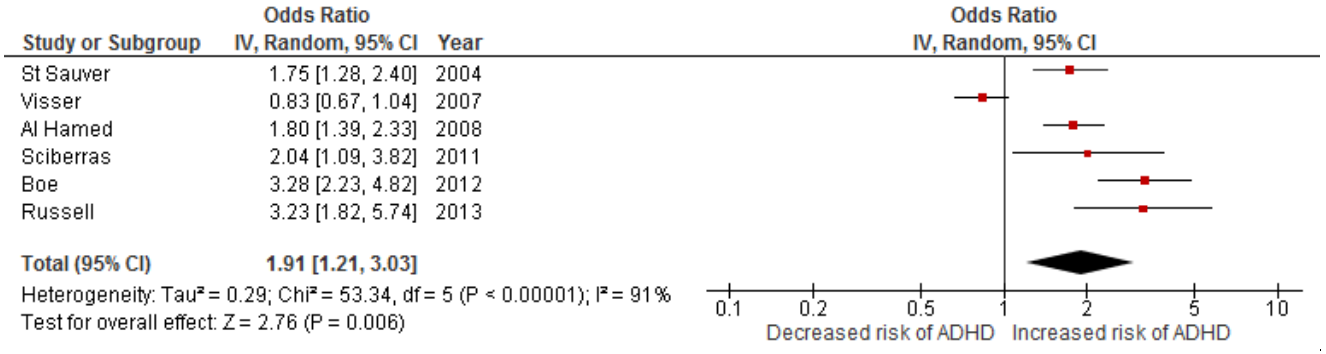
Six studies were sufficiently homogenous in their methodology to be synthesised in a meta-analysis to examine the effect of mothers' education on ADHD risk (Figure 2a). The pooled odds ratio (OR) is 1.91 (95% CI 1.21-3.03, p=0.006, I^2 =91%), demonstrating that on average in the included studies, children of a mother with no educational qualifications or high school qualifications only were almost twice as likely to have ADHD than children of mothers who are highly educated. The 95% prediction interval is 0.37-9.75, indicating that in spite of this evidence, statistical confidence in there being a robust association beyond the studies included in the meta-analysis is limited.

An additional 17 studies investigated this association but were not suitable for inclusion in the meta-analysis due to wide variation in the recording of educational attainment, e.g. many studies divide education into 'high' or 'low' based on years spent in full time education, but the boundary of division varied by study. Eight of these were in agreement with the pooled effect size from the meta-analysis, with estimates for effect sizes including OR 2.64 (95% CI 1.43-4.88) (de Oliveira Pires, da Silva and de Assis, 2013), OR 2.28 (95% CI 1.97-2.63) (Li et al., 2009), to OR 1.30 (95% CI 1.23-1.37) (Lingineni et al., 2012). Two studies reported associations for a subtype of ADHD only; One study reported an OR of 1.31 (95% CI 1.02-1.70), representing a slightly increased risk in children of mothers who left school before age 17 for the combined subtype of ADHD (Graetz et al., 2001) and another found an increased risk of low maternal education only for the inattentive subtype of ADHD (t(800) =-.39, p=0.001) (Khamis, 2006). Seven studies did not find any association between maternal education and offspring ADHD.

Father Education

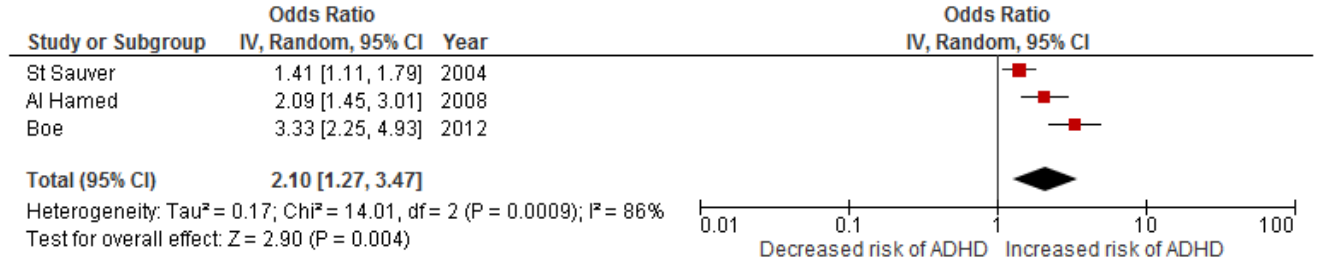
Six studies explicitly explored the association of fathers' educational level on child's risk for ADHD. Three of these were suitable for meta-analysis and generated a pooled OR of 2.10 (95% CI 1.27-3.47, p=0.004, I^2 =86%), indicating that on average in these studies, children of fathers who had none or few qualifications were more than twice as likely to have ADHD than their peers (Figure 2b). This estimate is slightly larger than that for mothers' education. Due to the small number of studies in this meta-analysis, we could not calculate a prediction interval.

Figure 2: 2a: Meta-analysis of association between mother education and offspring ADHD.



Notes: N's for each study; St Sauver- 5701; Visser- 79264; Al Hamed- 1287; Sciberras- 3474; Boe- 5781; Russell- 13305

2b: Meta-analysis of association between father education and offspring ADHD



Notes: N's for each study; St Sauver-5701; Al Hamed- 1287; Boe- 5781

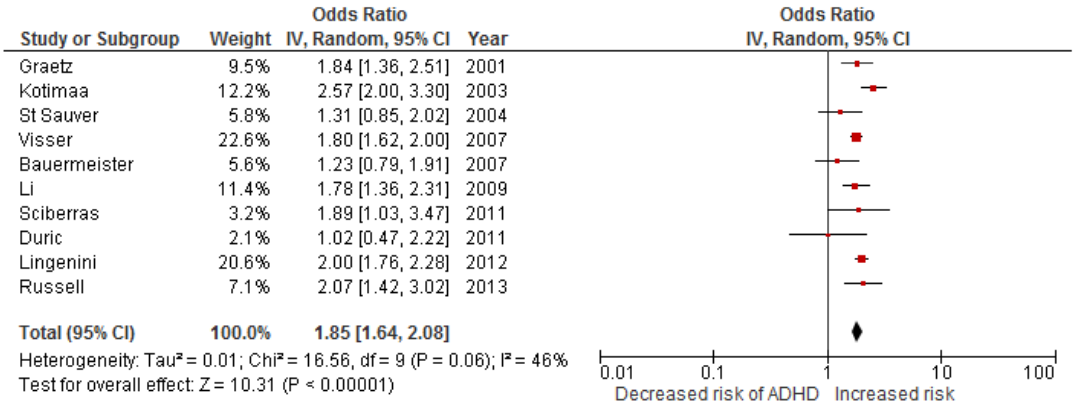
Of the three studies unsuitable for pooled analysis due to differing measures of education level, two report strong agreement with the meta-analysis results. One reports lower father education levels in their ADHD group (OR 2.3 95% CI 1.9-2.7) (Duric and Elgen, 2011), and another reports a strikingly similar effect size (OR 2.27 95% CI 1.96-2.62) (Li et al., 2009).

Single Parent Families

Ten studies provided data for a meta-analysis of the unadjusted effect of living in a single parent family on a child's risk of ADHD (Figure 3a). The pooled effect size OR 1.85 (95% CI 1.64-2.08, $p<0.001$ $I^2 = 46\%$), demonstrates that on average across the included studies, children living with single parents were 1.85 times more likely to have ADHD than their peers in two-parent families. The 95% prediction interval for this meta-analysis is 1.42-2.42, indicating that for 95% of similar studies conducted, an effect size between 1.42 and 2.42 will be found, adding weight to the estimate. The results from the study by Duric and Elgen (2011) stand out; this lack of association may have been due to their sample, which consisted of 187 children who were referred to a child and adolescent mental health clinic for suspected ADHD, with the control group being those who did not meet ICD-10 criteria on assessment.

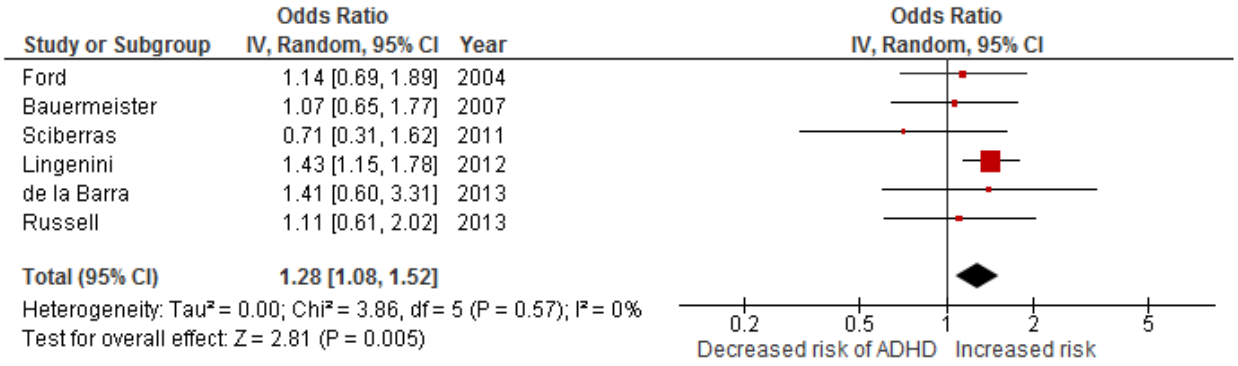
Six studies provided results from adjusted analyses exploring single parent families as a risk factor for ADHD (Figure 3b). The magnitude of the effect size reduced from that of the unadjusted analysis; however the adjusted results do support the finding from this (pooled OR 1.28, 95% CI 1.08-1.52, $p=0.005$, $I^2 =0\%$), the 95% prediction interval is 1.00-1.63. There does not appear to be a pattern in which variables were adjusted for with the change in results, however one study appeared to be driving the overall effect, which remained statistically significant. The authors adjusted for socioeconomic factors as well as other demographic variables, and have over 68,000 children in their sample (Lingineni et al., 2012). When the meta-analysis is repeated without this study, the pooled effect estimate becomes nonsignificant: OR 1.08, 95% CI 0.82-1.42.

Figure 3: 3a: Meta-analysis of association between single parent families and offspring ADHD (unadjusted studies)



Notes: N's for each study; Graetz-3597 ; Kotimaa-9357 ; St Sauver- 5701; Bauermeister-1896; Visser- 79264; Li-20152 ; Sciberras- 3474; Duric-494 ; Lingenini-68634 ; Russell 13305

3b: Meta-analysis of association between single parent families and offspring ADHD (adjusted studies)



Notes: Adjusted for- Ford: age, gender, general health, neurodevelopmental disorder, intelligence, reading, housing tenure, number of significant life events, family functioning, parent mental health, mother's age when child born, maternal educational qualifications, school disadvantage, Carstairs index of neighbourhood deprivation, anxiety disorder, depression, oppositional defiant disorder and conduct disorder. Bauermeister: number of disorders other than ADHD. Sciberras: maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal post-natal depression, intensive care at birth, birth weight, household income, maternal age at child birth, number of people in the household, primary caregiver education, marital status and male gender. Lingenini: BMI, sex, age, depression, anxiety, race/ethnicity, poverty, family members' smoking status, highest level of education in household, healthcare coverage, participation in sports and in clubs, average computer use on a weekday. De la Barra: age, family psychopathology, school dropout, perception of functional family, maltreatment, sexual abuse. Russell: parent and teacher strengths and difficulties questionnaire hyperactivity and impact subscales. N's for each study: Ford-10438 ; Bauermeister- 1896; Sciberras- 3474; Lingenini- 68634; de la Barra-1558 ; Russell- 13305

Six studies did not contribute data to the above meta-analyses for single parent status (Franz, Lensche and Schmitz, 2003, Sagiv et al., 2013, Yoshimasu et al., 2009, De Ridder and De Graeve, 2007, Schneider and Eisenberg, 2006, Khamis, 2006), often because the authors did not distinguish between single parent families and cohabiting/ unmarried families with two parents. One reported a non-significant association between single parent families and ADHD (De Ridder and De Graeve, 2007). Another also reported no association; although using symptom scores as a continuous measure they did find slightly higher average scores for children of single mothers (Franz, Lensche and Schmitz, 2003). Khamis (2006) found a significant association between marital status (χ^2 (1,773)=5.78, p=0.01) and ADHD combined type, finding a higher proportion of unmarried parent(s) of children with combined type ADHD as compared with their peers with married parents, although this association was not significant for the inattentive and hyperactive-impulsive subtypes.

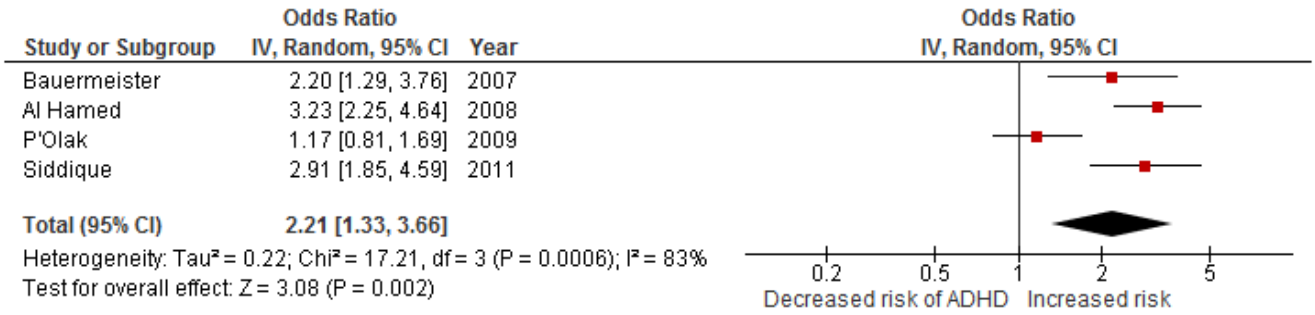
Index of SES

We meta-analysed results from the four studies that used an index of SES divided in to three bands: high, middle and low, comparing the risk of a child having ADHD if their parents were classed as low SES as opposed to high. The pooled effect size was larger than that seen for the other SES measures (OR 2.21 95% CI 1.33-3.66 p=.002, I^2 =83%), indicating that on average children of families classed as low SES were 2.21 times as likely to have ADHD than their high SES peers (Figure 4). The 95% prediction interval is 0.22-22.13, which indicates that we currently have insufficient data to be confident in the true size of the association.

An additional ten studies used an index measure of SES, but were not suitable for meta-analysis because of use of continuous measures or a score-based SES measure, or insufficient data. One study reported an OR of 1.29 (95% CI 1.15-1.45), indicating that children with ADHD were 1.29 times more likely than their peers to have low SES (Russell et al., 2014). Similarly, others found higher prevalence rates of ADHD in children of low SES (7.3% prevalence in the low SES group, 5.1% in the middle SES group and 2.9% in the high SES group; χ^2 =13.28, p<0.001) (Döpfner et al., 2008), the same trend was reported by a further study (Cornejo et al., 2005), who found a dose-response gradient of SES and ADHD prevalence (low SES 21.3%, medium

20.8% and high SES 10.7%), although this pattern was not replicated repeating the analysis with children who have an IQ over 80. Ornoy (2003) also reported a difference in ADHD prevalence by SES, with those of low SES having an ADHD prevalence of 12.62% and those of average SES 5.13%. The large variety in prevalence rates is likely to reflect differing ADHD measures and potentially geographic variation between studies; in a German sample, DSM-IV prevalence is reported (Döpfner et al., 2008); in Colombia a DSM symptom questionnaire was used in conjunction with the Conners' scale (Cornejo et al., 2005), and Ornoy (2003) utilised the Conners' questionnaire with a cut-off point of 21 and over, in an Israeli sample. Using the Duncan Socioeconomic Index, one study found no significant difference of SES between children with and without ADHD (Counts et al., 2005), similarly one study did not find an association between Index of Multiple Deprivation (IMD) and hyperactivity (Flouri et al., 2010), however two studies found an association between low SES and ADHD (Biederman, Faraone and Monuteaux, 2002, Andres, Catala and Gomez-Beneyto, 1999).

Figure 4: Meta-analysis of association between Index of SES and offspring ADHD



Notes: Bauermeister- used poverty perception as measure of SES; Al Hamed used a score based on fathers' education, occupation and income; P'Olak used a composite score of family income, and both parents' education and occupational level; Siddique used housing tenure, material possessions, education, occupation and income. N's for each study: Bauermeister- 1896; Al Hamed- 1287; P'Olak- 2230; Siddique- 1819

Occupation

Three studies explored the association between parental occupation and ADHD, however due to the variation between studies in types of occupation assessed, the way these were categorised, and reporting of results it was not possible to synthesise the data in a meta-analysis. One study found no association between occupational class (divided into 6 categories) and ADHD (Ford, Goodman and Meltzer, 2004); similarly another reported finding no association between occupational class of fathers (divided into three categories) and ADHD in their child, although they did report that mothers' who reported being a housewife as opposed to working were more likely to have a child with ADHD (OR 2.85, 95% CI 2.02-4.03, p<.001) (Al Hamed et al., 2008). Another study found that children with hyperactivity problems were more likely to have parents in the skilled (OR 1.53 95% CI 1.28-1.83) and unskilled (OR 1.93 95% CI 1.52-2.45) occupational classes than the professional occupational class (Kotimaa et al., 2003).

Income

Due to the wide variety of measures used for income it was not possible to meta-analyse the results from studies. This was partly due to between-country differences, i.e. differences in currency, minimum wage and poverty lines, as well as relative living costs, and partly due to the lack of standardisation of measures of income e.g. of those studies using US dollars as their metric, one study (Bener et al., 2008) measured monthly income in 3 bands: >$2740, $1370-$2740 and <$1370 whereas others use continuous measures of annual income, either in increments of varying values or not (Sagiv et al., 2013, Wagner et al., 2009). Others dichotomise into 'low' and 'high' income, based on cut-offs of wages or percentage of the nation's poverty line, or used the current minimum wage or quintiles based on responses to define categories. Statistical combination of these widely varying measures would be inaccurate as they are not estimating the same quantity in a statistical sense.

Of the studies exploring the association between income and ADHD, 15 found significantly increased risk of ADHD for those in the lowest income band of each study. These ranged from an OR of 4.51 (95% CI 2.58-7.88) with a metric based on minimum wage (Anselmi et al., 2010) to 1.33 (95% CI 1.17-1.51) for a study using a cut-off of 200% of the poverty line (Lingineni et al., 2012). Several studies however found that confidence intervals for the effect

size overlapped one, in spite of having an odds ratio in the same direction. For example one study (Schneider and Eisenberg, 2006) reported an OR of 2.50 (95% CI 0.87-7.18), breaking income into five bands. Only one study reported an OR below one, although this was not statistically significant (Sciberras, Ukoumunne and Efron, 2011). Overall the vast majority of the studies exploring income found an association between low family income and child ADHD, although of the studies which adjusted for other variables the majority find that this association is no longer significant (Sciberras, Ukoumunne and Efron, 2011, Lingineni et al., 2012, Russell et al., 2014, Ford, Goodman and Meltzer, 2004). This may be because the factors that studies adjusted for lie on the causal pathway between ADHD and SES (for example, parent mental health), and several of these studies adjusted for other dimensions of SES, which may themselves be more strongly associated with ADHD than income.

Synthesis of results

Thirty five of the 42 articles reported a significant association between a measure of socioeconomic disadvantage and increased risk of ADHD at the 5% level. Only six studies found no association between ADHD and low SES, and one U.S. study reported a significant association between ADHD and socio-economic advantage (Getahun et al., 2013), these authors used an area-based median income measure which may not be indicative of the SES of the individual child's family.

Studies that accounted for other factors such as gender and comorbid mental disorders had mixed results, in that for some the SES-ADHD association remained (e.g. Braveman et al., 2005) and for others it did not (e.g. Getahun et al., 2013). There was little overlap between the types of variables adjusted for between studies.

Of the studies that could be meta-analysed, effect sizes for the association between socioeconomic disadvantage and ADHD ranged from OR 1.28 (95% CI 1.08-1.52) for the adjusted single parent analysis, but of those not restricted to adjusted analyses from OR 1.85 (95% CI 1.64-2.09) for single parent families to OR 2.21 (95% CI 1.33-3.67) for the index of SES. We calculated prediction intervals in response to the high heterogeneity (I^2) in the meta-analyses, and these demonstrate that more, similarly designed studies are needed to establish a robust association for the domains of education and

index of SES, although the prediction interval for the meta-analysis of single parent status implies this association will remain robust.

Associations by continent

There was a clear skew with included publications more likely to originate from Europe (n=15) or North America (n=12) rather than Asia (n=6), South America (n=7) or Australia (n-2). No included publications were based in Africa. However, statistically significant results are distributed between the continents and there are no cases where studies from one continent find no significant associations between ADHD and low SES, suggesting that the association is indeed universal. Overall, significant associations were found on half or more of the occasions studied; Australian studies found significant results in 6/7 SES-ADHD associations studied, USA-based studies found significant results on 17/22 occasions, European studies 20/30, Asian studies 8/15 and South American studies found significant results on 5/11 instances.

Discussion

This review is the first to systematically evaluate evidence of associations between socioeconomic disadvantage and ADHD. Studies from across five continents contributed to the review, and conclusions drawn are relevant in many different countries. The review found evidence to support claims that socioeconomic disadvantage is indeed associated with an increased prevalence of ADHD in children.

One major finding of the review was the striking lack of homogeneity between study methodologies, which hampered the extent to which findings could be pooled. Studies measured various combinations of parental income, education, occupation, index of SES and marital status in order to represent SES, and there was little consistency between studies in how these disparate variables were estimated. There is a strong theoretical argument that different aspects of SES represent different but overlapping concepts. These different aspects may have differential associations with the outcome when examining child development (McLaughlin et al., 2014). Because many of the included articles reported different aspects of SES and their data separately, we have synthesised the results by SES measure. Although there are arguments for pooling the facets of SES and attempting to generate an overall estimate of the

effect size of the SES-ADHD association, the heterogeneity of variables and the way that they have been measured would result in reporting an effect size that would be potentially misleading and not methodologically robust. However, the consistent association of a wide-range of variables, measured using disparate methods suggest that each aspect of socioeconomic disadvantage confers an increased risk of ADHD in children.

Children from families whose mothers (or fathers) have few educational qualifications are on average 1.91 (95% CI 1.21-3.03) times more likely to have ADHD or have more symptoms of ADHD than their peers with highly educated mothers, and this although there is less evidence, the same magnitude of effect was found for father's educational attainment. Similarly, we found that children of single parents are 1.85 (95% CI 1.64-2.08) times more likely to have ADHD than children in families with two parents. The magnitude of the increased risks for education and marital status overlap, although because they are measuring different things they cannot be said to mean the same thing. Studies using an index of SES (using a composite score of different facets of SES), estimate the increased odds to be slightly higher than for the other individual aspects; with a child in a low SES family being on average 2.21 (95% CI 1.33 3.66) times more likely to have ADHD than their high SES peers. Whether this higher figure is of theoretical significance we cannot be sure, but it may represent an additive risk of different SES dimensions; with those in families that are disadvantaged across the board being at even higher risk of ADHD than those who are "low SES" in only one dimension. Cumulative risk models or emergent risk models may therefore be relevant to the aetiology of ADHD, and there is a comprehensive overview of using these models in child development research and outline recommendations for future practice (Evans, Li and Whipple, 2013).

Child Mental Health

How do our findings regarding ADHD compare to risks conferred by low SES for other childhood mental health outcomes? A narrative review of studies examining the link between socioeconomic disadvantage child mental health (which they divided between internalising and externalising disorders) concludes that low SES increases the risk of child mental health problems by 1.18-3.34 times, which was reflected in the author's reporting of the overall differing prevalence of mental disorder by SES group: with low SES having a

prevalence of 13.2% whilst high SES is 8.9% (Reiss, 2013). The author recommends systematic examination of individual mental health disorders and their association with SES: we have answered this call. Other systematic reviews exploring child mental health have examined the association between SES and depressed mood or anxiety in 10-15 year olds and concluded that young people in low SES families were 2.49 times (95% CI 2.33-2.67) more likely than higher SES youth to have these symptoms (Lemstra et al., 2008). Similarly, others have found a small but reliable association between lower SES and antisocial behaviour (Piotrowska et al., 2015). On the other hand, not all childhood neurodevelopmental disorders are clearly associated with socio-economic disadvantage; for example, US studies have found autism is more prevalent in high SES groups (Durkin et al., 2010). Our findings, in contrast, suggest the association between SES and ADHD may follow the same pattern seen in a wide range of other childhood mental health outcomes where low SES confers a small but significant risk.

Putative Mechanisms

This review has established evidence that ADHD in childhood is associated with socio-economic disadvantage in children's families. The key question raised by this work surrounds the mechanisms through which this association acts. Many studies in our review adjusted for potentially confounding or explanatory variables, and on adjustment, the number of studies finding an association between low SES and ADHD was substantially reduced. This suggests that these factors lay on the causal pathway or acted as confounders in the relationship. Factors adjusted for by studies in this review that accounted for part of the SES-ADHD association include parental mental health, suboptimal health behaviours during pregnancy, and child comorbidities. Unfortunately, there is little or no overlap between these other factors across studies, and so we are no closer to uncovering the precise mechanisms by which SES is linked with ADHD.

Previous research has shown that socioeconomic disadvantage is highly correlated with a large variety of outcomes and behaviours that may be relevant to the causal mechanisms of ADHD. For example, smoking during pregnancy is associated with both socioeconomic disadvantage and ADHD, although this seems to be an unlikely causal factor as demonstrated both by genetically

informed study designs (Thapar et al., 2009), and that, similar to SES, once other factors are adjusted for the association is no longer significant (Lindblad and Hjern, 2010). Parenting behaviours are another hypothesised causal mechanism for ADHD; Ellis and Nigg (2009) report that aspects of parenting are associated with child ADHD over and above the impact of parental ADHD symptoms. There is evidence that those of low SES are less likely to be actively engaged parents, spending less time on child rearing than high SES parents, due perhaps lack of resources in the family environment (Kiernan and Huerta, 2008). The association of early psychosocial risk with ADHD has perhaps been under-appreciated.

Other factors that also display a socioeconomic gradient have been hypothesised to be associated with ADHD; for example bullying and SES (Tippett and Wolke, 2014), with victims of bullying and those who bully and are victims both being more likely to come from a low SES household, and children with ADHD are more likely to be bullied or bullies themselves (Holmberg and Hjern, 2008). Diet may also be a mediator, for example, a randomised, double-blinded, placebo-controlled, crossover trial found artificial colours or a preservative (or both) in the diet result in increased hyperactivity in three-year-old and eight/nine-year-old children in the general population (McCann et al., 2007).

It has been argued that severe family disadvantage has a role in the aetiology of ADHD, and this has implications for the nosology of the condition (Webb, 2013). Webb suggests there may be two types of ADHD, one primarily caused by genetic predisposition, and the second ‘phenocopy’ ADHD which may result from early experiences of violence and abuse. She maintains such experiences make children hyper-vigilant and these symptoms are easily mistaken for true ADHD (Webb, 2013). This is a similar phenomenon to ‘quasi-autism’ seen in severely neglected Romanian orphans (Rutter et al., 1999). Could the ADHD-SES association observed in this review be driven by this extreme ‘quasi ADHD’ where symptoms of severe deprivation mimic those of ADHD? Future research could examine the strength and nature of the ADHD-SES association in socio-economic gradients that exclude the most deprived families.

Heritability

ADHD is known to have substantial heritable components, and the mechanisms by which ADHD and low SES may be transmitted between generations may overlap. This is illustrated in a paper on health inequalities that aims to bring together the social causation and social selection theoretical approaches into an interactionist model of how socioeconomic inequalities impact on development (Conger and Donnellan, 2007). This kind of model could be applied to ADHD; e.g. those with psychological illness are more at risk for being socioeconomically disadvantaged (Miech et al., 1999), and so their children are brought up in a disadvantaged environment, which in turn makes them more vulnerable to psychological difficulties (Reiss, 2013). Children with ADHD are more likely to leave school at an early age and have lower educational attainment (Young, 2000), and therefore be considered low SES, and their children are likely to have inherited genetic traits for ADHD.

Direction of effect

In addition, a child with ADHD may elicit changes in the family environment, for example the stress of parenting a child with ADHD may lead to conflict between parents, resulting in separation or divorce and thus being classed as low SES, or the demands of the child may lead to a parent giving up their job in order to be able to spend more time caring for them, again likely leading to a decrease in SES (Russell et al., 2014). These effects are unlikely to occur in isolation, and they are more likely to be a complex web of circular and interrelated associations (Conger and Donnellan, 2007). Future work should use longitudinal, genetically informed designs in order to tease apart the relative impacts of each SES-ADHD mechanism, and the direction(s) it operates in. It is especially important to disentangle to what extent the SES-ADHD relationship observed is driven by predisposition to ADHD inherited from parents with poor SES outcomes. Adoption and surrogacy designs are well suited for this, as are second-generation birth cohort studies i.e. longitudinal birth cohorts where the original intake of children now are adults and have children themselves.

Methodological Heterogeneity

The lack of cohesion in the methodologies of included studies has limited the ability of this review to expound on the strength of the association between

SES and ADHD. Data harmonisation initiatives such as the CLOSER programme (www.closer.ac.uk) have specific remits to maximise the use and comparability of data across cohort and longitudinal studies. Authors conducting work that explores socioeconomic concepts should adhere to guidelines or best practices for data comparability, and many studies included in our review would have benefitted from more transparent reporting of results. However, the varied measures and methodologies included in this review lend weight to our findings, and in spite of substantial heterogeneity between studies, the majority found similar magnitudes of association, and when meta-analyses were possible, the findings of studies using similar measures and methodology consistently demonstrated the increased risk of ADHD with socioeconomic disadvantage. The results of this review clearly emphasise the need for researchers to use homogenous measures of SES across studies. The lack of consistency in measures of SES is a hindrance both to clinicians' and policy makers' understanding of this association with ADHD and impacts on their ability to make informed decisions.

Other findings

A further aim of this review was to examine whether the ADHD-SES association differs by continent. In spite of the large number of countries and continents covered by included publications, results by continent were as mixed as those overall. This does however suggest that findings across continents do not differ. Further work could explore within and between-country variations in SES and prevalence of ADHD in more depth.

The largest study in the review was the only one to find a significant association in the opposite direction from that expected (Getahun et al., 2013). The authors used area-level median income as their measure for SES, and used child health clinic records to examine ADHD cases, however those of higher socioeconomic status are more likely to access healthcare services, which may have influenced these results. Results from the current review suggest that area level SES may either account for some of the association found, for example Ford, Goodman and Meltzer (Ford, Goodman and Meltzer, 2004) did not find a significant ADHD-family SES association but only reported results that had adjusted for school and neighbourhood disadvantage. Future studies would benefit from measuring both family and school/neighbourhood

indicators of SES, as negative effects of low SES in one realm of a child's life may be ameliorated by higher SES in other areas, or indeed risk of ADHD may be greater for children who are exposed to socioeconomic disadvantage in more than one area of their lives.

Limitations

The study of an association such as that between socioeconomic disadvantage and ADHD is impossible to measure in a controlled experimental manner. Instead, evidence is in the form of observational cohort, cross-sectional or case control studies. These studies are inherently different from each other due to different sampling strategies, definitions of ADHD and what is considered as representing SES, and so are difficult to combine in a systematic manner. Due to the heterogeneity of studies included in the review, meta-analysis was only possible for a small sub-sample of studies which were sufficiently similar in design and measure to combine results. In addition, reporting of results was poor in some studies, with information that would be needed for meta-analysis not reported. There was varying quality in individual studies, both in terms of strengths and flaws. Some were open to selection bias, some had very small samples and those that had sufficiently large samples may have only measured one or two indicators of SES.

This review excluded seven studies (at full text screening, more were excluded prior to this) where prescription of stimulants was used as a proxy for ADHD diagnosis. This was due to concern over selection bias in individual studies, especially in countries without free healthcare such as the USA. However, this also meant excluding potentially important studies from Scandinavian countries, where national databases and records are used to link detailed information about children and families, allowing for strong conclusions to be drawn due to the large sample sizes in countries with social insurance and accessible services (Skoglund et al., 2014). Although not included in this review, the Scandinavian literature generally supports our conclusions: for example Swedish children prescribed stimulant medication are more likely to hail from socioeconomically deprived backgrounds (Hjern, Weitoft and Lindblad, 2010). Other studies that may have contributed data were excluded due to not using a validated measure of ADHD.

Quantitative assessment of the likelihood of publication bias found evidence of publication bias. Future reviews on this topic should be aware that publication bias in this area is likely to exist and as such aim to include grey literature as well as contacting key researchers in the field in order to include unpublished as well as published data. It is unknown what impact publication bias has on the findings of this review and as such caution should be used when interpreting the results. Another methodological option in conducting a systematic review is to utilise individual-level data in meta-analysis. This is considered to be the gold standard for meta-analysis as it allows for consistent analysis across included studies and the ability to explore hypotheses related to individual patient rather than group characteristics (Simmonds et al., 2005). Future studies synthesising information on associations between SES and ADHD may benefit from collating data on the individual participant level.

When conducting meta-analyses we found that the measure of heterogeneity (I^2) was very high, in most cases between 46 and 91%. Higgins and Thompson (2002) evaluate the quantification of heterogeneity in meta-analysis and suggest that an I^2 statistic above 56% signifies considerable heterogeneity. As such, our findings must be interpreted with caution and further research is needed to determine whether the associations we found are accurate.

Summary

An association between disadvantaged parental socioeconomic status (SES) and an increased risk of childhood attention deficit/hyperactivity disorder (ADHD) is commonly noted but is seldom the primary focus of research. The current review systematically evaluated whether parental socioeconomic disadvantage is associated with a diagnosis, or increased risk of a diagnosis of ADHD, the size of this association, and whether this association varies by continent or developmental stage. Eight databases were searched for peer-reviewed articles that reported both on childhood diagnoses of ADHD and measures of family or neighbourhood SES. Articles were screened by two independent raters for inclusion suitability, forward and back citations of included publications were also hand searched. Eight hundred and thirty eight articles were initially identified, of which 42 publications met inclusion criteria.

The current review has shown that there is increasing evidence for an association between socioeconomic disadvantage and ADHD, suggesting socioeconomic disadvantage may lie on a causal pathway between, or may be caused by, ADHD genotype and phenotype. The association was only partially explained by other variables such as parental mental health, parental smoking behaviour and neighbourhood level deprivation. The strength of this association varies substantially between studies. These mixed results likely represent other causal or risk factors for ADHD which are themselves more prevalent in families who are socioeconomically disadvantaged. Further research with a primary aim of investigating this association in more depth and looking into the possible mechanisms, and at different levels of SES is needed.

Acknowledgements

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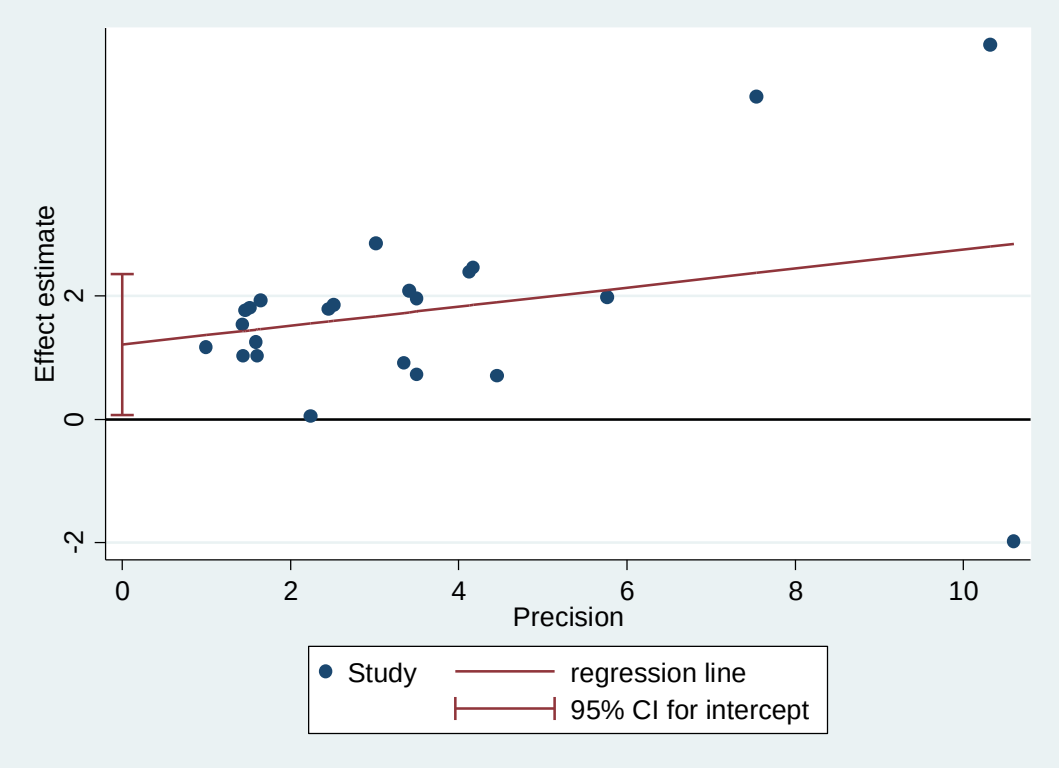
Supplementary Figure 1: Egger's regression asymmetry plot to assess publication bias



Note: Egger's regression conducts a regression of the standardised effect estimates against their precision in order to detect funnel plot asymmetry. If the confidence interval does not include zero this indicates asymmetry.

Chapter Five: Educational practitioners' beliefs and conceptualisation about the cause of attention deficit/ hyperactivity disorder (ADHD): A qualitative study (study 2)

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Abstract

Objectives: Educational practitioners play an important role in the referral and treatment of children with attention-deficit/hyperactivity disorder (ADHD). This study aimed to explore how educational practitioners' conceptualise their beliefs about the causes of symptoms of ADHD. Method: Forty one educational practitioners from schools in the UK participated in focus groups or individual interviews. Data were analysed using thematic analysis. Results: Practitioners' beliefs fell into two categories: biological and environmental. Practitioners conceptualised the causes of ADHD in lay-theoretical models: a 'True' ADHD model considered that symptoms of ADHD in many cases were due to adverse environments; and a model whereby a biological predisposition is the root of the cause of the child's symptoms. Conclusion: Differential beliefs about the causes of ADHD may lead to practitioners blaming parents for a child's behaviour and discounting ADHD as a valid condition. This has implications for the effective support of children with ADHD in schools.

Keywords: ADHD, teachers, schools, theory, mental health

Introduction

Scientific understanding of causes of ADHD

Current understanding of the causes and aetiology of attention deficit/hyperactivity disorder (ADHD) considers the interaction of a network of biological, psychological and social factors, with a strong genetic predisposition that may be differentially expressed (Faraone et al., 2015). These factors may interplay to increase or decrease risk of ADHD. ADHD is also considered as a dimensional disorder where symptoms can be considered a trait-like measure rather than as a distinct category (Shah and Morton, 2013). The inter-relationship between genetic and environmental risk factors has led to the suggestion that it may be unhelpful and incorrect to dichotomise genetic/biological and environmental explanations at all (Thapar et al., 2013). Despite this, much research has focused on disentangling these two influences (Knopik et al., 2006, Nikolas and Burt, 2010), although researchers more recently have promoted the study of gene-environment interactions (Ficks and Waldman, 2009, Rutter, Moffitt and Caspi, 2006). Evidence is mounting for environmental moderation of genetic influences on ADHD (Nikolas, Klump and Burt, 2015) and although ADHD is still considered to be influenced by heritable factors, environmental factors at home and school may amplify or diminish the development and/or the impact of ADHD symptoms (Tarver, Daley and Sayal, 2015). Thus, current research suggests that the causes of ADHD are complex, multi-dimensional and interacting.

ADHD and school

Children spend much of their lives in school. As educational practitioners often work with large numbers of children, they are aware of developmental norms and are well-placed to recognise when a child is struggling, either academically or socially. Therefore educational practitioners play an important role in referral of children for potential diagnosis of ADHD. Educational practitioners are also well placed to deliver treatment to support these children in a setting where inattention, restlessness and impulsivity pose particular challenges. Phillips (2006) frames teachers' involvement as 'sickness and treatment broker' (p433) as well as 'an informal role as disease-spotters' (p434). The UK's National Institute for Health and Care Excellence (NICE) clinical practice guidelines recommend that teachers who have received training about

ADHD and its management should provide behavioural interventions in the classroom to help children and young people with ADHD (NCCMH, 2011).

Educational practitioners are key in identifying when children may have ADHD and communicating this to parents, however their beliefs about the cause of these symptoms may impact on whether they advocate referral of children with suspected ADHD (Hillman, 2011). When considering a diagnosis of ADHD, medical professionals investigate whether the symptoms occur across settings, thus multiple perspectives on a child are often sought. Lee (2008) asked early childhood teachers in the USA about their interactions with the parents of children with ADHD symptoms, and all had experience of liaising with parents who viewed their child's behaviour differently to the teacher, emphasising the need for multiple perspectives to inform understanding of the problems the child is experiencing.

Educational practitioners' beliefs about what underpins ADHD behaviour may affect the use of any teacher-led interventions in school (Vereb and DiPerna, 2004). It has been suggested that if the treatment recommended by healthcare professionals is in line with teachers' beliefs, teachers are more likely to implement and adhere to it (Eckert and Hintze, 2000). This applies to both medication and behavioural management for children with ADHD, and may impact on the effectiveness of school-based interventions and strategies used in order to facilitate the progress of the child (Moore et al., 2015). If practitioners are unaware of causes of ADHD or endorse beliefs that lead them away from using school-based interventions recommended for children with ADHD, this can have long term impacts on the child's achievement and well-being.

Existing research

Teachers' knowledge of the causes of ADHD has been explored in quantitative research, which suggests that many teachers endorse biological and medical models of ADHD, and do not typically believe that it can be caused by poor parenting (Anderson et al., 2012, Bekle, 2004, Couture et al., 2003). The majority of qualitative research exploring the causes of ADHD samples parents rather than teachers. For instance, Harborne, Wolpert and Clare (2004) interviewed ten parents who had sons with ADHD. They found that parents believed the causes of ADHD to be biological in nature; however they felt that

others (including teachers) believed the cause to be poor parenting, leading parents to feel blamed.

One study used vignettes (written descriptions of an often-hypothetical child) and open-ended questions to explore what teachers believe is the cause of a child's problem behaviour (Hillman, 2011). Hillman found that responses fell into two categories: medical and non-medical, although she did not discuss whether teachers endorsed both categories or had polarised beliefs (Hillman, 2011). Vignette studies such as these leave little room for exploration of what teachers experience in their day-to-day work with real children with ADHD, however there is limited research of any kind in this field. Einarsdottir (2008) interviewed 16 Icelandic teachers about their experiences around ADHD. The teachers expressed the opinion that ADHD was innate within the child. The teachers further distinguished between a 'badly behaved' child and a child with ADHD by whether, given time, the child could and would learn the rules of the school. Lee (2008) found that three of ten teachers interviewed about ADHD suggested that in their experience ADHD was more often found in children from socioeconomically disadvantaged backgrounds, and the notion of a child having 'no structure at home' was also mentioned. This reflects quantitative findings that ADHD is more prevalent in socioeconomically disadvantaged groups (Russell, Ford and Russell, 2015).

A recent review of non-pharmacological interventions for ADHD notes the gap in research conducted in the United Kingdom (UK) surrounding teachers' beliefs about the causes of ADHD (Richardson et al., 2015). Previous qualitative research with teachers has been conducted in the USA, Iceland, and Korea. To our knowledge the current study is the first to explore these issues in the UK. Existing studies are limited by a narrow age range of children taught (often ages 4-7) and have not explicitly explored educators' beliefs about the children with ADHD they have worked with. Previous research is often restricted to teachers rather than other educational practitioners who have experience working with children with ADHD in schools. In addition, educational practitioners have a wealth of first-hand experience of children with ADHD symptoms, and their insights, beliefs and theories about the causes of ADHD may be captured to usefully inform current research directions about causes and nosology of ADHD.

Aims of the current study

The current study therefore aims to use qualitative research methods in order to address a topic that we know little about: how do educational practitioners in the UK conceptualise the causes of ADHD? The study also aims to go beyond some previous research to include views of the wide range of educational staff who may work with children with ADHD within their job role, for example teaching assistants (TAs), head teachers, pastoral care workers and special educational needs and disabilities co-ordinators (SENDCo's) in addition to teachers. This is in order to capture the experiences of the full range of practitioners who work with children with ADHD in the school setting. There are two specific research questions:

1. What do educational practitioners believe are the causes of symptoms of ADHD?
2. How do educational practitioners conceptualise these causes?

Methods

Participants

Participants were 41 educational practitioners that self-identified as having worked with children or young people with ADHD, recruited from 223 schools in the South West of England. Schools were approached either by email from the lead researcher to a named contact or through a newsletter. If a school expressed interest in participating, a named contact, often the head teacher or SENDCo, acted as gate-keeper and liaised with the researcher in identifying staff with relevant experience who were interested in participating.

Practitioners were recruited from three types of school; primary (ages 4-11), secondary (ages 11-18) and pupil referral units (PRUs; also known as alternative provision, for pupils excluded from mainstream education, ages 5-18). Practitioners had a range of educational roles: 11 were teaching or learning support assistants (LSAs); 18 were teachers, team leaders or head of year; six had responsibilities as SENDCo's; three were involved in pastoral support for students; three were deputy head teachers and two were head teachers. There was a wide range of experience represented across practitioners: the average length of experience was 14 years (range 0-35 years). Nine practitioners were male. Practitioners could not recall precisely how many children they had

worked with that had a diagnosis of ADHD, although estimates ranged from 1-40. Most practitioners stated that over their career they had worked with many more children who had symptoms of ADHD but had no formal diagnosis that practitioners were aware of. Table 1 supplies a summary of participant information.

Table 1: Characteristics of participants

Characteristic	**N**
Female	32
Primary	19
Secondary	7
PRU	15
Worked with ages 0-4	14
Worked with ages 5-11	33
Worked with ages 11 and up	25
Worked with <10 children with ADHD diagnosis	13
Worked with ≥10 children with ADHD diagnosis	12
Teacher	16
TA/LSA	11
Co-ordinator or team leader or head of year	11
Pastoral support	3
SENDCo	6
Head/deputy head teacher	5

Notes: Numbers may not add up as several practitioners had several roles within the school and some had worked with a large range of age groups. TA: Teaching assistant, LSA: learning support assistant, SENDCo: special educational needs and disabilities co-ordinator, PRU: pupil referral unit

Data collection

Forty one practitioners took part in either one of six focus groups or three individual interviews. We used focus groups where there was more than one participant from a school, otherwise individual interviews were conducted. Focus groups had on average seven participants. Interviews and focus groups took place at the school where the practitioners worked; with minor exceptions based on participant request and convenience. The use of focus groups in combination with individual interviews in qualitative research is well established (Morgan, 1996). Focus groups allow breadth of experience and views around a topic to be elicited as well as exploring mutual experiences and understandings. Interviews can explore individuals' experiences and views in greater depth, thus the two techniques complement each other to allow for a rich understanding of both individual experiences and beliefs, and how these are understood and expressed in the wider social context of the school (Michell, 1999, Bauer, Yang and Austin, 2004).

Each interview or focus group lasted between 40 minutes and one hour, the length was determined by the amount of time practitioners had available. Both interviews and focus groups followed the same topic guide (Appendix 2) which covered various areas of experiences working with children with ADHD, including what practitioners believed about the causes of ADHD, and were semi-structured. Practitioners provided informed consent before taking part and were given the opportunity to choose a pseudonym to be used for the study analysis and write-up. The University of Exeter Medical School research and ethics committee provided ethical approval for this study (Appendix 2).

Procedure

All focus groups and interviews were conducted by the lead author (AER), who has prior experience working as a TA in a specialist school, and an academic background in psychology. In focus groups she was assisted by one of two psychology undergraduate research students who took field notes in order to aid later transcription and to ensure all topics were covered. To encourage participation and discussion in focus groups all practitioners were encouraged to express their views, and at the end of each focus group or interview practitioners were given an explicit opportunity to add or raise any

other issues they wished to discuss. Incentives were not provided with the exception of light refreshments during the session.

Analysis

Audio recordings were transcribed verbatim by the two research students and transcriptions were checked by AER prior to data analysis. Transcripts were then read and re-read by AER and DM. Data were analysed using thematic analysis as outlined by Braun and Clarke (2006). Thematic analysis is a flexible method for analysing qualitative data that assumes no specific epistemological or theoretical approach and can be used to identify, analyse and organise repeating patterns within data. There is a focus on identifying features of the data, known as codes, then organising these into patterns of responses related to research questions, known as themes (Braun and Clarke, 2006). In order to generate initial codes AER and DM first read and discussed two focus group transcripts to generate an initial overarching coding framework. AER and one of the two research students then independently coded each transcript within this framework, which also allowed space for new codes to be generated. Coding each transcript twice increased the reliability of the analysis. This coding was amalgamated using NVivo version 10 with similar codes or synonyms being merged and novel codes preserved in order to retain the maximum level of detail at this stage.

The coded data were grouped into tentative themes and subthemes by AER and DM. These were reviewed to ensure that collated extracts formed a pattern and we explored whether these themes appeared credible in the context of the entire data set as well as ensuring that all data relevant to a theme had been coded appropriately. This process continued in an iterative manner until a thematic map was drafted. Themes were clearly defined in order to identify and describe their core aspects. Although this process is described linearly, in actuality analysis was cyclical and reflexive (Braun and Clarke, 2006).

Results

The thematic analysis identified six themes relevant to the two research questions. Themes and key findings are summarised in Table 2.

Table 2: Research questions, themes and key findings

Research Question	Theme	Findings
What do educational practitioners believe about the causes of ADHD?	Biological	Practitioners put forth a variety of biological attributions for the causes of ADHD including those based in the brain and genetic causes. Practitioners displayed a lack of detailed knowledge about these biological attributions.
	Environmental	Practitioners commonly attributed the cause of ADHD behaviours to be due to the home or parenting. Others mentioned diet as an exacerbating factor. Practitioners infrequently discussed the role of the school context in the child's symptoms.
How do educational practitioners conceptualise the causes of ADHD?	'True' ADHD	Practitioners in several focus groups put forward the theory of there being a true or pure ADHD that is biologically caused, rarely seen in their experience, and the child is perceived to have no volitional control over their symptoms. This is positioned at one end of a continuum, with the other end being environmentally-caused ADHD.
	Environmental ADHD	This is the other end of the spectrum from True ADHD. Environmental ADHD was discussed by a number of practitioners as being a misdiagnosis of ADHD, the symptoms of which were caused entirely by the environment and thus were not truly ADHD. Practitioners believed this to be the most common cause of ADHD behaviour that was seen in their particular school.
	Biology exacerbated by environment	The majority of practitioners believed that ADHD was caused by biological factors; however the impacts of this predisposition could be exacerbated or ameliorated by the environment in which the child is raised.
	Environment becoming biology	Some practitioners discussed a critical or sensitive period early in childhood where negative experiences due to the environment could become biologically entrenched and therefore lead to ADHD as a biological manifestation

1. What do practitioners believe about the causes of ADHD?

Most practitioners discussed ideas around both biological and environmental causes for ADHD and factors that exacerbate or ameliorate symptoms. These were, however, differentially endorsed and expressed, with biological factors most frequently assumed to be the main cause of ADHD. Practitioners described these biological factors as being 'in the brain' or genetic. However, compared to biological causes, practitioners discussed environmental factors for longer, and in more detail and depth. In terms of environmental causes for symptoms, practitioners had more elaborate views that included areas of home and parenting, diet and school. These views mirror those reported by Hillman (2011), who categorized beliefs into 'medical' (in this case biological) and 'non-medical' (environmental) viewpoints. In this study practitioners did not often consider these polarised views as mutually exclusive and were accepting of colleagues with opposing views within focus groups.

Biological

Many practitioners acknowledged ADHD as a disorder with a biological cause, as Rose summarises: '*Well it has to be biologically caused if we're going to give it a medical label doesn't it really' (teaching role: SENDCo, school type: Secondary).* When practitioners spoke about the biological basis for ADHD they distinguished between neurological deficits, including imbalances of neurotransmitters, and genetics. Practitioners were explicit about their lack of detailed knowledge about the biological causes of ADHD; Tarquin finishes a discussion with colleagues about the possibilities: *'yeah, I dunno if genetics affects it or what… you know, some sort of biological thing' (deputy head teacher, PRU).*

In the brain*.* The majority of practitioners discussed biological or neurological causes, with attributions for symptoms being varied. Practitioners provided explanations that clearly situated the cause of ADHD as neurological: *'I think it's partly just the way the brain sort of fires off really' (Janet, teacher and co-ordinator, Secondary).* Hannah discusses this further: *'I have heard…that brain scans can show a difference in the brains of people with ADHD and people without' (LSA, Primary).* Occasionally practitioners explicitly based their assumptions on the basis that methylphenidate/Ritalin is given as a treatment for ADHD, thus assuming that ADHD has a neurological basis:

'I assumed it's some sort of chemical imbalance, I've always assumed that because then if you give them Ritalin which is a chemical it affects, it in some way it calms that' (Briony, SENDCo, Secondary).

Genetic. Some practitioners mentioned that the causes of ADHD are '*like a genetic thing' (Tarquin, deputy head teacher, PRU)*. Others mentioned the heritability of ADHD, for example Victor discusses children who are strikingly like their parents: *'they were literally carbon copies of each other and you think is that in the gene pool somewhere possibly' (teacher and co-ordinator, Primary).* As ADHD known to be highly heritable (Faraone et al., 2015), it is likely that a substantial proportion of children with ADHD have a parent with ADHD. When practitioners describe ADHD as running in families, these influences on the child may be a mixture of genetics compounded by the environment created by the parent, who may struggle with maintaining routine and consistency due to their symptoms (Weiss et al., 2000).

Lack of knowledge*.* In discussing biological causes of ADHD, practitioners often used vague language or stated that they were unsure, reflecting their lack of expertise on the subject. Kitty frames this as a lack of sufficient qualification: *'I wouldn't be qualified to say what that [medical/genetic element] was and where you draw the line' (SENDCo, Primary, author edits in square brackets).* This reflects findings of studies with parents, who report that they do not know about causes of ADHD (Bussing et al., 2003). Practitioners in the current study often discussed ways in which they attempted to acquire this knowledge, be it asking colleagues, reading research or from the wider media:

'One of the teaching assistants at school has an ADHD son and I asked her what she thought the causes were' (Ellen, teacher and co-ordinator, Primary);

'[I] watched a documentary on it; it's about a woman who had a diagnosis' (Victor, teacher and co-ordinator, Primary).

Neurological and genetic research into ADHD suggests high heritability, genetic links to neurotransmitters and anatomical differences in structural and functional brain imaging (Cortese et al., 2012, Faraone et al., 2005). However, these are not sufficiently elucidated to inform assessment and intervention so perhaps this lack of detailed knowledge is unsurprising.

Environmental

The majority of discussion around the subject of what causes ADHD symptoms was environmentally focussed, with elaborate and specific references to environment being common. Perhaps this was because practitioners felt they had sufficient experience and knowledge to elaborate on environmental causes. The environment was sometimes talked about in the context of ameliorating symptoms:

> *'I think it can be exacerbated by various environmental factors, like…how much support, emotional support and guidance kids are given and probably also diet' (Hannah, LSA, Secondary).*

Environmental causes and exacerbating factors mentioned by practitioners included home/parenting; diet; and school, which are discussed in the following subthemes.

Home/parenting. A number of practitioners talked about parents and the home environment as being the cause of many of the behaviours seen in children with ADHD: *'I would say it was to do with upbringing or amount of contact with parents' (Kate, TA, Primary).* This attribution was often framed negatively: *'It could be bad parenting, it could be absent parenting' (Sally, TA, Primary); 'What he's…come from and experienced is really quite crippling for any child' (head teacher, Primary).* This finding is in contrast to previous research, where teachers and education students were more likely to endorse statements that placed the cause of ADHD as biological rather than consider parenting as a cause (Bekle, 2004, Couture et al., 2003).

There were instances where practitioners were empathetic towards parents, whilst still holding them responsible for their child's symptoms, as Ryan sympathises:

> *'the parents of these children are just people as well who come with their own baggage…you may see that parent doing things which aren't healthy and aren't great for the child, actually maybe it's because they're struggling to really make sense of how to parent as well' (pastoral leader, Primary).*

This resonates with literature around the challenges of parenting a child with ADHD, and the criticisms and stigma endured by such parents (Peters and

Jackson, 2009), as well as parents' opinions that others blame them for their child's difficulties (Harborne, Wolpert and Clare, 2004).

Most of the practitioners who blamed environmental factors considered the behaviours shown by the children to be learned from home, Sparky sums up her experiences:

> *'All the children that I've worked with ADHD, my opinion would be that it's very…learnt behaviours from birth, in the sense that they have no structure, they have no boundaries, they haven't ever learnt to sit still and listen…and then they can't cope later on in life with sitting still and listening' (deputy head teacher, Primary).*

Diet. Although practitioners did not often explicitly name diet as a cause of ADHD, it was discussed several times due to the perceived role practitioners thought it plays in exacerbating children's hyperactive behaviour, as Kate emphasises: *'If you gave them certain foods, they would be completely uncontrollable and you would not have any…sort of ability to keep up with them' (TA, Primary).* In a different school setting Bryony reflects on the same issue: *'We've got some of course that possibly have ADHD behaviours but have a high sugar intake…which cannot be helping [their] behaviours' (teacher, PRU).* Whilst empirical evidence has shown no causal association of diet with ADHD, the current findings are in line with evidence that fatty acid supplementation and exclusion of artificial food colourings may be effective methods for improving symptoms of ADHD (Bloch and Qawasmi, 2011, Sonuga-Barke et al., 2014).

School. Few practitioners mentioned the role that school can have in creating or exacerbating behaviours. Aspects of the school that practitioners did speak about included school context, classrooms, peers and particular lessons. TA's were most likely to discuss the implications of context on behaviour; Jemima presents a broad view: *'I don't think classrooms are necessarily the best, they are not set up really…to suit children, they're set up to suit adults' (TA, PRU);* whereas Alice discusses specific examples where she sees her pupil's behaviour worsen: *'German lessons…because it's a language lesson they are encouraged to call out things…and that's when she goes completely…hyper' (LSA, Secondary).* This lack of explicit mention of the school context by teachers is found in other research (Gwernan-Jones et al., 2015). Potential explanations for this are that because practitioners are unable or

unwilling to alter this context they do not discuss its role in children's behaviour. This might explain why it is practitioners in support roles who are more likely to acknowledge the role of school in ADHD symptoms. Alternatively, because school practitioners are immersed in the same context as the child, they may not see how this context impacts the child's behaviour (Gwernan-Jones et al., 2015).

2. How do educational practitioners conceptualise the causes of ADHD?

Practitioners went further than listing simple causal factors of ADHD as discussed in section 1. We now describe how practitioners theorise how this range of causes fit together in the context of their experiences with students with ADHD. These lay-theories about the precise causes of ADHD and what exactly should be diagnosed as ADHD are interpreted in this section. These ideas include a continuum with 'True' ADHD at one end and Environmental ADHD at the other, as well as alternative theoretical explanations: Biology exacerbated by environment and Environment becoming biology.

Extremes of the spectrum: 'True' ADHD and environmental ADHD

Several focus groups discussed the idea of there being a pure, real or true form of ADHD that would be characterised by several aspects. Practitioners considered true ADHD as:-

- biologically caused/innate: '*true ADHD people who have either got a chemical imbalance or the genetic disposition*' (Kate, TA, Primary)
- rarely seen: '*Probably about 10% of the children [with ADHD have] that pure*' (Tommy, teacher, Primary)
- the child has a perceived lack of control over their behaviour: '*Those that seem not to be able to help themselves*' (unknown, Primary)
- symptom intensity is severe: '*really active or…extreme [symptoms]*' (Katie, SENDCo, Primary).

This 'true' ADHD is considered to represent *'The end of the end of the continuum' (Victor, teacher and co-ordinator, Primary)* of ADHD-like behaviours. Practitioners describe this type of 'true' ADHD as pure, or high, contrasting with

other literature where pure ADHD is defined as when a child has no coexisting disorders in addition to their ADHD (Kadesjö and Gillberg, 2001).

At the far end of the spectrum away from 'true' ADHD, practitioners consider there to be ADHD that is currently clinically diagnosed yet is caused by the environment:

> *'A lot of the children that I've worked with who've had that diagnosis…a lot of it I would say was to do with upbringing or amount of contact with parents or…almost like attachment' (Kate, TA, Primary)*.

Several practitioners express the opinion that if this is indeed the cause, a diagnosis of ADHD should not be given, either because a developmental or attachment-related disorder is more appropriate, or because they consider this as labelling bad behaviour with no evidence of a medical cause:

> *'I wonder if it is misdiagnosed and I see similarities between children with ADHD and children with developmental disorders, ones that have had trauma in their lives, family breakdowns, mothers not always there' (Laura, student support co-ordinator, Secondary)*

> *'It would be nice if it was a medical problem you could then call it ADHD and if it wasn't a medical problem and you grew up and you've learnt it or something, it's just "you're a little bit naughty"' (Tommy, teacher, Primary)*.

Only one participant overtly rejected ADHD as a concept, with practitioners in general having *'no doubt ADHD exists' (Laura, student support co-ordinator, Secondary)*; this contrasts with findings that 20% of SENDCo's surveyed in the UK in 2008 did not believe that ADHD is a 'real' neurological condition (O'Regan, 2009). This may be due to increased social visibility of ADHD or to an increase in rates of diagnosis (Akinbami, Liu, Pastor, & Reuben, 2011; Atladottir et al., 2015).

One method that practitioners used to differentiate between true and not-true ADHD was to speculate: for example Tommy questions his colleagues *'and if that child had been taken at birth and given to another parent, would that child mentally be different?' (teacher, Primary).*

Webb (2013) puts forward the idea that there may be two discrete aetiological pathways to ADHD: one due to genetics, and the other due to severe adverse childhood experiences. Practitioners' theory of 'True' ADHD reflects these two groups. However, unlike the practitioners that endorsed 'True' ADHD, Webb also acknowledges that there will be a group of children who overlap, those who have a genetic predisposition toward ADHD-like behaviours and environmental factors which exacerbate this. This is reflected in the findings of a separate theory proposed by practitioners, described in the following theme (Biology exacerbated by environment).

Biology exacerbated by environment

Many practitioners conceptualise ADHD as being caused by a biological entity, but state that environmental conditions that the child grows up in can ameliorate or exacerbate their behavioural problems: Alice describes her own theory: *'it's something that you're born with …however I think that home situations can improve it or make it worse' (LSA, Secondary)*.

In general, practitioners talked more about the exacerbating factors than those that may help the child overcome the problems:

> *'it's genetic and then the way you're brought up your sort of channelled in the right direction …you could turn it down a bit … but if you then have that kind of upbringing it's going to make it worse' (Jane, SENDCo/teacher, PRU).*

Research supports associations between environmental adversity and ADHD (Russell, Ford and Russell, 2015, Biederman, Faraone and Monuteaux, 2002, Webb, 2013), and indeed focus on building resilience and ameliorating risk may be an effective management approach for children with ADHD who have also experienced environmental adversity (Alvord and Grados, 2005).

Environment becoming biology

Several practitioners discussed how things that happen early in a child's life can become biologically hardwired and therefore not alterable by changing the environment:

> *'I think the child's younger years [before age six] as well are so formative in their lives… that I think possibly by the time a child is that much older,*

that it, the patterns are so entrenched, perhaps hard to tell the difference between what was nature and what was nurture... so fundamentally it actually has become a physical part of how they work' (Ryan, pastoral leader, Primary)

This appeared to be linked to knowledge of attachment and attachment disorders with which practitioners seem more familiar than ADHD, as Laura says: *'I've done a little bit about attachment disorders and I think there are similarities there' (student support co-ordinator, Secondary)*. Practitioners also imply that there is a critical or sensitive period of development (Bornstein, 1989), whereby by the age of six they believe that further changes to environment will not change the child's underlying pathology. Anna discusses both of these ideas in combination, putting forward the idea that neurological changes occurring because of poor attachment early in life lead to ADHD behaviours later in childhood *'you know links in your brain that don't happen because of poor attachment…so I do think it's all to do with those first' (teacher, Primary).*

Discussion

Summary

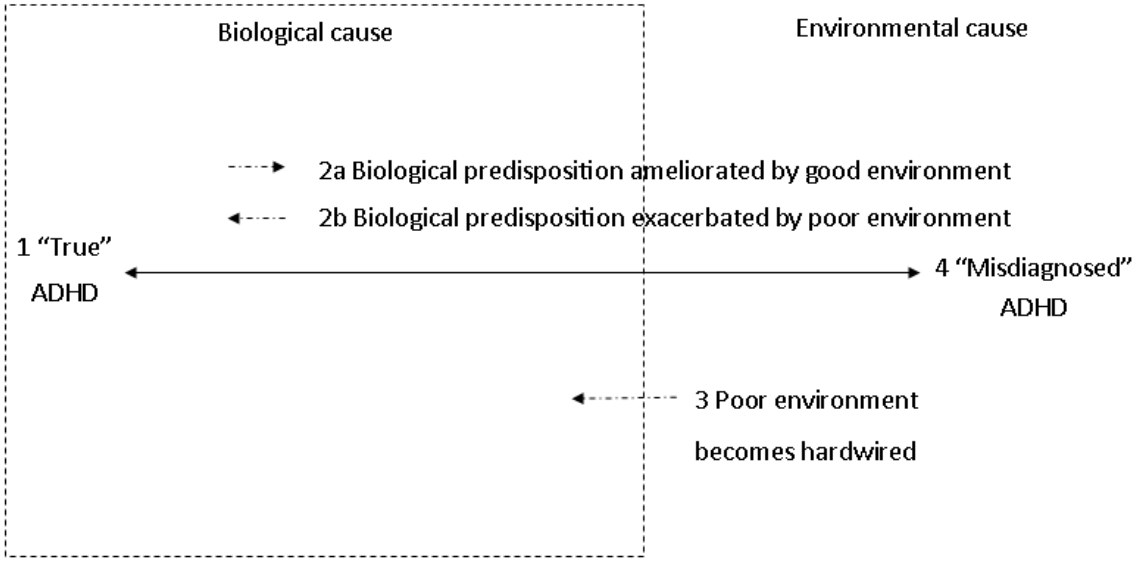
Practitioners in this study represented a range of experience, roles and viewpoints around the topic of ADHD. When discussing what causes ADHD, practitioners endorsed two points of view: that it was either biological in nature, or it was environmentally constructed, often due to an adverse home environment. The views held by practitioners were nuanced and sophisticated, and the range of theories put forward reflects current research literature, despite practitioners' opinions that they lacked knowledge regarding the specific biological causes of ADHD. However, practitioners emphasised more their understanding of theories that have less empirical support (e.g. those of Webb) and were likely to dismiss well-supported theories (e.g. the high heritability of ADHD) as not applying to the majority of children they have worked with. It is important not to consider the lay-theories of practitioners and empirical evidence as representing 'right' or 'wrong'; indeed, they can be viewed as complementary.

Practitioner theories as evidenced by this study can inform future research directions about the causes of ADHD. Educational practitioners have a wealth of experience working with children with these difficulties, and their understandings could allow epidemiologists to take advantage of expertise of those with direct and personal knowledge of ADHD by incorporating the ideas about causes and nosology into future research designs. In addition this study contributes to understanding dilemmas educational practitioners face when working with children with ADHD and enables us to identify reported gaps in their knowledge.

Further theoretical elaboration

Based on the views of the practitioners around causes of ADHD, we have constructed a model to capture beliefs about the causes of ADHD (see Figure 1). Theory 1 reflects that severe ADHD symptoms (in the presence of a good environment) are due to solely biological predisposition; these were considered by practitioners to be ‘True’ ADHD. At the other extreme (Theory 4), symptoms can be caused entirely by the environment with minimal or no biological contribution; practitioners considered this to be a misdiagnosis of ADHD. Practitioners believe severe adversity early in life can become biologically ‘hardwired’ (Theory 3); these thoughts were based on practitioners’ knowledge of child development and attachment disorders, where early experiences are thought to alter the formation of neural pathways. It would therefore be of interest to explore and further understand whether educational practitioners’ causal beliefs moderate their adherence to treatments for children with ADHD.

Figure 1: Practitioners' causal explanations for ADHD



Notes: 1– 'True' ADHD characterized as biologically caused, severe, uncontrolled and rare. 2a– Biological predisposition to ADHD ameliorated by good environment, symptoms are milder. 2b– Biological predisposition to ADHD exacerbated by poor environment, symptoms are more severe. 3– Poor environment causes symptoms, becomes hardwired and therefore a biological condition. 4– Symptoms caused entirely by poor environment, considered by educational practitioners to be a misdiagnosis of ADHD.

Theories 2a and 2b focus on how the environment affects biological predisposition and encompasses symptom severity. In both 2a and 2b all children with ADHD have a biological predisposition to the constellation of symptoms. This in turn can then be ameliorated (2a) or exacerbated (2b) by the environment that the child grows up in. Most practitioners acknowledged home and parents to be key elements of this, and some mentioned the impact of peers and the school context as other pertinent factors.

How do these beliefs compare to the current empirical literature on ADHD?

ADHD is currently thought to be a highly heritable disorder, with environmental factors impacting on risk and resilience (Faraone et al., 2015). However, recently the idea that there may be two discrete causes for ADHD, or types of ADHD has been forwarded (Webb, 2013, Russell, Ford and Russell, 2015); one environmentally caused by extreme adversity and one with biological origins. If this is indeed the case it is of interest that practitioners consider environmentally-caused ADHD to be a 'misdiagnosis' rather than the same disorder with different aetiological pathways. Practitioners do however propose a separate environmental pathway to ADHD, whereby early adversity has negative impacts on the developing brain that lead to symptoms becoming irreversible. Whether or not they would consider this to then be 'True' ADHD is unknown. We suggest that participants' theories around this subject appear to be based on their understanding of the impact of attachment on development, and the impacts of early problems with attachment on brain development. On the whole however, practitioners were vaguer about biological concepts than environmental. We suggest that this is because educational practitioners feel most comfortable talking about their field of expertise, but also that this reflects their knowledge; practitioners are likely to have more experience of how environmental adversity affects children than knowledge of the specific biological mechanisms of ADHD, thus they draw on their knowledge in order to conceptualise and form an understanding of the causes of ADHD.

Our findings somewhat reflect those of Couture et al. (2003) in that the majority of practitioners felt that 'True' ADHD had a biological cause. However, practitioners in our study rarely reflected on and endorsed societal level explanations for ADHD, unlike those in Couture et al.'s study. The themes 'biological' and 'environmental' also reflect the findings of Hillman (2011) where practitioners' classifications fell into two categories of cause: medical or non-medical. However, unlike Hillman, we found an interaction between these two classifications as some practitioners described ADHD being primarily caused by biological factors but exacerbated by environmental factors, as well as the concern that early adversity may predispose children to develop entrenched behaviours.

The source of information and theory generating among practitioners was often interesting. Because practitioners are aware that the medicines used to treat ADHD work ‘in the brain’, they reason that ADHD must have some biological root. The interviewer was often asked questions before and after the data collection about how Ritalin works and how it was developed, and practitioners were often surprised when informed that it was discovered to work by chance and not because of an elaborate neurochemical understanding of ADHD (Lange et al., 2010). Practitioners discussed obtaining information from a variety of sources that they drew upon in order to form their own conceptualisations of the causes of ADHD including parents, media and direct experience, although they considered their knowledge of biological causes of ADHD under-developed.

How practitioners’ beliefs about the causes of ADHD align with the school ethos and behavioural management practices may play a role in how the practitioner responds to the individual child (Ajzen and Fishbein, 1977). This is supported by one focus group run in a secondary school where the practitioners had a very clear stance on ADHD as a medical disorder. This allowed them to put forward a coherent plan as to how both the school and individual staff could best support any child with this diagnosis whilst allowing for the individual needs of each child. Taken together with the lack of (and thirst for) knowledge of ADHD displayed by practitioners in the study, research and development of accessible psychoeducational programs for practitioners as well as evidence based guidelines for schools are called for.

Strengths and Limitations

This study is the first qualitative study of UK teachers’ attitudes and experiences of ADHD. The methodology and recruitment had a variety of strengths; schools of varying provision were included covering the full age range of compulsory education in the UK, and tapping into specialist provisions for children who were not educated within the mainstream setting. We also recruited any educational practitioner who had experience working with children with ADHD, not just teachers. Limitations are that the study was conducted in a relatively small geographical area, and the sample cannot be inferred to be representative of all educational practitioners, so generalisability of findings is limited. However, conceptualisations of ADHD were validated within other focus

groups and interviews within the study, which allows us to tentatively infer that these views may be present in the wider educational community in the UK. Our sample was self-selected, therefore they might not be representative of those who would not volunteer to participate in research or engage in a focus group with colleagues. However, we believe we have managed to capture the views of those with a wide range of experience by including all educational practitioners and by the participation of those with a spectrum of years of experience.

Recommendations for future research

This study has a variety of implications. Firstly, if educational practitioners believe that when a child's ADHD difficulties are seen to be caused by an adverse home life this may be a misdiagnosis of ADHD, they may then be less likely to take the child's problems seriously. However, multiple routes to health outcomes are not unknown. For example diabetes can be caused by both heritable and lifestyle factors: the cause does not influence how we treat individuals. Therefore any child with a diagnosis of ADHD should be able to access treatment. However this may be compromised by the beliefs of educational practitioners if they block access to treatment or stigmatise the child for the perceived cause of their behaviour. Further research would also benefit from extending the ideas and models presented here with both qualitative and quantitative research techniques.

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Chapter Six: Socioeconomic associations with attention deficit/hyperactivity disorder (ADHD): findings from a mediation analysis (study 3)

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Abstract

Background: Children from disadvantaged socioeconomic backgrounds are at greater risk of a range of negative outcomes throughout their life course than their peers; however the specific mechanisms by which socioeconomic status relates to different health outcomes in childhood are as yet unclear. **Aims**: The current study investigates the relationship between socioeconomic disadvantage in childhood and attention deficit/hyperactivity disorder (ADHD), and investigates putative mediators of this association in a longitudinal population-based birth cohort in the UK. **Methods**: Data from the Avon Longitudinal Study of Parents and Children were used (n=8,132) to explore the relationship between different measures of socioeconomic status at birth-3 years and their association with a diagnosis of ADHD at age 7. A multiple mediation model was utilised to examine factors occurring between these ages that may mediate the association. **Results**: Financial difficulties, housing tenure, maternal age at birth of child and marital status were significantly associated with an outcome of ADHD, such that families either living in financial difficulty, living in council housing, with younger or single mothers were more likely to have a child with a research diagnosis of ADHD at age 7. Financial difficulties was the strongest predictor of ADHD (OR 2.23 95% CI 1.57-3.16). In the multiple mediation model, involvement in parenting at age 6 and presence of adversity at age 2-4 mediated 27.8% of the association. **Conclusions**: Socioeconomic disadvantage, conceptualised as reported difficulty in affording basic necessities (e.g. heating, food) has both direct and indirect impacts on a child's risk of ADHD. Lower levels of parent involvement mediates this association, as does presence of adversity; with children exposed to adversity and those with less involved parents being at an increased risk of having

ADHD. This study highlights the importance of home and environmental factors as small but important contributors toward the aetiology of ADHD.

Introduction

Groups and individuals differ in societal position by the amount and type of resources held, be these economic, social or political (Braveman et al., 2005). Individuals and groups in differing socioeconomic strata are known to have disparate health outcomes, with those in the most disadvantaged groups at highest risk of poor health (Shavers, 2007). Children from disadvantaged socioeconomic backgrounds are at a greater risk of a range of negative outcomes throughout their life course compared with their peers (Bradley and Corwyn, 2002), however the specific mechanisms by which socioeconomic status (SES) relates to different health outcomes in childhood are as yet unclear, perhaps due to the complex relationships between SES and health as well as individual patterns of resilience in each child. The current study investigates the relationship between socioeconomic disadvantage in childhood and one particular outcome: attention deficit/hyperactivity disorder (ADHD), and investigates putative mediators of this association in a longitudinal population-based birth cohort in the UK.

Low SES has been linked to poor health in childhood, specifically (but not limited to) an increased risk of dental caries (Spencer, 2000), behavioural problems (Schneiders et al., 2003, Kalff et al., 2001, Boe et al., 2012), increased risk of smoking initiation (Keyes et al., 2012), slow growth/shorter stature (Graham, 2002), suboptimal cognitive development (Bradley and Corwyn, 2002, Aber et al., 1997, Kiernan and Mensah, 2009) and low birth weight (Aber et al., 1997). Children from socioeconomically disadvantaged backgrounds are also more at risk of mental health problems (Reiss, 2013). In a systematic review of 55 studies that explored relationships between SES and childhood mental health outcomes 52 reported an inverse relationship between the two. Overall, children were 1.18-3.34 times more likely to have poor mental health if they were from socioeconomically disadvantaged backgrounds (Reiss, 2013).

The current study focusses on associations between socioeconomic disadvantage and ADHD. ADHD is a psychiatric disorder with onset in childhood, which can persist throughout the life course (Shah and Morton,

2013). ADHD is characterised by symptoms of hyperactivity, impulsivity and/or inattention that cause impairment for the individual across multiple settings (American Psychiatric Association, 2013). It has been reported to have a prevalence in young people of 2-5% (Polanczyk et al., 2007) and has a complex aetiology. Although the majority of risk is thought to be incurred through heritable factors -with data from 20 twin studies estimating heritability at around 0.76 (Faraone et al., 2005), environmental and social influences are also likely to contribute to aetiology (Thapar et al., 2013). An individual with ADHD has an increased risk of a range of negative outcomes such as poor educational achievement and substance abuse (Bernfort, Nordfeldt and Persson, 2008), and this may interact with or exacerbate risks incurred through socioeconomic disadvantage. Although effective pharmacological and non-pharmacological treatments for ADHD exist, these target ADHD symptoms rather than causal processes (Tarver, Daley and Sayal, 2014). Identification of social and environmental risk factors is an important alternate avenue for tackling this prevalent and impairing condition.

The association between socioeconomic disadvantage and ADHD appears to be complex and potentially mediated by other factors that may co-occur with low SES (Russell et al., 2013). This may be because these other factors lie on a causal pathway between SES and ADHD, and therefore alter or account for this relationship (also known as mediation). Confounding may also play a role; socioeconomic status is measured in many ways and these are known to be inter-related, and many health-related behaviours occur differentially by an individual's SES, for example those of lower SES are more likely to smoke (Brion et al., 2010, Keyes et al., 2012). Furthermore, as ADHD and its associated traits are known to be highly heritable (Faraone et al., 2005), parental low education as an SES indicator could in fact be confounded with the parent's own ADHD traits, which led to their low educational attainment, and/or predisposition to smoke (Kollins, McClernon and Fuemmeler, 2005). The same traits could also lead to a parent having a lower occupational status due to their preference for hands-on or active work, which has been classed as socioeconomically lower than other occupations. The child being diagnosed with ADHD may therefore reflect inherited genetic traits rather than ADHD being caused by their parents' low SES. An alternate hypothesis is that having a child with ADHD causes socioeconomic disadvantage within the family. One study

found that lower labour supply and increased risk of relationship instability in parents of children with ADHD was only half accounted for by socioeconomic disadvantage, and conclude that having a child with ADHD reduces parental SES (Kvist, Nielsen and Simonsen, 2013), although others have found little or no support for such theories of reverse causality (Russell et al., 2013).

An alternate explanation for the association between SES and ADHD is passive gene-environment correlation, whereby the environment and the genes provided to children by their parents may themselves be correlated (Petrill et al., 2004). For example the home environment, parenting behaviours and the socioeconomic standing of parents are all potentially influenced by their ADHD genotype. Their children then inherit this genotype which will influence their own developmental and socioeconomic pathways (Lemery-Chalfant et al., 2013).

Existing literature suggests a strong association between ADHD and SES, and possible mediators in the family and home environment as these have been highlighted as potential mechanisms to explain the association (Russell et al., 2013, Sagiv et al., 2013). Putative mechanistic factors that have been proposed include maternal mental health (Sagiv et al., 2013), substance abuse (Lingineni et al., 2012) and aspects of the home environment (Sagiv et al., 2013).

Parental depression is known to negatively affect child outcomes (Cummings and Davies, 1994), and parental substance abuse or other psychopathology can also impact negatively on the parent-child relationship (Barnard and McKeganey, 2004). Parental depression and anxiety have been associated with attention problems in young children, which may be due to negative impacts on parenting and parent-child attachment (Batenburg-Eddes et al., 2013). Others have found that the negative association between income and child health has been almost entirely accounted for by mother's mental-health (Burgess, Propper and Rigg, 2004). The level of involvement that a parent has with their child's upbringing impacts upon the way that self-regulatory mechanisms develop (Gonzalez-DeHass, Willems and Holbein, 2005), which theoretically could underlie the symptoms of ADHD (Sonuga-Barke, 2005). Parents who are highly involved in a child's upbringing may promote joint attention and self-regulation. Fathers' with higher incomes report more involvement with their child (Romirowsky and Chronis-Tuscano, 2013). Childhood diet (specifically increased additives such as preservatives and

colouring) may increase hyperactivity in children (McCann et al., 2007). Family adversity such as partner cruelty, substance abuse and parental criminal involvement are considered risk factors for various forms of psychopathology including ADHD (Biederman, Faraone and Monuteaux, 2002, Counts et al., 2005). Research using indices of adversity has found it is the number of risk factors (and their cumulative effects) rather than the specific risk which is of importance (Mick et al. 2002).

Using a large, population-based birth cohort from the UK, our objectives for the current study were to:-

- Assess if there are there individual-level associations between parental income, occupation, education and single-parent status and ADHD in the child
- Establish which of these socioeconomic associations with ADHD is strongest
- Examine proximal home and family factors such as parent mental health, parenting involvement and psychosocial adversity as potential mediators of this effect

We hypothesised that indicators of SES would be independently negatively associated with an outcome of ADHD, and that parental education would be the strongest predictor of this association due to genetic confounding (i.e. parents of children with ADHD will themselves tend to have the difficulties with attention, hyperactivity and impulsivity associated with ADHD and therefore, be more likely to have poor educational attainment). We also hypothesised that the association between ADHD and SES would be mediated in part by family and home environmental factors such as parental psychopathology, family adversity (e.g. presence of domestic violence, substance abuse) and parenting involvement.

Methods

Design and Participants

This study utilises longitudinal data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Full details of the methodology and profiles of the cohort are published elsewhere (Boyd et al., 2013, Fraser et

al., 2013, Golding, Pembrey and Jones, 2001). In brief, all pregnant women living in a defined geographical area (Avon) in South-West England with an estimated delivery date between 1st April 1991 and 31st December 1992 were initially invited to enrol in the study, with supplementary recruitment taking place in two further phases. Of the 15,458 foetuses, 14,775 were live births and 14,701 were alive at one year of age.

Mothers, their partners [the term 'partner' will be used henceforth to encompass both fathers and partners of the mother who are not the study child's biological parent] and the study child have been followed up by a combination of questionnaires, clinic visits and assessments (Golding, Pembrey and Jones, 2001). Sample size was limited to children whose parents completed the Development and Wellbeing Assessment (DAWBA), a standardised diagnostic measure used in the current study to assign research diagnoses of ADHD at age seven. ALSPAC collected data at every time point for both twins when there was a twin birth but excluded triplets and quadruplets from the cohort. For the purpose of this study, one twin in each pair was randomly deleted as ADHD is commonly concordant in twins (Faraone et al., 2005). These criteria resulted in an overall sample size for the current study of 8,132 children and their parents/carers.

Measures

Socioeconomic Status

SES was measured in eight ways in order to test the relative predictive abilities of different indicators. The exact wording of the questions that parents responded to can be seen in supporting information S1 (ALSPAC, 2014).

Parental income: Self-reported family income (mother report) was measured when the study child was 33 months old. This was reported in five increments of £100, from less than £100 per week, to £400 and over. A binary measure 'financial difficulties' was also included, when the parent reported difficulty in affording heating, clothing, rent/ mortgage, food and/or things for the study child (Steer, 2004).

Parent Education: Mother and partner education levels were classified as less than GCSE, GCSE (or equivalent), and higher than GCSE. GCSE's are the UKs standard exams at age 16, and mark the end of mandatory schooling. The educational attainment of mothers was recorded at 32 weeks gestation;

however data on partners' education level was not available until the child was aged eight. It is unlikely however, that many partners' education substantially changed during that time, as most of the study sample will have completed their education prior to having children.

Parent Employment: Employment of mothers and partners (as reported by mothers) was recorded 32 weeks into the pregnancy and was classified into four categories; unemployed; housewife/husband or retired; in education/training and employed.

Marital Status/Family structure: Mothers provided information at 8-12 weeks gestation about their family structure which was classified into single/ cohabiting /married.

Maternal age at birth of study child: Mothers' age in years at the birth of the study child was recorded.

Housing Tenure: Mothers reported on their housing status at 8-12 weeks gestation. This was divided into renting through the council/housing association (social housing); private renting and home owner.

Large family size: Mothers who had reported living with more than three biological children or more than two other children during the period where the study child was aged 0-2 was classed as large family size. Having a large family is known to put pressure on a household's economic resources (Wray, 1971) and so was included as a socioeconomic measure in the current study.

Mediators

When exploring aetiological theories or mediational models, the use of longitudinal as opposed to cross-sectional data are important, as researchers can ensure that the exposure is measured before the mediator and the mediator is measured prior to the outcome (Selig and Preacher, 2009). Due to ongoing data collection throughout the child's life, family and home-based mediators were chosen that had occurred (or impacted) on the child between birth and age seven. This allows a model that occurs across time; SES at birth may be mediated by factors throughout early childhood leading to a diagnosis of ADHD.

Parental psychopathology: Mother and partners were classed as being depressed if they had a score of 13 or more on the Edinburgh Postnatal Depression Scale, a scale validated for use both during and outside of pregnancy (Eberhard-Gran et al., 2001). Data were collected from mothers

when the child was 2 years 9 months old and in partners when the child was 1 year 9 months.

Parenting activities age 6: Mothers were asked in detail when the child was aged 6 years 9 months about activities herself and her partner engaged in with the child. This gave a total score out of 75 for each parent, with higher scores indicating more involvement in activities with the child.

*Fizzy drinks/caffeine consumption at 3 years old***:** Parents were asked to report on how often their child drank cola and fizzy drinks, which was aggregated to form a variable for each time point of "never" "less than once a week" and "more than once a week", based on reports of the frequency the child was drinking fizzy drinks or cola.

Family adversity age 2-4: The family adversity index (FAI) (Steer, 2004) is an index developed in ALSPAC based on Rutter's original indicators of adversity (Rutter, 1977) and records family-based risk factors. The presence of at least one of the following factors was considered to indicate exposure to adversity in the current study; lack of partner affection; partner cruelty (considered present if the mother had reported she had been hurt by her partner physically or experienced emotional cruelty from her partner); family major problems; psychopathology of mother, substance abuse (this included use of "hard" drugs or alcohol consumption of more than three glasses a day for more than ten days) and crime (trouble with the police). In addition to this dichotomised indicator, partner cruelty and substance abuse were investigated as putative mediators.

Outcome: research diagnosis of ADHD

When the study child was seven years old their parents and teachers were asked to complete the DAWBA. The DAWBA comprises three elements for children under the age of 11: a parent interview, a teacher questionnaire and a computer-assisted assessment by a clinician based on the parent and teacher information. The assessment allows for parents and teachers to include free text responses to describe a child's behaviour beyond responding to symptom checklists and other structured items including the Strengths and Difficulties Questionnaire (Goodman, 1999). The DAWBA is designed to assess a spectrum of psychiatric disorders, in the current study presence or absence of a research diagnosis of ADHD was the outcome measure. In a study investigating

the validity of the DAWBA utilising both community and clinical samples, the DAWBA was found to have 89% specificity in the community sample and 92% sensitivity in the clinical sample for psychiatric disorders (Goodman et al., 2000).

Analysis

Continuous variables were checked to ensure that they were normally distributed. For ease of interpretation, scores were reversed so for all the mediators an increase in score represented a more negative impact (e.g. more fizzy drinks, less parental involvement). Descriptive statistics detailed differences in means/frequencies between those with an outcome of ADHD and those without for the predictors and mediators. Unadjusted logistic regression was carried out between each SES predictor and ADHD outcome. Multivariable regression was then used with those significant predictors to derive an SES model that explained the largest possible variance in the outcome.

The predictor with the strongest relationship to the outcome was then used in a mediation model. Multiple mediation analysis was carried out as recommended by Preacher and Hayes (2008), using the products of coefficients approach. Candidate mediators that showed significant associations with both the predictor and the outcome were included in the final mediation model, which was adjusted for gender. Bootstrapping was used in order to estimate bias-corrected confidence intervals. Mediation analysis was carried out with the commands "*binary_mediation* " and "*bootstrap"* in Stata 13 (StataCorp, 2013).

Although the same results would be found by applying a standard regression model, the benefits of using a mediation model are that it allows for explicit representation of the hypothesised pathways between the exposure and outcome measures. The use of mediation models in the current study allow us to demonstrate the theoretical pathway through which we believe the SES-ADHD association is likely to operate.

To assess the effect of missing data, descriptive statistics were reported to examine differences in the predictors between the entire ALSPAC population and the study sample (a subsample who completed the DAWBA assessment at age 7). These are shown in supporting information S2. Between 66% and 93% of the eligible sample did not respond to individual questionnaires, thus some data were missing from analysis. These data were not missing at random, as

low SES itself predicted drop-out (Wolke et al., 2009). Multiple imputation was therefore conducted and used for the analyses with the exception of the mediation model, where the statistical commands were incompatible. We imputed based on the SES variables and birth weight, gender and gestation using the *mi impute* command in Stata 13.

Ethical approval

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The University of Exeter Medical School Research and Ethics Committee also provided approval for the current study (Appendix 3).

Results

Mothers of children with ADHD had slightly lower levels of education, and proportionately more of the ADHD group had incomes within the lowest two bands (see Table 1). The ADHD group had proportionately more participants in the lower housing bands: council/housing association housing (17.8% in the ADHD group vs 10.1% in the no diagnosis group). Mothers with children with ADHD were less likely to be married than mothers of children with no ADHD diagnosis; 72.6% compared with 81.2% respectively. Proportionately more of the families of children with ADHD reported being in financial difficulty (27.78% vs 14.44% respectively) or having a large family (7.74% vs 4.87% respectively). There was a larger proportion of boys in the ADHD group (83.9% vs 50.5% in the no ADHD diagnosis group), and more mothers reported smoking during pregnancy in the ADHD group (26.6% vs 19.2% of the no ADHD diagnosis group).

As shown in Table 2, in unadjusted logistic regression significant predictors of ADHD were housing tenure, marital status, mothers' age at birth and financial difficulties, such that a child is more likely to have an outcome of ADHD if either they lived with a single parent (OR 1.70 95% CI 1.09-2.66) or their family lived in a council/housing association property (OR 1.84 95% CI 1.22-2.76). Children were marginally less likely to receive a diagnosis of ADHD if their mother was older when the child was born (OR 0.96 95%CI 0.93-0.99). Children were over twice as likely to have ADHD if their family was in perceived financial difficulty when they were an infant (OR 2.23 95%CI 1.57-3.16).

Table 1: Descriptive statistics; families with children diagnosed with ADHD at age 7 compared with those with no ADHD diagnosis

	Diagnosis of ADHD		No Diagnosis of ADHD	
Predictors				
Weekly Income (%)	*n=136*		*n=6,562*	
<£100		9.56		6.99
£100-£199		21.32		15.79
£200-£299		27.21		28.6
£300-£399		17.65		22.68
>£400		24.26		25.94
Education of mother (%)	*n=162*		*n=7,706*	
< GCSE		24.69		23.28
GCSE		38.27		35.08
>GCSE		37.04		41.64
Education of partner (%)	*n=109*		*n=5,694*	
<GCSE		8.26		4.79
GCSE		50.46		47.00
>GCSE		41.28		48.21
Housing tenure (%)	*n=157*		*n=7,521*	
Council/HA rent		17.83		10.09
Private rent		5.10		5.80
Own/mortgage		77.07		84.11
Marital Status (%)	*n=164*		*n=7,775*	
Single		14.63		9.27
Cohabiting		12.80		9.50
Married		72.56		81.22
Employment- mother (%)	*n=136*		*n=6,621*	
Unemployed		4.41		3.38
Housewife/retired/education		44.85		46.05
Employed		50.74		50.57
Employment- partner (%)	*n=151*		*n=7,352*	
Unemployed		7.95		6.24
Househusband/retired/education		1.99		2.16
Employed		90.07		91.59
Mothers age at birth, years, mean (SD)	*n=172*	28.11 (4.97)	*n=7,933*	28.97 (4.60)
Large family size (% with)	*n=168*	7.74	*n=7,757*	4.87
Financial difficulties (% with)	*n=162*	27.78	*n=7,720*	14.44
Covariates				
Gestation in weeks, mean (SD)	*n=172*	39.08 (2.34)	*n=7,933*	39.49 (1.81)
Male child (%)	*n=174*	83.91	*n=7,958*	50.53
Birth weight in g, mean (SD)	*n=172*	3390.12 (600.38)	*n=7,841*	3431.11 (535.86)

Note: number of observations- not all participants recorded data for every characteristic. Missing data were excluded from the analysis. HA= housing association, GCSE= General Certificate of Secondary Education.

Table 2: Logistic regression of each socioeconomic predictor on the outcome (ADHD diagnosis at age 7)

Predictors	**OR (95% CI)**	***p***
Weekly Income (%)	N=8,132	0.074
>£400	Reference	
£300-£399	0.88 (0.52-1.48)	
£200-£299	1.12 (0.71-1.77)	
£100-£199	1.61 (1.00-2.60)	
<£100	1.72 (0.94-3.15)	
Education of mother (%)	N=8,132	0.406
> GCSE	Reference	
GCSE	1.25 (0.88-1.79)	
<GCSE	1.23 (0.83-1.83)	
Education of partner (%)	N=8,132	0.067
>GCSE	Reference	
GCSE	1.34 (0.93-1.92)	
<GCSE	2.01 (1.09-3.71)	
Housing tenure (%)	N=8,132	0.014
Own/mortgage	Reference	
Private rent	0.97 (0.48-1.97)	
Council/HA rent	1.84 (1.22-2.76)	
Marital Status (%)	N=8,132	0.029
Married	Reference	
Cohabiting	1.48 (0.92-2.40)	
Single	1.70 (1.09-2.66)	
Employment- mother (%)	N=8,132	0.847
Employed	Reference	
Housewife/retired/education	0.99 (0.71-1.39)	
Unemployed	1.26 (0.56-2.84)	
Employment- partner (%)	N=8,132	0.610
Employed	Reference	
Househusband/retired/education	1.01 (0.33-3.10)	
Unemployed	1.34 (0.74-2.43)	
Mothers age at birth, years, mean (SD)	N=8,132	
	0.96 (0.93-0.99)	0.017
Large family size	N=8,132	
	1.59 (0.89-2.82)	0.115
Financial difficulties	N=8,132	
	2.23 (1.57-3.16)	<0.001

Note: OR= odds ratio. Unadjusted odds ratios are reported. CI= confidence interval Reported p value is p value for trend HA= housing association, GCSE= General Certificate of Secondary Education. A family was considered to be large if the mother reported having at least three biological children when the study child was aged 0-2. A family was considered in financial difficulty if they scored >8 on a mother-reported scale of 0-15 on how difficult it was to afford food, clothes, heating, things for the study child and rent.

What is the strongest predictor of ADHD (stepwise regression)

A multivariable regression model (see Table 3) using significant individual SES predictors of ADHD (financial difficulties, housing tenure, marital status and maternal age) was used to explore which predictors of ADHD explained the most variance. Financial difficulties was the only predictor which remained significant in the presence of the other significant SES indicators, therefore it was used in as the predictor in the mediation analysis.

Table 3: Multivariable regression with socioeconomic predictors which were significant in logistic regression model on the outcome (ADHD diagnosis at age 7)

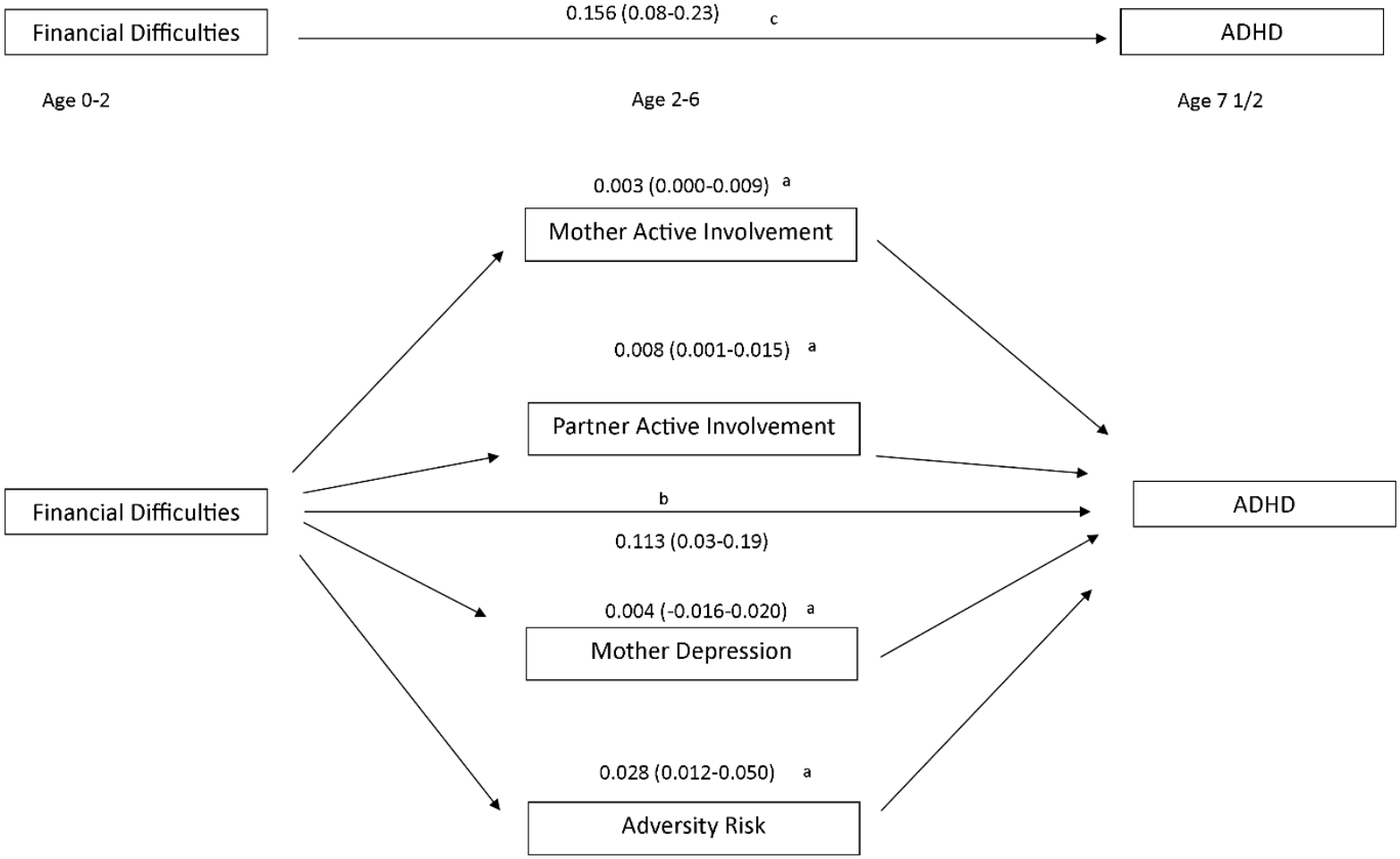
Variable	OR	95% CI	p value
Financial Difficulties	2.06	1.44-2.94	<0.001
Housing tenure			
Own/mortgage	*Ref*		
Rent	0.72	0.35-1.51	0.386
Council/HA	1.30	0.82-2.05	0.265
Marital Status			
Married	*Ref*		
Cohabiting	1.28	0.77-2.12	0.347
Single	1.35	0.83-2.18	0.224
Maternal age	0.97	0.94-1.01	0.138

Note: OR= odds ratio. Adjusted odds ratios are reported. CI= confidence interval Reported p value is p value for trend HA= housing association. A family was considered in financial difficulty if they scored >8 on a mother-reported scale of 0-15 on how difficult it was to afford food, clothes, heating, things for the study child and rent.

What are the mechanisms for this effect? (Mediation)

Parent report of financial difficulties was regressed on ADHD with adjustment for gender. Four mediators were then tested in one model with financial difficulties at age 0-2 as the predictor and ADHD diagnosis at age 7 as the outcome. These were mother and partner involvement with the study child, maternal depression and presence of family adversity. In the multiple mediation model, bias corrected confidence intervals excluded zero (representing statistical significance at the 5% level) for the direct effect (see Figure 1 (c) and Table 4), the total effect (b) and for three mediators (a). There was evidence that lower levels of parental involvement, both of the mother and partner and presence of family adversity mediated the link between financial difficulty and ADHD. Mothers' depression at 33 months was not a significant mediator in this model. The relative strength of each mediator can be seen in Figure 1. Overall, 27.8% of the total effect between financial difficulties at age 0-2 and ADHD at age 7 was mediated, with the majority of mediation occurring through adversity risk at age 2-4 (coefficient 0.03, bias-corrected (BC) CIs 0.01-0.05) while lower levels of both mother and partner involvement at age 6 also mediated the association (mother coefficient 0.003 BC CI's 0.000-0.009; partner coefficient 0.008, BC CI 0.002-0.016).

Figure 1: Mediation model.



Notes: a- indirect effects b- direct effects c- total effect. Values reported are standardised coefficients (bias-corrected 95% confidence interval) for each path. If bias-corrected confidence intervals cross zero the association is not statistically significant at $p<0.05$.

Table 4: Mediation analysis

Path	Coefficient	Bias corrected 95% Confidence Intervals
Total effect	0.156	0.082-0.228
Direct Effect	0.113	0.034-0.189
Indirect Effects:		
Adversity Risk	0.028	0.012-0.050
Mother involvement	0.003	0.000-0.009
Partner involvement	0.008	0.002-0.016
Mother depression	0.004	-0.012-0.020

Discussion

Our findings confirmed there were associations between some indicators of socioeconomic disadvantage, namely financial difficulties, social housing tenure, younger maternal age, single-parent status and ADHD in the child. Although ADHD was more prevalent in families whose parents had lower occupational status, and lower educational levels, these indicators did not show significant association with ADHD in children in the current sample. Financial difficulty, conceptualised as reported difficulty in affording heating, clothing, rent/ mortgage, food and/or things for the study child, was the socioeconomic indicator which was associated with the greatest increased odds for ADHD. Those whose mothers were classed as in financial difficulty when the child was aged 0-2 were 2.23 times more likely to have a research diagnosis of ADHD at age 7 than their peers. This association was mediated by how involved both parents were with their child and by the presence of family adversity, such that children with less involved parents and with at least one type of family adversity were more likely to receive a diagnosis of ADHD.

Although we hypothesised that parental education would be the strongest predictor of ADHD, this was not the case. The reasoning behind this hypothesis was that gene-environment correlation was likely to be high for ADHD and educational attainment, therefore those who did not attain highly in education would be more likely to have ADHD-like traits and pass these genes on to their children. Instead, financial difficulties emerged as the strongest predictor. Financial difficulties may be an indicator of very severe deprivation, which may be alter the aetiology of ADHD whereas more common, albeit disadvantageous, family circumstances did not emerge as a strong risk factor.

A substantial proportion of the relationship between financial difficulties and ADHD was mediated by adverse family factors and adversity risk (28% of the relationship was mediated by the factors tested). This lends weight to theory that parent involvement mediates the relationship between SES and ADHD. Severe financial difficulties may co-exist with extremely under-resourced parenting, in some cases leading to lack of parent involvement. There are numerous studies that show ADHD is more common in extremely challenging home environments: for example among children who are looked after, neglected or who have been abused (Ford et al., 2007b, Ouyang et al., 2008). The finding that many aspects of home life can mediate the pathway to ADHD supports models that suggest a number of risk factors (and their cumulative effects) may be important (Mick et al., 2002).

Webb (2013) suggests that epigenetic mechanisms may underpin the association observed. She argues that family environments of profound neglect may lead to alterations in gene expression as a result of DNA methylation, and convincingly demonstrates there is a socioeconomic gradient associated with child abuse and child neglect. Our findings suggest severe adversity was the biggest single mediator linking low SES to ADHD. This meant the presence of major family problems, family psychopathology, family substance abuse, physical violence or crime could engender hyperactivity and inattentive behaviours in children. Our finding does suggest that it is these very extreme family circumstances that are likely to elicit ADHD-type behaviours.

SES has been defined as “a broad concept that refers to the placement of persons, families, with respect to the capacity to create or consume goods that are valued in our society” (Miech and Hauser, 2001). The breadth of SES as a concept means there are many potential ways to conceptualise and measure SES, both at the individual and geographical/group level (Galobardes, Lynch and Smith, 2007). Common individual-level SES measures in children are parental educational level, occupation, income, marital status (or number of adults in the household), maternal age at the child’s birth and/or housing tenure (Hauser, 1994). The SES measures in ALSPAC were, as expected, inter-related. Logistic regression of the socioeconomic predictors on ADHD showed that a mothers’ report of whether the family struggled to afford goods is a more accurate predictor of ADHD than their actual weekly income or other socioeconomic measures. The measure of financial difficulties asks about being

able to afford goods that may directly impact on health; inadequate food, clothing and housing may all contribute to poor child health and impaired development. Results from the mediation analysis suggests that there are both direct effects of financial difficulties on ADHD as well as mediation by parental involvement and adversity risk, and that the mediators in total still do not have as much impact on the outcome as the direct effect.

Our findings concur with recent research that found that home learning environment, which included aspects such as reading to children (overlapping with current study measure of parent involvement), mediated the relationship between SES and ADHD (Schmiedeler, Niklas and Schneider, 2013). With regard to paternal involvement, a recent study reported that for fathers with ADHD symptoms, an association with conduct problems in the child (also with ADHD) were only found when the father also had high levels of involvement in childrearing (Romirowsky and Chronis-Tuscano, 2013). In addition, the authors found that those fathers with higher incomes reported higher levels of involvement with their child. This complex relationship needs to be further investigated to disentangle the directions of effects in order to best target intervention, as there may be different impacts of father involvement depending on their own ADHD symptoms as well as their socioeconomic circumstances.

Being a single parent has been associated with an increased risk of ADHD for the child both in the current study and previously (Kvist, Nielsen and Simonsen, 2013, Lingineni et al., 2012, Schneider and Eisenberg, 2006). There are various mechanisms through which single parenthood links with other measures of SES and through which this may influence a diagnosis of ADHD. For example, one parent must earn or bring in an income as well as raise any children. In addition a lone parent may experience increased stress, and as a result be more likely to use suboptimal parenting strategies(Batenburg-Eddes et al., 2013). Mental illness such as depression may precede or follow, further compounding the difficulties of effective parenting. As the majority of those diagnosed with ADHD in the current study were boys, the association with single parenthood may indicate that young boys lacking a male role model are more susceptible to the disorder, which is supported by our finding that partner involvement acts as a mediator between SES and ADHD. However, being a single mother may be positive for a family if she has left an abusive or unhealthy relationship (Kitzmann et al., 2003).

It is of interest that having married parents decreases the risk of ADHD more so than does having cohabiting parents. In the Millennium Cohort Study, single parent families have substantially lower household incomes than cohabiting parents, and married parents have a higher income than cohabiting parents, reflecting an interaction between marital status and other aspects of SES (Kiernan and Smith, 2003). There is little difference in child outcomes by marital status of the parents after controlling for background characteristics that indicate selection into marriage (e.g. relationship quality and parental cognitive ability), and other socioeconomic factors (parent education and income) (Goodman, Greaves and Joyce, 2011) which implies that the characteristics of those who chose to marry, rather than marriage itself, act as a protective factor for child outcomes.

In the current sample, ADHD is more prevalent among the children of younger mothers, although this association is small. Mothers' age again ties in with socioeconomic status; as wealth and resources accumulate over time, younger mothers are often financially worse off than their older counterparts, and their education may have been interrupted by their pregnancy. Being a younger mother may also represent an increased likelihood of the study child being the first-born and unplanned, and this could manifest in differences in parenting experience and management of disruptive behaviour between younger and older mothers with single or multiple children. If the child was unplanned this may also reflect on the mother's own ADHD-like tendencies; poor planning and risk taking behaviour, known facets of ADHD, may result in unplanned pregnancy.

We found that 27.8% of the direct effect of financial difficulty was mediated. This implies that there is a direct consequence of a family suffering financial difficulty on aspects of parenting and the family/home environment that exacerbate expression of a child's ADHD symptoms. Such family stressors could compound hyperactive behaviour. It may also be that other aspects of the home environment which lie on this pathway that were not investigated in the current study further mediate the SES-ADHD association, for example through disorganised attachment patterns (Crittenden and Kulbotton, 2007).

Limitations

The current study has many strengths; a large, representative longitudinal birth cohort allowed for modelling of causal processes that may occur throughout childhood. ADHD was measured in the whole population, as opposed to the selection biases inherent in a clinically referred sample, giving a much clearer picture of underlying risk. Multiple imputation was used to address the limitation of missing data in the first parts of the analysis, however the binary mediation with bootstrapping and multiple imputation commands were mutually incompatible, therefore the mediation analysis was carried out with the original data. Logistic regression using the original (missing cases omitted) data are shown in supporting information S3. The results were very similar to those with the imputed data; therefore we considered the mediation model that utilised the original data to be robust.

As discussed by Wolke et al. (2009) due to the systematic drop-out in ALSPAC of those of lower SES, conclusions drawn from the utilising the original data and not the imputed data in the mediation analysis are likely to underplay the effects found in this study as compared with the original ALSPAC population. The power of our analysis was limited by the relatively small number of children with ADHD in the study sample, and sadly there was no measure of parental ADHD or traits, which meant that we could not estimate whether genetic confounding and interaction between parent ADHD and their behaviours (such as in the case of father involvement; Romirowsky and Chronis-Tuscano, 2013) could not be investigated.

Future Research

Future studies using a sample exposed to a wider variety of adversities (such as the E-Risk study; Kim-Cohen et al., 2005) may be able to determine if there is a dose-response relationship between adversity exposure and ADHD symptoms. Future research could further attempt to unpack the effects of specific aspects of socioeconomic disadvantage on ADHD as well as other child mental health problems. Replication using a genetically informed study design or accounting for parental psychopathology, in particular ADHD, would add weight to the current findings.

Our results raise the question of whether, and to what extent the development of ADHD is influenced by the social, and specifically home and

family context. Although relative effects of socioeconomic, home and family factors are likely to be small, they are important because unlike genetic predisposition or genetic risk, they can be current targets for intervention. The results also underline that the notion of ADHD as an entirely fixed underlying biological entity requires qualification, as noted elsewhere (Johnston and Mash, 2001).

Clinicians should be aware that children and young people presenting with symptoms of ADHD are likely to have complex and often difficult family circumstances. Taking a holistic approach to treatment and referral on to other services that may support the families' to cope with their socioeconomic situation are important aspects of care for these children. On a societal level the results of this study question whether the current benefits system in the UK provides sufficient support for families with children to afford basic necessities such as food, heating and clothing, which are necessary in order to promote health and wellbeing. Cross-cultural research exploring the prevalence of ADHD in societies with differing social support systems may further elicit the impact that inadequate living conditions has on rates of ADHD.

Acknowledgements

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Supporting information S1: Exact question wording for study measures

Measure	Exact wording of question and use in current study	Possible Responses	Respondent	Age of child
Predictors				
Income	On average, about how much is the take home family income each week (include social benefits etc)?	Less than £100; £100-£199; £200-£299, £300-£399, £400 or more, don't know	Mother	33 months
Education	What educational qualifications do you, your husband or partner, your mother, and your father have? Please tick all that apply. (By husband or partner we mean your current live-in husband or partner). *Note: results categorised into <GCSE, GCSE or >GCSE based on highest educational level reported for mother and partner*	CSE or GCSE (D, E, F or G); O-level or GCSE (A, B, or C); A-level; d) Qualifications in shorthand/ typing/or other skills, e.g. hairdressing; Apprenticeship; State enrolled nurse; State registered nurse; City & Guilds intermediate Technical; City & Guilds final technical; City & Guilds full technical; Teaching qualification; University degree; No qualifications; Qualifications not known; Not applicable, no such person; Other	Mother Mother (for partner)	32 weeks gestation 97 months
Employment	What is the present employment situation of yourself and your partner? Please tick all that apply. *Note: categorised into unemployed; housewife/husband or in education or training or retired; employed.*	Working for an employer full-time (more than 30 hours a week); Working for an employer part-time (one hour or more a week); Self-employed, employing other people; Self-employed, not employing other people; On a government employment or training scheme; Waiting to start a job already accepted; Unemployed and looking for a job; At school or in other full-time education; Unable to work because of long-term sickness or disability; Retired from paid work; Looking after the home or family; Other (please describe)	Mother	32 weeks gestation

Measure	Exact wording of question and use in current study	Possible Responses	Respondent	Age of child
Housing Tenure	Is your home…? *Note: categorised into own/mortgage, private rent and council or housing association rent*	being bought/mortgaged; owned - with no mortgage to pay; rented from council; rented from private landlord – furnished; rented from private landlord – unfurnished; rented from housing association; other (please describe)	Mother	8 weeks gestation
Large family size	Calculated as >3 children and >2 other children We are interested in the other children who live with your baby. Please include half-brothers and half-sisters, step-brothers and step-sisters, fostered or adopted children. Do any other children live with you? How many boys/girls? How many people live in your household now? (including yourself)	Number of other children Number of children (under 16 years)	Mother Mother	6 months 21 months
Covariates				
Mothers age at birth	Supplied by ALSPAC			
Gender of child	Supplied by ALSPAC			
Birth weight	Supplied by ALSPAC			
Smoking during pregnancy	Did you smoke regularly at any of the following times in the last 9 months? *Note: dichotomised into smoked during the first trimester or not*	Before pregnancy; first 3 months of pregnancy; last 2 weeks	Mother	18 weeks gestation
Gestation	Supplied by ALSPAC			

Measure	Exact wording of question and use in current study	Possible Responses	Respondent	Age of child
Putative Mediators				
Parenting activities	Frequency of involvement of a mother or father figure with the study child on 19 everyday activities e.g. helping the child get ready for school, reading to the child, preparing food for the child *Note: used as a continuous score with higher scores representing less parental involvement*	For each item: nearly every day; 2-5 times a week; once a week; less than once a week; never	Mother	81 months
Adversity Present	At least one risk present on the 2-4 years of age family adversity index (for more information see Steer, 2004), with those used as predictors in this study (family size and financial difficulties) removed	Risks include: partner affection (lack of), partner cruelty, family major problems, maternal psychopathology, substance abuse and crime trouble with the police	Mother	0-2 years

Substance abuse	Derived from several variables at two time points including mother consumed ‘hard drugs’ since the child was 18 months old and mother and partner high levels of alcohol consumption. Either alcohol or drug abuse had to be present to be considered ‘substance abuse’ Since your study child was 18 months old have you taken the following? Heroin, methadone, crack, cocaine How much alcohol do you drink? Which of the following statements about alcohol best apply to your partner? If the mother reported drinking more than three glasses of wine a day for more than ten days or if she reported that her partner drank the same amount or more every day this was considered substance abuse.	Every day, often, sometimes, not at all Never drink alcohol, very occasionally (< once per week), occasionally (at least once a week), drink 1-2 glasses nearly every day, drink 3-9 glasses every day, drink at least 10 glasses a day (glass defined as half a pint of beer or a glass or wine)	Mother	33 months and 47 months

Measure	Exact wording of question and use in current study	Possible Responses	Respondent	Age of child
Partner cruelty	Derived from two questions repeated at two time points, present if the mother indicated she had been affected: Listed below are a number of events which may have brought changes in your life. Have any of these occurred **since the study child was 18 months old?** If so, please assess how much effect it had on you….Your partner was physically cruel to you?...Your partner was emotionally cruel to you?... If the mother reported she had been in any way "affected" by her partner being physically cruel or emotionally cruel, this was considered to indicate that 'partner cruelty' was present	Yes and affected me a lot; yes, moderately affected; yes, mildly affected; yes but did not affect me; no, did no	Mother	33 months and 47 months
Fizzy drinks	Based on the two below questions children were categorised as having fizzy drinks never, less than once a week or more than once a week. How many times in a week nowadays does [study child] drink…Cola drinks e.g. cola, pepsi?....other fizzy drinks e.g. lemonade?....	Never, once in two weeks, 1-3 times a week, 4-7 times a week, > once per day	Mother	38 months
Outcome				
ADHD	Clinician diagnosis of any type of ADHD based on the DAWBA, see Goodman et al. 2000 (Goodman et al., 2000)		Mother, teacher, clinician	91 months

Supporting information S2: Descriptive statistics by entire ALSPAC population (N=15,243) and study sample (N=8,132)

	ALSPAC Sample	**Current Study Sample**
Weekly Income (%)	*n=8,735*	*n=6,698*
<£100	8.76	7.05
£100-£199	17.65	15.90
£200-£299	28.39	28.58
£300-£399	21.19	22.57
>£400	24.01	25.90
Education of mother (%)	*n=12,338*	*n=7,868*
< GCSE	30.06	23.31
GCSE	34.62	35.14
>GCSE	35.31	41.55
Education of partner (%)	*n=6,487*	*n=5,803*
<GCSE	4.95	4.86
GCSE	47.43	47.06
>GCSE	47.62	48.08
Housing tenure (%)	*n=12,863*	*n=7,678*
Council/HA rent	16.62	10.25
Private rent	7.54	5.78
Own/mortgage	75.84	83.97
Marital Status (%)	*n=13,289*	*n=7,939*
Single	12.66	9.38
Cohabiting	12.53	9.57
Married	74.82	81.04
Employment- mother (%)	*n=10,424*	*n=6,757*
Unemployed	3.98	3.40
Housewife/retired/education	50.08	46.03
Employed	45.94	50.57
Employment- partner (%)	*n=11,535*	*n=7,503*
Unemployed	8.46	6.28
Househusband/retired/education	2.36	2.16
Employed	89.18	91.56
Mother's age at birth, years, mean (SD)	*n=13,894*	*n=8,105*
	27.98 (4.97)	28.95 (4.61)
Financial difficulties	*n=11,662*	*n=7,882*
	16.20	14.72
Large family size	*n=11,813*	*n=7,925*
	5.95	4.93
Gestation in weeks, mean (SD)	*n=14,422*	*n=8,105*
	38.41 (5.48)	39.48 (1.83)

Male child (%)	*n=14,665*	*n=8,132*
	51.35	50.24
Birth weight in g, mean (SD)	*n=13,716*	*n=8,013*
	3393.54 (570.73)	3430.23 (537.32)
Mother reports smoking at 18 weeks pregnant (%)	*n=13,188*	*n=7,965*
	25.14	19.33

Note: number of observations- not all participants recorded data for every characteristic. HA= housing association, GCSE= General Certificate of Secondary Education.

Chapter Seven: Longitudinal associations between socioeconomic disadvantage and childhood hyperactivity: a cohort study (study 4)

Abigail Emma Russell, Justin Matthews, William Henley, Tamsin Ford and Ginny Russell

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Abstract

Background: Studies report an increased prevalence of ADHD among children whose families are socioeconomically disadvantaged. In the current study, we aimed to explore the longitudinal association of low socioeconomic status (SES), conceptualised by self-reported financial difficulties, with levels of ADHD symptoms, measured by the Strengths and Difficulties Questionnaire (SDQ) Hyperactivity subscale, at an earlier versus later stage in children's lives. Methods: Data from the ALSPAC were used to explore the relationship between financial difficulty and ADHD symptoms (n=6011). A two-stage multilevel model was constructed to explore whether symptoms of ADHD differed by timing or cumulative levels of financial difficulty. Findings: We found evidence for a sensitive period between birth and age seven where financial difficulty is associated with increased levels of ADHD symptoms across childhood. Those who were not in financial difficulty during the early period (0 to 84 months) had a mean hyperactivity score of 3.55 SDQ points (95% CI 3.50, 3.61). Being in financial difficulty during this period resulted in a mean increase of 0.78 SDQ points (95% CI 0.54, 1.00, p<0.001). Children whose families were in financial difficulty in the early period had a 0.84 point mean increase (95% CI 0.59, 1.09, p<0.001) in their hyperactivity scores during the later period compared with those not in financial difficulty in the early period.

We also found that those spending a greater proportion of time in financial difficulty in early childhood are more likely to have higher levels of ADHD symptoms. Being in difficulty for the highest proportion of time was associated with a mean increase of 0.89 (95% CI 0.58, 1.23, p<0.001) SDQ points.

Interpretation: Our findings provide evidence to suggest that SES has a differential effect on ADHD behaviours at different stages in children's lives, and imply that factors linked to the social environment can modify expression of genetic risk factors, or may have an independent effect on developmental trajectory.

Introduction

Many poor health outcomes are associated with socioeconomic disadvantage (Bradley and Corwyn, 2002). Among these is attention deficit/hyperactivity disorder (ADHD), a developmental disorder where the primary symptoms comprise hyperactivity, inattention and impulsivity with onset before age 12 (American Psychiatric Association, 2013). These traits are highly heritable, but social and environmental factors may well contribute to its development and play a role in exacerbating or ameliorating symptoms (Faraone et al., 2015). Studies report an increased prevalence of ADHD among children whose families are socioeconomically disadvantaged (Bøe et al., 2013, Russell et al., 2015, Russell et al., 2013). In the current study, we aimed to explore the longitudinal association of low socioeconomic status (SES), conceptualised by self-reported financial difficulties, with levels of ADHD symptoms (Goodman et al., 2003) at an earlier versus later stage in children's lives. A differential effect would suggest the association between socioeconomic disadvantage and ADHD is not entirely due to genetic selection effects, and that SES may therefore lie on the causal pathway for ADHD, even if mediated through environmental factors (Miech et al., 1999).

Studies mapping longitudinal SES-health associations have been conducted with a variety of outcomes, including child and adult mental and physical health (Dearden, Sibieta and Sylva, 2011, Kiernan and Mensah, 2009, Aber et al., 1997, McLeod and Shanahan, 1996, Anselmi et al., 2012, Miech et al., 1999). Such studies can reveal aetiological pathways, assessing whether changes in patients' socioeconomic circumstances lead to immediate or delayed changes in their health. Findings have varied, although many find persistent poverty is associated with the most negative outcomes (Aber et al., 1997, Kiernan and Mensah, 2009, McLeod and Shanahan, 1996). These differences are evident in childhood (Dearden, Sibieta and Sylva, 2011, Kiernan and Mensah, 2009).

Two factors in patterns of association between low SES and ADHD symptoms that could lend support for different mechanistic pathways are the timing of exposure to disadvantage and the duration of exposure: these patterns may be unique to the specific outcome measured (McLeod and Shanahan, 1996, Miech et al., 1999). Timing of exposure relates to the putative existence of a sensitive period in early childhood, where environmental risks are at their most influential (Ben-Shlomo and Kuh, 2002). Evidence relating to the role of critical or sensitive periods in ADHD or other psychiatric disorders is limited: McLeod and Shanahan (1996) found that early disadvantage but not later disadvantage was associated with depressive symptoms, suggestive of a sensitive period in development. The duration spent in disadvantaged conditions could have a cumulative impact on the outcome, for example it was found that the longer a child spends in low SES, the stronger the association with antisocial behaviour (McLeod and Shanahan, 1996).

As children inherit their parent's ADHD traits, and these parental traits lead to poor SES outcomes, factors related to socioeconomic disadvantage may be a result of genetic selection: evidence for this has been found regarding educational attainment and ADHD (Miech et al., 1999). If SES has a differential effect on ADHD behaviours at different time-points this would provide further evidence that environment can modify expression of genetic risk factors for ADHD (Nikolas, Klump and Burt, 2015), and/or may have an independent effect over and above genetic risk.

We aim to explore two hypotheses, using differing thresholds to define low SES:

1. Sensitive period. Children exposed to low SES early in life will demonstrate more childhood ADHD symptoms than their peers who have higher SES in their early years. Those exposed to low SES later in life will have a weaker association between SES and ADHD symptoms.
2. Cumulative. Children who spend a higher proportion of their childhood living in low SES will have more symptoms of ADHD. There will be a dose-response relationship.

Methods

Design and Participants

The current study utilised the ALSPAC to explore the relationship between financial difficulty and ADHD-like behaviour. ALSPAC is a birth cohort study that aimed to recruit all pregnant women living in the county of Avon, UK, with estimated delivery dates between 1st April 1991 and 31st December 1992 (Fraser et al., 2013, Boyd et al., 2013). 13,988 of these children were alive at one year of age. ALSPAC did not enrol triplet or quadruplet births in the cohort, and we included the first-born of twin pairs in the current study.

This study included only those children who had at least partial data on the study measures (n=6011). The ALSPAC study website contains details of all available data (ALSPAC, 2014). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees, and the University of Exeter Medical School Research Ethics Committee (Appendix 3).

Measures

<u>Predictors</u>

Financial difficulty scores were used to represent family level SES, as we have previously established its association with an increased risk of a research diagnosis of ADHD in the ALSPAC population (Russell, Ford and Russell, 2015). Mothers were asked to rate how difficult it was to afford the following: food, clothing, heating, rent or mortgage, things needed for the study child. Answers were rated on a Likert scale (scored 1–4). This measure was repeated five times (see Figure 1). Financial difficulty was therefore measured as a score (5–20) of decreasing financial difficulty at each time point. We applied a threshold to dichotomise those in financial difficulty: this was chosen through discussion as to the level of financial difficulty that may represent individuals' struggling to make ends meet. The chosen threshold represents individuals with at least some financial difficulty across the areas asked about. Additionally, we conduct sensitivity analyses with higher and lower thresholds for financial difficulty to determine whether our results are robust.

Outcome

The Strengths and Difficulties Questionnaire (SDQ) is a widely-used dimensional questionnaire that evaluates childhood psychopathology. The hyperactivity subscale is often used when making judgements about the levels of ADHD symptoms a child displays, both clinically and in research (Goodman et al., 2003, Carballo et al., 2014, Huss et al., 2008), and has been demonstrated to correlate meaningfully with other measures of ADHD symptoms (Muris, Meesters and van den Berg, 2003, Huss et al., 2008). Mothers completed the SDQ at four time points of interest before puberty (Figure 1).

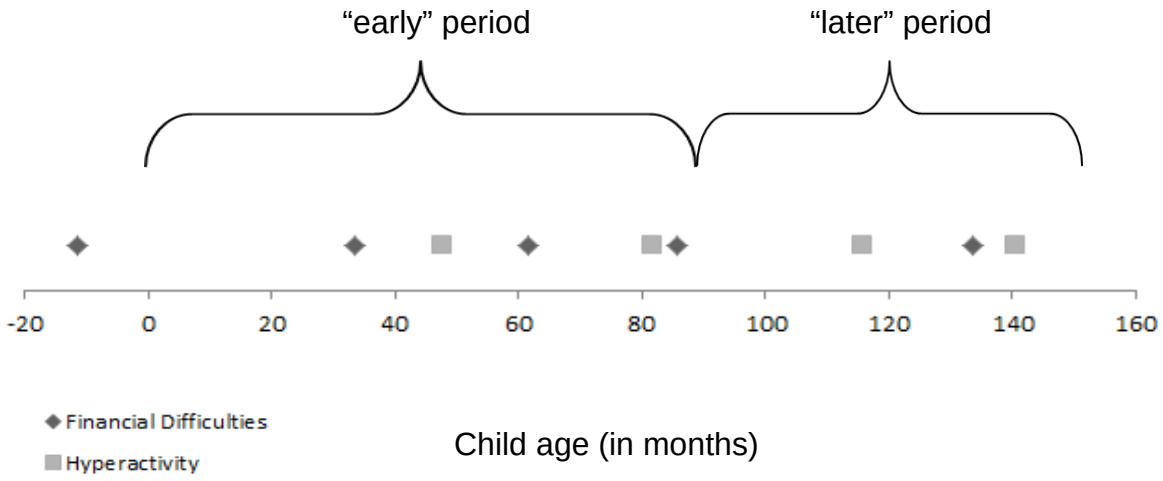
As with many mental health problems, there is an imbalance in the prevalence of ADHD between genders: in the case of ADHD, a ratio of 4:1 boys: girls (Ford, Goodman and Meltzer, 2003). Analyses were therefore repeated as a sub-group for each gender.

Defining thresholds and periods of interest

We transformed the original financial difficulties score (f') to $f = \log_e(20 - f' + 1)$ to provide a more intuitive scale (higher values mean more difficulty), that better approximates normality.

Prior to analysis, we specified the number of time periods of interest and their boundaries in order to delineate early and late periods for hyperactivity, and the threshold financial difficulties score. These choices were informed by theory but also limited by the data. We used two periods of interest; the "early" period was defined as birth to age seven, and the "later" period as age seven to twelve years six months (see Figure 1). We applied a pre-specified threshold of f'=14 (f=1.95) to the scores to generate dichotomous groups in or out of financial difficulty. Individuals that had data on less than two time points within each period were excluded from the analysis. Details of participants with missing data can be seen in the Supplementary information.

Figure 1: Illustration of time periods used to address research questions.



Notes: The two hyperactivity time periods are separated at 84 months; this is a theory-driven choice that also captures two hyperactivity measurements within each period.

Analysis

In the first stage of analysis a growth curve model was devised for financial difficulties by fitting a linear spline over two time periods, with the join or 'knot' at 75 months. These two time periods were chosen *a priori* taking into account the timing of financial difficulty measurements, they were separated at 75 months which does not coincide exactly with the two periods of interest (early and later) for the hyperactivity outcome. The model allows for the dependence between observations within each individual (see supplementary information for details). The estimates under this type of model are 'partially pooled' or 'shrunk', meaning that an individual's estimates are formed under the combined influence of their own data and others in the population (Gelman and Hill, 2006). It has been shown that this type of approach provides superior estimates (Efron and Morris, 1977). Supplementary information Figure 1 illustrates the trajectories for a random sample of individuals. The growth curve modelling allowed us to estimate an average financial difficulties score (under shrinkage) for each individual in each time period, and thus determine whether they were above or below the financial difficulties threshold.

In the second stage, hyperactivity was modelled using a multilevel model (see supplementary information). A combined model was constructed by incorporating the

financial difficulties model into the hyperactivity model, and this two-stage model was modified further for use with each hypothesis (see below). Overall analyses were conducted; these were then repeated by gender. Analysis was carried out using R 3.1 and the 'nlme' package (Pinheiro et al., 2016).

Hypothesis 1 (sensitive period): we estimated the average hyperactivity score for individuals not in financial difficulty within each period as the baseline. We then predicted the change in score for individuals in financial difficulty during each period, exploring the effect of financial difficulty in the early period on the early period, the early period on the later period, and the later period on the later period.

Hypothesis 2 (cumulative): individuals were grouped by the proportion of time within the early period that they were in financial difficulty. We calculated the hyperactivity score of those in no difficulty during the period, and the difference in hyperactivity for those in financial difficulty none to one third of the period, one third to two thirds, and two thirds to all of the period. Due to data constraints and shrinkage, very few individuals were classified as being in financial difficulty towards the end of the later period; this analysis is therefore restricted to the early period.

Sensitivity analysis

We adapted the models and parameter values in the following ways and assessed their impact on the results and interpretation:

(i) "Severe" (reversed score ≥17) and "Low" (reversed score ≥11) thresholds for financial difficulty.
(ii) A 'fixed effects' model for financial difficulty.
(iii) Replacing 'linked' with 'unlinked' bootstrapping (see Supplementary Material for a detailed description of these adaptations).

Role of the funding source

The funders of this study had no involvement in the study methodology or design.

Results

Main analysis

6011 individuals had data on at least two financial difficulty time points within both early and later periods; this comprised our sample. Table 1 shows the number and percentage of participants above the threshold (thus in financial difficulty) for each threshold at each time point. Mean hyperactivity decreased over subsequent measurement occasions (see Figure 2). Boys had a higher mean hyperactivity score than girls.

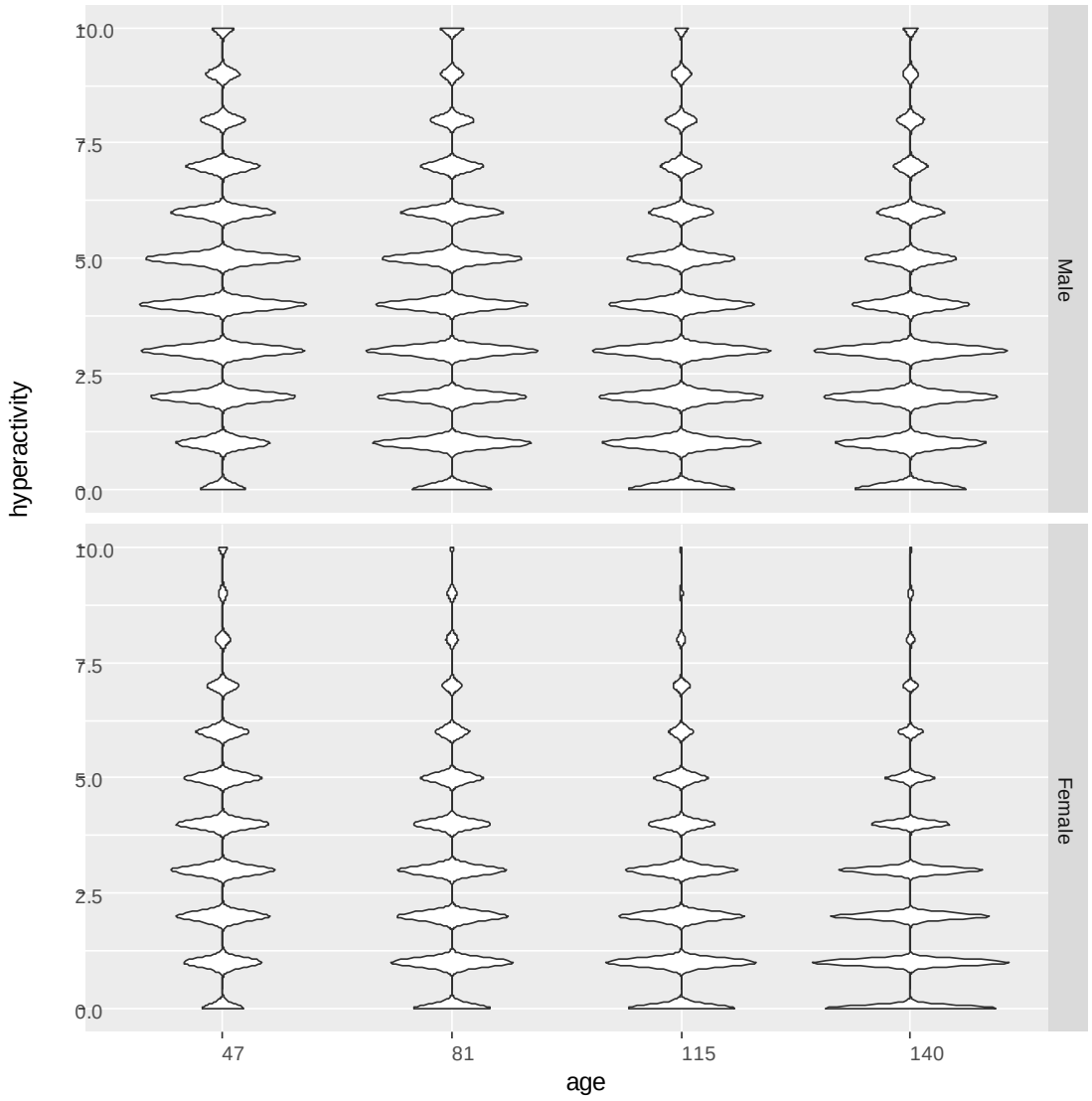
1. Hypothesis 1: Sensitive period

Early period: Those who were not in financial difficulty during the early period (0 to 84 months) had a mean hyperactivity score of 3.55 SDQ points (95% CI 3.50, 3.61) (Table 2). Being in financial difficulty during this period resulted in a mean increase of 0.78 SDQ points (95% CI 0.54, 1.00, p<0.001). There were no significant differences by gender: boys 0.85 (95% CI 0.51, 1.19), girls 0.72 (95% CI 0.41, 1.04).

Table 1: Financial difficulties descriptive information- (note: moderate threshold used for main analysis)

		Percentage in financial difficulty at threshold		
Child age	N	"Low"	"Moderate"	"Severe"
32 weeks gestation	5820	26.0	12.0	5.6
33 months	5694	30.0	15.0	7.1
61 months	5694	24.0	10.6	4.9
85 months	6011	16.0	5.8	2.5
133 months	6010	13.0	4.7	1.7

Figure 2: Hyperactivity descriptive information showing distribution of SDQ hyperactivity scores by gender at each time point



Effect of the early period on the later period: Children whose families were in financial difficulty in the early period had a 0.84 point mean increase (95% CI 0.59, 1.09, p<0.001) in their hyperactivity scores during the later period compared with those not in financial difficulty in the early period (Table 2). There were no significant differences by gender (boys mean increase 0.91, 95% CI 0.51, 1.30; girls 0.78, 95% CI 0.46, 1.09). Being in financial difficulty in the early years had a significant association with hyperactive behaviour both at the time and later in childhood.

Later period: Those not in financial difficulty in the later period had a mean hyperactivity score of 2.76 (95% CI 2.71, 2.82). Those in financial difficulty during

this period did not have a significantly different hyperactivity score compared with those not in financial difficulty (mean change from no difficulty average 0.10 95% CI -0.35, 0.60 p=0.65). The effect remained non-significant when analysing by gender. Being in financial difficulty in the later years had no tangible effect on hyperactive behaviour, after adjusting for the effect of being in financial difficulty in the early years.

2. Hypothesis 2: Cumulative

To address this hypothesis we split the data by the proportion of time each individual spent above the financial difficulty threshold within the defined early period (birth-age 7). The mean hyperactivity score for those never in financial difficulty was 3.56 (95% CI 3.51, 3.62; Table 3). Those who were in financial difficulty between none and one third of the period did not differ in their mean hyperactivity (mean change from never in financial difficulty 0.62, 95% CI -0.10, 1.18).

Being in difficulty between one and two thirds of the period was associated with a 0.68 point increase (95% CI 0.12, 1.28, p=0.02) and being in difficulty for the highest proportion of time was associated with a mean increase of 0.89 (95% CI 0.58, 1.23, p<0.001). Separate analysis by gender showed an increase in mean hyperactivity for those in difficulty two thirds to the whole of the period relative to those never in difficulty of 0.78 (95% CI 0.45, 1.24) for girls, and 0.99 (95% CI 0.50, 1.50) for boys. The association strengthened with increased duration of exposure.

Table 2: Results of sensitive period hypothesis

	Not in financial difficulty -early period	Not in financial difficulty -later period	Effect of financial difficulty in early period on early period	p	Effect of financial difficulty in later period on later period	p	Effect of financial difficulty in early period on later period	p
All	3.55 (3.50, 3.61)	2.76 (2.71, 2.82)	0.78 (0.54, 1.00)	<0.001	0.10 (-0.35, 0.60)	0.65	0.84 (0.59, 1.09)	<0.001
Female	3.20 (3.13, 3.28)	2.32 (2.26, 2.39)	0.72 (0.41, 1.04)	<0.001	-0.11 (-0.60, 0.38)	0.67	0.78 (0.46. 1.09)	<0.001
Male	3.90 (3.82, 3.97)	3.20 (3.12, 3.28)	0.85 (0.51, 1.19)	<0.001	0.35 (-0.44, 1.13)	0.38	0.91 (0.51, 1.30)	<0.001

Table 3: Results from cumulative hypothesis

	Never in financial difficulty (reference)	In financial difficulty 0-1/3 (mean 95% CI)	p	In financial difficulty 1/3-2/3 (mean 95% CI)	p	In financial difficulty 2/3-1 (mean 95% CI)	p
All	3.56 (3.51, 3.62)	0.62 (-0.10, 1.18)	0.03	0.68 (0.12, 1.28)	0.02	0.89 (0.58, 1.23)	<0.001
Female	3.21 (3.14, 3.28)	0.66 (-0.04, 1.39)	0.08	0.69 (-0.05, 1.53)	0.09	0.78 (0.35, 1.24)	<0.001
Male	3.90 (3.82, 3.97)	0.61 (-0.13, 1.38)	0.11	0.69 (-0.16, 1.57)	0.11	0.99 (0.50, 1.50)	<0.001

Notes for Tables 2 and 3: scores given are mean scores on hyperactivity subscale of the Strengths and Difficulties Questionnaire (range 0-10) and their average (95%CI) increase or decrease relative to the reference mean. Financial difficulties threshold: 14, linked bootstrap, random effects model.

Sensitivity Analysis

Hypothesis 1: Sensitive. Sensitivity analyses with unlinked or no bootstrapping, fixed effects modelling and varying thresholds did not substantively alter our findings (see supplementary information). When linked bootstrapping is utilised within the fixed effects model, the overall association between financial difficulty in the later period on the later period is marginally significant (mean hyperactivity increase 0.20, 95% CI 0.00, 0.41, p=0.05), the association for males is small but statistically significant (mean hyperactivity increase 0.47, 95% CI 0.12, 0.80, p=0.002) but not for girls (mean hyperactivity change -0.03 95% CI -0.30, 0.24, p=0.85). When the threshold for financial difficulty was lowered, effect sizes became slightly smaller, however do not change substantively.

Hypothesis 2: Cumulative. When repeating the analysis using the “severe” financial difficulties threshold, there are significant associations at p=0.01 for being in financial difficulty between none and one third of the time (mean hyperactivity increase 0.45, 95% CI 0.13, 0.78, p=0.01), and for being in difficulty between one and two thirds of the time (mean hyperactivity increase 0.51, 95% CI 0.17, 0.87, p=0.01), as well as the highest proportion of time having the strongest association. Although the effect sizes increase as proportion of time increases, the confidence intervals overlap substantially: it appears that each group experiences a comparable increase in hyperactivity scores for those experiencing severe difficulty. For the “low” financial difficulties threshold the only association significant at p=0.01 is for those in difficulty between two thirds and the whole period (mean hyperactivity increase 1.20, 95% CI 0.22, 2.20, p=0.01).

Discussion

Our results support the hypothesis of a sensitive period between birth and age seven where early financial difficulty is associated with more symptoms of ADHD. The magnitude of the increase is not insubstantial: on average 0.8 SDQ points higher for children whose family experiences financial difficulty than for those children who do not. We also found evidence that early financial difficulty predicts higher average ADHD symptoms from age seven to 15, but financial difficulty during this later age was not related to hyperactivity scores in the main analysis. These results suggest that financial difficulty experienced early in life has a lasting impact

on the course of a child's ADHD symptoms across childhood, whereas financial difficulty later in childhood may not be strongly associated with ADHD symptoms.

The length of time spent in financial difficulty is also associated with higher hyperactivity scores: our findings demonstrate that those spending a greater proportion of time in financial difficulty in the early period are more likely to have higher levels of ADHD symptoms. In summary, there is evidence of a sensitive period during which time there is an increased risk of higher ADHD symptoms for those experiencing prolonged financial difficulty.

We have shown that mothers' conceptualisation of financial difficulty from pregnancy to age seven is associated with their child's ADHD symptoms across childhood. Whilst these two concepts are diffuse, the relation between them has implications for policy and practice. Financial stress for families with young children may combine with other factors that may exacerbate symptoms of ADHD, such as parents' emotional availability; suboptimal parenting strategies; or to impair the development of children who are genetically vulnerable. Kelly, Kelly and Russo (2014) put forward a strong argument for the need to consider social determinants of health as being proximal factors in models of disease. Our findings provide evidence to suggest that SES has a differential effect on ADHD behaviours at different stages in children's lives, and imply that factors linked to the social environment can modify expression of genetic risk factors, or may have an independent effect on developmental trajectory.

Strengths and limitations

The current study has several strengths: longitudinal design with repeated measures of financial difficulties and hyperactivity across childhood allowed for multilevel modelling. The model estimates are subject to 'shrinkage', which in principle provide better estimates by pooling data. However, these shrunken estimates can appear counterintuitive and are also influenced by the underlying model, however the sensitivity analysis gave results with a similar interpretation. One limitation of the growth curve model for financial difficulties is that we cannot estimate the effect of a sudden spike in financial difficulties. Unfortunately we did not have sufficient data points per individual to fit a more complex spline model.

The large sample size is also a strength, however we excluded participants with substantial missing data. As participants that dropped out of ALSPAC were

more likely to be socioeconomically disadvantaged, our results may be biased towards an underestimation of the true association (Wolke et al., 2009). One limitation of the study is the inability to account for genetic selection effects (Mackenbach, 2005). An additional further explanation of this effect may be that ADHD in children causes parental financial stress (Doshi et al., 2012), however we account for this in part with our longitudinal study design. The study is observational and is not sufficient alone to infer causation.

Future Directions

Future studies should be designed to allow for genetic selection effects, for example sampling the children of the original ALSPAC children. If further evidence of this association emerges after controlling for genetic selection, policy level interventions reducing socioeconomic disadvantage in at-risk families with young children may reduce the societal burden of ADHD. In a further study we explore in more detail the links between changing SES and ADHD; this may elucidate further information on the role played by SES in the aetiology of ADHD.

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Putting Research into Context

Evidence before this study: Associations between socioeconomic disadvantage and ADHD have been reported in previous studies, however the context across which this association operates is unknown. Studies exploring the impact of socioeconomic disadvantage on child mental health outcomes finds different patterns of association depending on the outcome measured, and no studies have investigated the impact of the timing or duration of family socioeconomic disadvantage on symptoms of ADHD across childhood.

Added value of this study: This study explores the longitudinal association between socioeconomic disadvantage and symptoms of ADHD across childhood, and finds that the timing of exposure to disadvantage indicates evidence of a sensitive period between birth and age seven when the impact of socioeconomic disadvantage may be most detrimental. We also find evidence that longer duration of disadvantage is associated with higher levels of ADHD symptoms.

Implications of the available evidence: Our findings provide evidence to suggest that SES has a differential effect on ADHD behaviours at different stages in children's lives, and imply that factors linked to the social environment can modify expression of genetic risk factors, or may have an independent effect on developmental trajectory. If further evidence of this association emerges after controlling for genetic selection, policy level interventions reducing socioeconomic disadvantage in at-risk families with young children may reduce the societal burden of ADHD.

Supplementary Material

Model details

1 Stage 1: modelling of financial difficulty

The model is a piecewise-linear (spline) random slope model over two periods.

For individual j and financial difficulty observation k:

$$fd(t)_{jk} = \beta_0 + \beta_1 t + \beta_2 (t - t_\eta) + u_{0j} + u_{1j} t + u_{2j} (t - t_\eta) + e_k$$

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \end{pmatrix} \sim N(0, \Sigma)$$

$$\Sigma = \begin{pmatrix} \sigma^2_{u_0} & & \\ \sigma_{u_{01}} & \sigma^2_{u_1} & \\ \sigma_{u_{02}} & \sigma_{u_{12}} & \sigma^2_{u_2} \end{pmatrix}$$

$$e_k \sim N(0, \sigma^2_f)$$

and t_η is the knot.

The fitted financial difficulty provides a predicted value at any time point or can be summarised over a time period of interest (a, b). We use the following averages of an individual's fitted $fd(t)$:

(i) Average financial difficulty:

$$\overline{fd} = \frac{1}{(b-a)} \int_a^b fd(t)\, \mathrm{d}t$$

(ii) Proportion of time spent in financial difficulty:

$$\overline{p} = \frac{1}{(b-a)} \int_a^b I_\xi(t)\, \mathrm{d}t$$

where

$$I_\xi(t) = \begin{cases} 0, fd(t) \leq \xi \\ 1, fd(t) > \xi \end{cases}$$

2 Stage 2: modelling of hyperactivity

For period i, individual j and hyperactivity observation k :

$$h_{ijk} = \alpha_i + v_j + e_k$$

where

α_i is the overall average hyperactivity for period i,

$$v_j \sim N(0, \sigma^2_v)$$

$$e_k \sim N(0, \sigma^2_h)$$

2.1 Hypothesis: critical

We include the effects of financial difficulty in either period $i = 1, 2$ on hyperactivity as :

$h_{1jk} = \alpha_1 + v_j + I_{1j}\gamma_{11} + e_k$
$h_{2jk} = \alpha_2 + v_j + I_{2j}\gamma_{22} + I_{1j}\gamma_{12} + e_k$

where

γ_{11} is the effect of financial difficulty in period 1 on hyperactivity in period 1 (and similarly for γ_{22}).

γ_{12} is the effect of financial difficulty in period 1 on hyperactivity in period 2.

and the indicator variables are:

$$I_{ij}(t) = \begin{cases} 1, \overline{fd}_{ij} \leq \xi \\ 0, \overline{fd}_{ij} > \xi \end{cases}$$

where $\overline{fd}_{ij}$ is the average financial difficulty of individual j in period i.

The critical period hypothesis is that $\gamma_{12} > 0$ and $\gamma_{11} > 0$.

i.e. financial difficulty in the early period influences hyperactivity in both early and late periods.

2.2 Hypothesis: cumulative

We include the effects of the proportion of time in financial difficulty as:

$h_{ijk} = \alpha_i + v_j + \theta_{m[j]} + e_k$

where $m[j]$ is an index variable relating to accumulated time in financial difficulty,

and $\theta_{m[j]}$ is its effect on hyperactivity for individual j.

For this analysis, $m = 1, 2, 3, 4$ and data limitations mean the period of interest was restricted to $i = 1$. The value $m[j]$ of individual j is dependent on the proportion of time in financial difficulty $\overline{p}_j$. The cutpoints were defined *a priori* as follows:

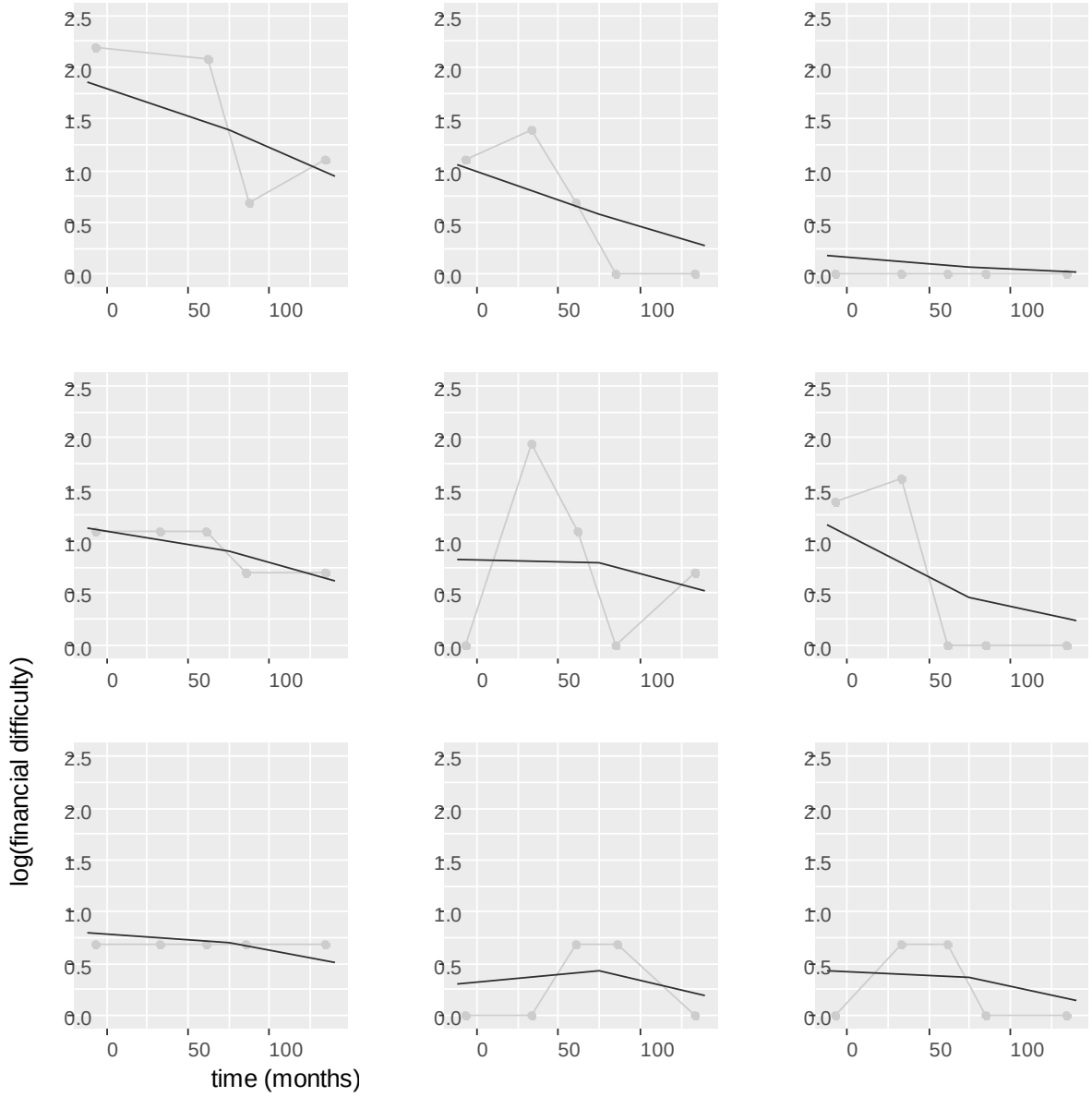
$$m[j] = \begin{cases} 1, \text{if } \overline{p}_j = 0 \\ 2, \text{if } 0 < \overline{p}_j \leq \frac{1}{3} \\ 3, \text{if } \frac{1}{3} < \overline{p}_j \leq \frac{2}{3} \\ 4, \text{if } \frac{2}{3} < \overline{p}_j \leq 1 \end{cases}$$

with the constraint $\theta_1 = 0$.

The cumulative hypothesis is that $\theta_1 \leq \theta_2 \leq \theta_3 \leq \theta_4$

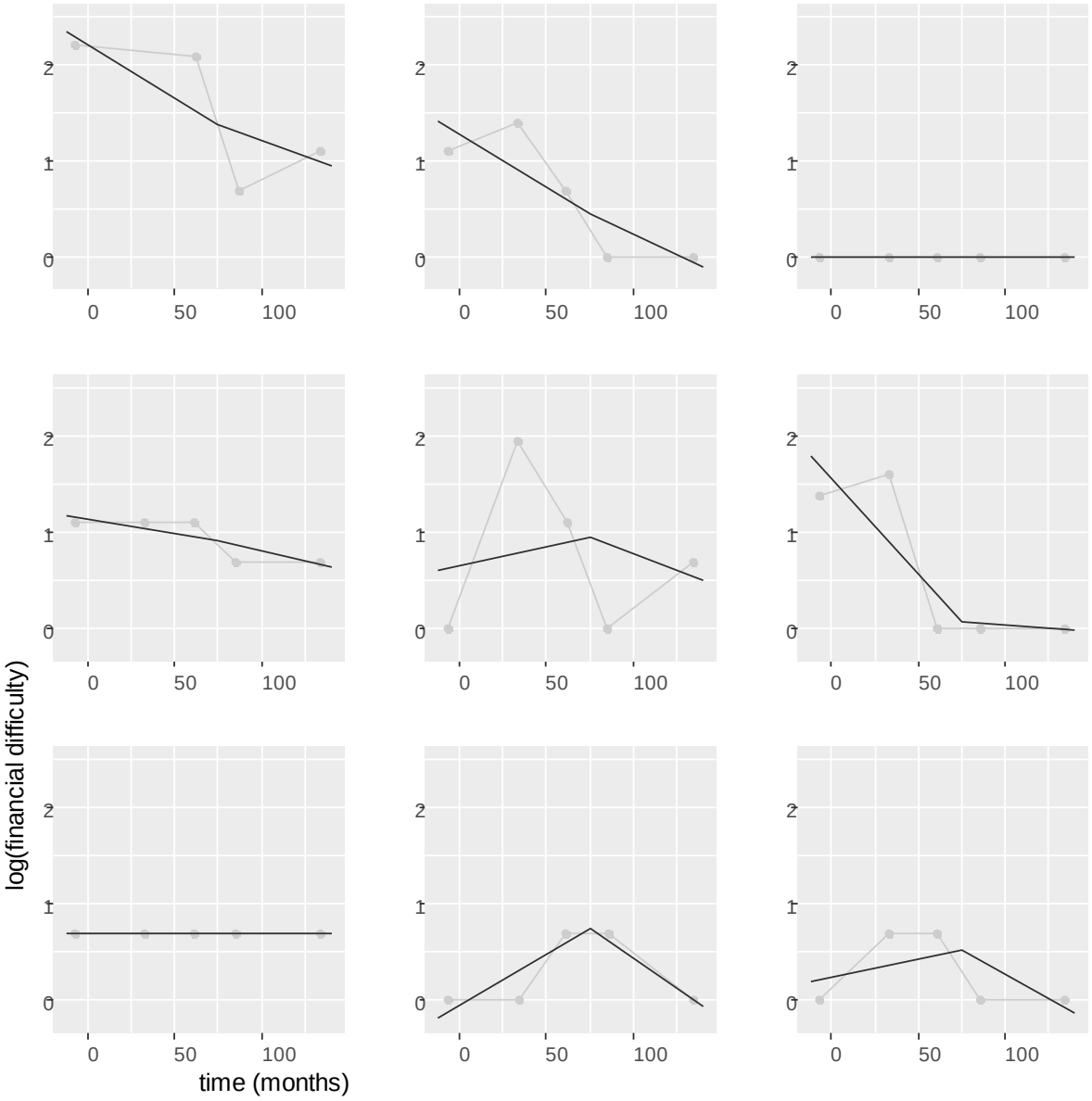
i.e. more time spent in financial difficulty is associated with more hyperactivity.

Supplementary Figure 1: graphs showing financial difficulties modelling, examples for 9 individuals, random effects.



Note: Each trajectory is influenced by a combination of the individual's own data and that of other trajectories in the population.

Supplementary Figure 2: trajectories for the same individuals as supplementary Figure 1 under a fixed effects model (without shrinkage).



Supplementary Information:

Hyperactivity modelling: This included fixed effects for the average hyperactivity in each time period and random effects for the hyperactivity of each individual. Two-level 'linked' bootstrapping was used to obtain revised estimates of the variances.

Sensitivity analysis

We adapted the models and parameter values in the following ways and assessed their impact on the results and interpretation:

- Lower and higher thresholds for financial difficulty. We repeated our analysis for two other potential thresholds, "severe" (at f'=11; f= 2.30) and "low" (at f'=17; f=1.39), to explore whether our results varied by severity of financial difficulty.
- A 'fixed effects' model for financial difficulty. The financial difficulty data were volatile and consequently shrinkage effects were strong. We assessed the alternative of fixed effects models for financial difficulty. This approach requires a much larger number of parameters and has theoretically an inferior fit to a population, but gives a better fit to any particular individual's data in isolation. (See supplementary figure for examples of fixed effect model applied to individual data).
- Replacing 'linked' with 'unlinked' bootstrapping. The linked bootstrap resamples residuals within individuals, but since the number of data points per individual is small, we investigated the effect of resampling residuals from all individuals.

Supplementary Table 1: Details of participants with missing data compared with the study sample

	% male	Hyperactivity scores	n (number of individuals)	Mean of hyperactivity score	Mean of transformed financial difficulties
Included in current study	50%	available	6013	3.22	0.78
		all missing	8	-	0.97
Less than two financial difficulty measures in each period	52%	available	4616	3.70	0.93
		all missing	2297	-	0.99
No financial difficulty measures	51%	available	178	3.79	-
		all missing	2015	-	-

Results tables for sensitivity analysis

Supplementary Table 2: Results of sensitive period hypothesis, severe (threshold 17), linked bootstrap, random effects

subgroup	Not in financial difficulty - early period	Not in financial difficulty - later period	Effect of financial difficulty in early period on early period	p	Effect of financial difficulty in later period on later period	p	Effect of financial difficulty in early period on later period	p
All	3.47 (3.42, 3.53)	2.68 (2.63, 2.74)	0.64 (0.51, 0.77)	<0.001	0.13 (-0.06, 0.32)	0.18	0.60 (0.44, 0.77)	<0.001
Female	3.11 (3.04, 3.19)	2.25 (2.18, 2.32)	0.64 (0.46, 0.83)	<0.001	0.12 (-0.13, 0.36)	0.36	0.52 (0.30, 0.74)	<0.001
Male	3.82 (3.73, 3.90)	3.10 (3.02, 3.19)	0.65 (0.45, 0.85)	<0.001	0.12 (-0.18, 0.39)	0.41	0.71 (0.45, 1.00)	<0.001

Note: numbers represent mean difference in SDQ points (95% CI)

Supplementary Table 3: Results of sensitive period hypothesis, moderate threshold 14, linked bootstrap, fixed effects

subgroup	Not in financial difficulty - early period	Not in financial difficulty - later period	Effect of financial difficulty in early period on early period	p	Effect of financial difficulty in later period on later period	p	Effect of financial difficulty in early period on later period	p
All	3.54 (3.49, 3.59)	2.75 (2.69, 2.80)	0.73 (0.55, 0.94)	<0.001	0.20 (0.00, 0.41)	0.05	0.70 (0.50, 0.91)	<0.001
Female	3.20 (3.12, 3.27)	2.31 (2.24, 2.38)	0.65 (0.39, 0.91)	<0.001	-0.03 (-0.30, 0.24)	0.85	0.76 (0.48. 1.05)	<0.001
Male	3.88 (3.80, 3.95)	3.18 (3.10, 3.26)	0.82 (0.55, 1.09)	<0.001	0.47 (0.12, 0.80)	0.002	0.62 (0.30, 0.56)	<0.001

Note: numbers represent mean difference in SDQ points (95% CI)

Supplementary Table 4: Results of sensitive period hypothesis, moderate threshold 14, unlinked bootstrap, random effects

subgroup	Not in financial difficulty - early period	Not in financial difficulty - later period	Effect of financial difficulty in early period on early period	p	Effect of financial difficulty in later period on later period	p	Effect of financial difficulty in early period on later period	p
All	3.58 (3.52, 3.63)	2.79 (2.74, 2.84)	0.85 (0.53, 1.18)	<0.001	0.04 (-0.92, 1.05)	0.91	0.95 (0.58, 1.32)	<0.001
Female	3.22 (3.16, 3.30)	2.34 (2.28, 2.41)	0.74 (0.30, 1.15)	<0.001	-0.09 (-1.11, 0.99)	0.86	0.79 (0.37. 1.19)	<0.001
Male	3.92 (3.84, 4.00)	3.22 (3.14, 3.30)	0.94 (0.51, 1.39)	<0.001	0.16 (-1.37, 1.60)	0.82	1.09 (0.56, 1.63)	<0.001

Note: numbers represent mean difference in SDQ points (95% CI)

Supplementary Table 5: Results of cumulative hypothesis for low threshold of financial difficulty (threshold 11), linked bootstrapping and random effects

subgroup	**Never in financial difficulty (reference)**	**Financial difficulty 0-1/3**	**p**	**Financial difficulty 1/3-2/3**	**p**	**Financial difficulty 2/3-1**	**p**
All	3.59 (3.54, 3.65)	0.78 (-0.15, 1.73)	0.11	0.94 (-0.24, 2.18)	0.13	1.20 (0.22, 2.20)	0.01
Female	3.24 (3.17, 3.31)	0.78 (-0.46, 2.13)	0.24	0.85 (-0.59, 2.70)	0.32	0.89 (-0.29, 2.11)	0.13
Male	3.93 (3.85, 4.01)	0.85 (-0.55, 2.39)	0.24	1.09 (-0.77, 3.02)	0.23	1.44 (-0.00, 3.08)	0.06

Note: numbers represent mean difference in SDQ points (95% CI)

Supplementary Table 6: Results of cumulative hypothesis for severe threshold for financial difficulty (threshold 17), linked bootstrapping and random effects.

subgroup	Never in financial difficulty (reference)	Financial difficulty 0-1/3	p	Financial difficulty 1/3-2/3	p	Financial difficulty 2/3-1	p
All	3.46 (3.40, 3.52)	0.45 (0.13, 0.78)	0.01	0.51 (0.17, 0.87)	0.01	0.70 (0.56, 0.85)	<0.001
Female	3.10 (3.03, 3.18)	0.50 (0.07, 0.93)	0.02	0.55 (0.08, 1.01)	0.02	0.70 (0.49, 0.90)	<0.001
Male	3.81 (3.72, 3.89)	0.40 (-0.05, 0.84)	0.08	0.46 (-0.02, 0.96)	0.07	0.72 (0.49, 0.95)	<0.001

Note: numbers represent mean difference in SDQ points (95% CI)

Chapter Eight: Trajectories of socioeconomic status over childhood and their association with symptoms of attention deficit/hyperactivity disorder (ADHD): a UK longitudinal cohort study (study 5)

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Abstract

Background: Attention deficit/hyperactivity disorder (ADHD) is associated with socioeconomic status (SES), in that those children who grow up in low SES families are at an increased risk of ADHD symptoms and diagnosis. The current study aims to explore whether changes in SES across childhood are associated with different levels of ADHD symptoms following this change. If changing SES is associated with parallel changes in ADHD symptoms, it would suggest that factors associated with such socioeconomic disadvantage may play a causal role in the aetiology of ADHD, rather than being due to a higher chance of disadvantaged families having children with ADHD traits (social selection). **Methods:** Using the Avon Longitudinal Study of Parents and Children (ALSPAC) (n=8036), we examined symptoms of ADHD measured by the Strengths and Difficulties Questionnaire (SDQ) hyperactivity subscale with relation to parent-reported changes in financial difficulty (grouped into four SES trajectories) at four time points across childhood. We used a multilevel mixed-effects linear regression model with an unstructured covariance matrix to test whether different trajectories of SES were associated with changes in ADHD symptoms across childhood. **Results:** There was a significant association between differing trajectories of financial difficulty and level of hyperactivity, with those in the permanently *In difficulty* group being having significantly higher ADHD symptom scores than all other trajectories (*No difficulty* mean SDQ hyperactivity 3.10, 95% CI 3.04, 3.17, *In difficulty* mean SDQ hyperactivity 3.51, 95% CI 3.46-3.57, p<0.001). Those in the *In difficulty* group had a mean hyperactivity score 0.41 SDQ points higher than the *No difficulty* group.

The two groups defined by change in SES: increasing or decreasing SES, had mean hyperactivity scores that are significantly lower than those of the in difficulty group and higher than the no difficulty group. **Conclusions:** Our findings imply that any experience of low SES is associated with increased hyperactivity scores of around 0.2 - 0.4 SDQ points.

Introduction

The aetiology of attention deficit/hyperactivity disorder (ADHD) is complex and multifaceted. Current theory suggests that multiple small common and rare genetic variants have a large influence on an individuals' traits of inattention, hyperactivity and impulsivity, which when severe comprise the syndrome of ADHD (Faraone et al., 2015). Evidence around environmental factors that may cause ADHD often centres on prenatal exposures to toxins such as those associated with smoking and alcohol consumption. Some studies have suggested exposure to these and other toxins increase the risk of a child being diagnosed with ADHD (Linnet et al., 2003), however there is debate around causality, with other studies suggesting that these findings are due to unmeasured familial confounding or social selection (Thapar et al., 2009, Skoglund et al., 2014).

Having a diagnosis of ADHD is associated with an increased risk of negative outcomes across many domains: a recent systematic review found that those with ADHD were more likely than individuals without ADHD to have the following outcomes: drug use or addictive behaviour, antisocial behaviour, problems with social function, problems with occupation, poor academic outcomes, low self-esteem, driving and car accidents, increased use of services and increased risk of obesity (Shaw et al., 2012).

In spite of the prevalence of ADHD, often estimated at 2-5% worldwide (Polanczyk et al., 2007) and reported at around 1.5% in children in UK cohort studies (Ford, Goodman and Meltzer, 2003, Russell et al., 2014), relatively little is known about its association with social and environmental factors early in life, such as socioeconomic status (Russell et al., 2015).

Although not established as a causal link, ADHD is associated with socioeconomic status (SES), in that those children who grow up in low SES families are at an increased risk of ADHD symptoms and diagnosis (Reiss,

2013). In a recent study, we found that children whose mothers reported difficulty in affording basic necessities when the child was born were over twice as likely to receive a research diagnosis of ADHD when the child was age seven (Russell, Ford and Russell, 2015). Some have suggested this is likely due to social selection: one study using the Dunedin cohort found evidence for social selection; adolescents with ADHD were less likely to have good educational outcomes, which then could determine low SES circumstances for them. As ADHD is highly heritable, their offspring, genetically predisposed to ADHD, will be born into socioeconomically disadvantaged circumstances (Miech et al., 1999, Galera et al., 2012). Others argue that having a child with ADHD causes the parents' SES to decrease due to disruption to ability to work (Kvist, Nielsen and Simonsen, 2013). Alternately it could be that SES-ADHD associations are due to social causation: a mechanism by which SES exerts an influence on the aetiology or severity of ADHD, which is not mutually exclusive to the social selection theory (Miech et al., 1999, Galera et al., 2012).

The current study aims to explore whether changes in SES across childhood are associated with different levels of ADHD symptoms following this change. If changing financial difficulties are associated with parallel changes in ADHD symptoms, it would suggest that factors associated with such socioeconomic disadvantage may play a causal role in aetiology of ADHD, rather than being due to social selection where ADHD traits would be inherited in low SES groups but unaffected by changing SES circumstances. A lowering of SES circumstances followed by an increase in hyperactivity/inattention would suggest factors associated with SES are on the causal pathway. We utilised data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to examine symptoms of ADHD in children, grouped by changes in SES at four time points across childhood. This allowed us to address our question of interest: whether changes in SES are associated with subsequent differences in levels of ADHD symptoms.

Methods

Sample

ALSPAC is a longitudinal birth cohort study in the UK that initially aimed to recruit all pregnant women living in the county of Avon, UK, with estimated delivery dates between 1st April 1991 and 31st December 1992 (Fraser et al., 2013, Boyd et al., 2013). 14,701 of these children were alive at one year of age. ALSPAC did not enrol triplet or quadruplet births in the cohort. In the case of twin pairs, one was included at random in the current sample.

This study included children who had at least partial data on the study measures. The ALSPAC study website contains details of all the cohort data that is available through a fully searchable data dictionary (ALSPAC, 2014). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees, and the University of Exeter Medical School Research Ethics Committee (Appendix 3).

Measures

Exposure variable: SES change trajectory

SES was conceptualised using the financial difficulties measure, a self-report scale constructed of a series of five questions where the mother is asked to rate on a scale from zero to three how difficult it is currently to afford food, clothes, heating, rent/mortgage and other things the parent considered essential for the child, with higher scores indicating more difficulty. We chose this as it was the SES measure most highly predictive of ADHD in a previous study with the ALSPAC population(Russell, Ford and Russell, 2015), and because it was repeatedly measured five times between gestation and when the child was aged 11 years 8 months (see Table 1). For the main analysis, and because the majority of participants reported no financial difficulties, we dichotomised this measure into no financial difficulty (score of 0) vs any financial difficulty (score of 1 or more) at each time point. Sensitivity analyses use thresholds of ≥5 and ≥10 (out of 15) to represent thresholds corresponding to those experiencing moderate and severe financial difficulty.

Outcome variable: ADHD symptoms

Symptoms of ADHD were measured using the parent report version of the hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ)

(Goodman et al., 2003). This scale asks about five symptoms of ADHD: restlessness/over activity, fidgeting/squirming, easily distracted/concentration wandering, whether they think things through before acting (which is reversed scored), and sees tasks through to the end (also reversed scored). Parents are asked to indicate whether these behaviours are “not true” (scored 0) “somewhat true” (scored 1) or “certainly true” (scored 2) of their child in the past six months. Scores are added for a total out of ten in the subscale, with higher scores indicating more symptoms. The SDQ is frequently used in clinical and research assessments of ADHD (Goodman et al., 2003, Carballo et al., 2014, Huss et al., 2008) and the scores correlate meaningfully with other validated ADHD symptom measures (Muris, Meesters and van den Berg, 2003, Huss et al., 2008, Russell et al., 2014). We utilised the parent-report version that mothers filled in about their child at four time points (measurement occasions) across childhood (Table 1). We included three covariates: exact child age at measurement occasion, calculated in months from the child’s birth date to the date the parent reported filling in the questionnaire, gender and parity.

Analysis

Defining analysis time frames

With repeated measures we were able to define four points across childhood where we could measure the change in financial difficulties and then the outcome of SDQ hyperactivity. These are outlined in Table 1 and supplementary material Figure 1 and the four analyses will be referred to henceforth as A (outcome at 3 years 11 months), B (outcome at 6 years 9 months), C (outcome at 9 years 7 months) and D (outcome at 10 years 2 months). Table 1 shows the mean measurement points for each analysis and the time in months until the outcome measure. Due to the lack of standard intervals between measures, each analysis A-D has a different change period and a different length of time to outcome, however we include child age at measurement occasion as a covariate in our model.

Table 1: Mean child age in months at completion of measures for each analysis timepoint

Analysis	Child age at measurement occasion (months): Financial difficulties 1	Financial difficulties 2	Hyperactivity	Period over which financial difficulty change calculated (months)	Time from 2nd financial difficulties measurement to outcome (months)
A	-2	33	47	35	14
B	33	61	81	28	20
C	61	85	115	24	30
D	85	133	140	48	7

Defining SES trajectory groups

For each analysis (A-D), we defined four groups of SES trajectory: "*No difficulty*"; participants in this group were below the threshold for low SES at both the first and second measurement occasion. "*Decreasing difficulty*" participants were above the threshold for low SES at the first measurement occasion, and below it at the second. "*Increasing difficulty*" participants were below the low SES threshold at the first measurement occasion and above it at the subsequent occasion, and "*In difficulty*" participants were above the threshold and in low SES at both financial difficulty measurement occasions.

Analysis

We used a multilevel mixed-effects linear regression model with an unstructured covariance matrix to test whether children with different trajectories of SES have different levels of ADHD symptoms across childhood using the "xtmixed" command in Stata 13. As we have repeated measures for each child in the study this mixed model takes these into account, with the other variables being included as fixed effects. These fixed effects coefficients are equivalent to and can be interpreted as standard regression coefficients.

In order to determine which covariates were significantly predictive of SDQ score across the four time points, in addition to SES change and child age at SDQ score measurement, we first ran the full model including all variables outlined above to determine which covariates were statistically significant (at the 0.05 threshold), re-ran the model with only the significant covariates and then introduced the other covariates individually; any further significant covariates

were added to the model. We used likelihood ratio tests to determine whether these covariates improved the model fit alongside the Akaike information criterion (AIC) values. We conducted a sensitivity analysis utilising two more stringent thresholds for low SES of ≥5 and ≥10 (out of 15) to evaluate whether any findings are replicated or indeed are more pronounced using more stringent criteria. We then repeated the models using different SES trajectory groups as the reference category to determine how each differed from the others. Posthoc tests were carried out to examine interactions between SES trajectory group, child age and gender, to examine whether boys or girls (or younger children) were more sensitive to SES circumstances and/or changing SES.

We also conducted linear multivariable regression (including SES trajectory and child age as well as all covariates) for each analysis A-D to explore the association between trajectory of SES and ADHD symptoms at different points throughout childhood. This method allowed us to address our question of interest: whether change in family SES during childhood was associated with ADHD symptoms. We used observed data only and did not impute missing data as those of low SES and with children who have higher scores on the SDQ are more likely to have missing data or drop out from ALSPAC, and are thus not missing at random (Wolke et al., 2009).

Results

Descriptive

Available data for the sample varied by measurement, however the mixed effects model included data from 8036 individuals, and the multivariable regressions had samples of 7565 (analysis A), 6188 (B), 5285 (C) and 4399 (D). The decreasing numbers reflect the drop-out in ALSPAC and higher proportion of uncompleted measures as the children age, however the sample was still substantial. Descriptive statistics for the repeated measures model for differing SES trajectory thresholds, and the mean and standard deviation for SDQ hyperactivity scores group and overall are described in Table 2, and supplementary material Tables 1 and 2 contain this information for each analysis A-D. Mean SDQ hyperactivity scores decreased over the course of childhood.

Primary analysis

Differences in ADHD symptoms by financial difficulties trajectory group

The multilevel mixed-effects linear regression model showed the best fit when including gender and child's age at both the financial difficulties measurements. Parity and age at hyperactivity report did not significantly contribute to the model fit and so were not included in the final model.

There was a significant association between differing trajectories of financial difficulty and level of hyperactivity, with those in the permanently *In difficulty* group being having significantly higher ADHD symptom scores than all other trajectories (*No difficulty* mean SDQ hyperactivity 3.10, 95% CI 3.04, 3.17, *In difficulty* mean SDQ hyperactivity 3.51, 95% CI 3.46-3.57, $p<0.001$: see Table 3 for marginal means and supplementary material Table 3 for coefficients and standard errors). Those in the *In difficulty* group had a mean hyperactivity score 0.41 SDQ points higher than the *No difficulty* group. Marginal mean SDQ scores and their standard errors can be seen in Figure 1.

Table 2: Descriptive statistics

Repeated measures model (N obs=24054)

	Descriptive Statistics			***SDQ Hyperactivity***	
	Frequency (n)	%		***Mean***	***SD***
			Overall	3.30	2.34
SES Trajectory Group (threshold ≥1)					
No difficulty	32.84	32.84		2.79	2.19
Increasing difficulty	2,548	10.59		3.41	2.31
Decreasing difficulty	3,469	14.42		3.26	2.30
In difficulty	10,137	42.14		3.69	2.40
SES Trajectory Group (threshold ≥5)					
No difficulty	17,390	72.30		3.09	2.26
Increasing difficulty	1,802	7.49		3.88	2.43
Decreasing difficulty	2,311	9.61		3.59	2.36
In difficulty	2,551	10.61		4.10	2.51
SES Trajectory Group (threshold ≥10)					
No difficulty	21,956	91.28		3.22	2.31
Increasing difficulty	755	3.14		4.25	2.58
Decreasing difficulty	921	3.83		3.94	2.5
In difficulty	422	1.75		4.24	2.63
Gender					
Male	12,243	50.90			
Female	11,811	49.10			
Parity					
0	10,943	46.34			
1	8,522	36.09			
2	3,147	13.33			
3	788	3.34			
4	164	0.69			
5+	51	0.22			

Note: SDQ: strengths and difficulties questionnaire

Table 3: Results from multilevel mixed-effects linear regression model exploring association between SES trajectory and SDQ Hyperactivity

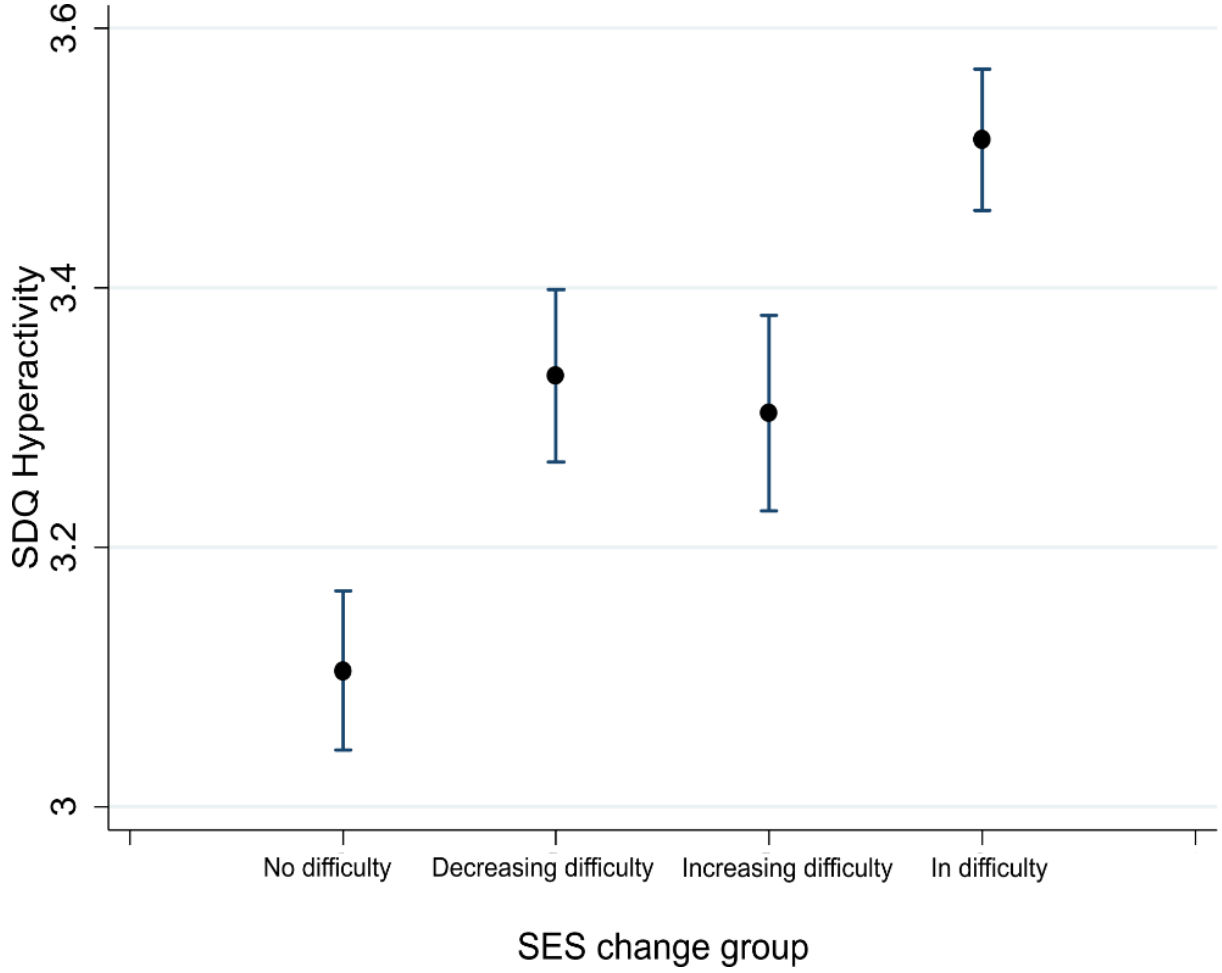
Predictor	Threshold ≥1 Mean SDQ hyperactivity score (95% CI)	p	Threshold ≥5 Mean SDQ hyperactivity score (95% CI)	p	Threshold ≥10 Coefficient (95% CI)	p
Financial Difficulties Trajectory						
No difficulty	3.10 (3.04 - 3.17)		3.23 (3.19 – 3.28)		3.30 (3.26 – 3.35)	
Increasing difficulty	3.30 (3.23 – 3.38)		3.50 (3.40 – 3.59)		3.63 (3.50 – 3.77)	
Decreasing difficulty	3.33 (3.27 – 3.40)		3.49 (3.41 – 3.57)		3.61 (3.49 – 3.73)	
In difficulty	3.51 (3.46 – 3.57)	<0.001	3.72 (3.62 – 3.81)	<0.001	3.81 (3.63 – 4.01)	<0.001
Male gender	3.69 (3.63 – 3.75)		3.69 (3.63 – 3.75)		3.69 (3.63 – 3.75)	<0.001
Female gender	2.96 (2.90 – 3.02)	<0.001	2.96 (2.90 – 3.02)	<0.001	2.96 (2.90 – 3.02)	
	Change in mean SDQ hyperactivity score	p	**Change in mean SDQ hyperactivity score**	p	**Change in mean SDQ hyperactivity score**	p
Age at SES measurement 1 (months)	-0.02 (-0.03 - -0.02)	<0.001	-0.02 (-0.03--0.02)[b]	<0.001	-0.02 (-0.03 - -0.02)	<0.001
Age at SES measurement 2 (months)	0.01 (0.01 - 0.01)[a]	<0.001	0.01 (0.01 - 0.01)[c]	<0.001	0.01 (0.01 - 0.01)[d]	<0.001

Note: some values small for interpretation to 2 decimal places, confidence interval values to 3dp are as follows: a: 0.006 - 0.011. b -0.025 - -0.020. c- 0.006 - 0.011. d- 0.006 - 0.010. In all cases the No difficulty trajectory SDQ mean is significantly lower than all other groups (p<0.001), the In difficulty trajectory SDQ mean is significantly higher from all groups apart from for the highest threshold (≥10) and the two changing SES groups (increasing and decreasing) do not differ significantly from each other and sit in between the in and no difficulty values. N=8,036. Thresholds refer to the cutoff for calculating change in financial difficulty on a scale from 0 to 15. SES: socioeconomic status, SDQ: strengths and difficulties questionnaire

Changing financial difficulty groups do not differ from each other

The changing SES groups: *Increasing* and *Decreasing difficulty,* were associated with an increase in ADHD symptom scores relative to those in the *No difficulty* group: those in the *Increasing* group had an average SDQ score of 3.30 (95%CI 3.23, 3.38) and those in the *Decreasing* group had a mean score of 3.33 SDQ points (95%CI 3.27, 3.40). The changing SES groups were significantly different from the *No difficulty* group and the *In difficulty* group ($p<0.001$) but not from each other (see Figure 1).

Figure 1: Marginal mean SDQ Hyperactivity values (95% CI) for multilevel model exploring association between SES change and ADHD symptoms.



Note: SDQ: strengths and difficulties questionnaire. SES: socioeconomic status The SDQ Hyperactivity subscale is scored from 0-10 with increasing scores reflecting increasing levels of symptoms. Graph shows a small range of the total scale.

Associations with child gender and child age when measurements recorded

Male child gender was associated with a 0.73 point higher mean SDQ hyperactivity score than for females when all other variables were held constant (average SDQ hyperactivity for males: 3.69, 95%CI 3.63, 3.75 and for females: 2.96, 95% CI 2.90, 3.02, p<0.001). Posthoc analyses found no significant interaction between gender and SES change group. The age that financial difficulties were measured had a significant influence on SDQ hyperactivity score (child age in months at first measurement B=-0.02, 95% CI -0.03, -0.02, p<0.001, and child age in months at second measurement B=0.01, 95% CI 0.006, 0.011, p<0.001). Older child age when financial difficulties was first measured is associated with lower SDQ hyperactivity scores, and those who are relatively older when the second measurement of financial difficulties was recorded had higher SDQ scores. Posthoc analyses for interactions between age at SES measure and SES change group found significant interactions for the *Increasing difficulty* group in opposite directions for the two SES measurement ages, such that it appears that younger children may be more sensitive to exposure to low SES. This interaction was in the opposite direction at the later SES measure: this was difficult to interpret.

Using more stringent thresholds for low SES does not alter the findings

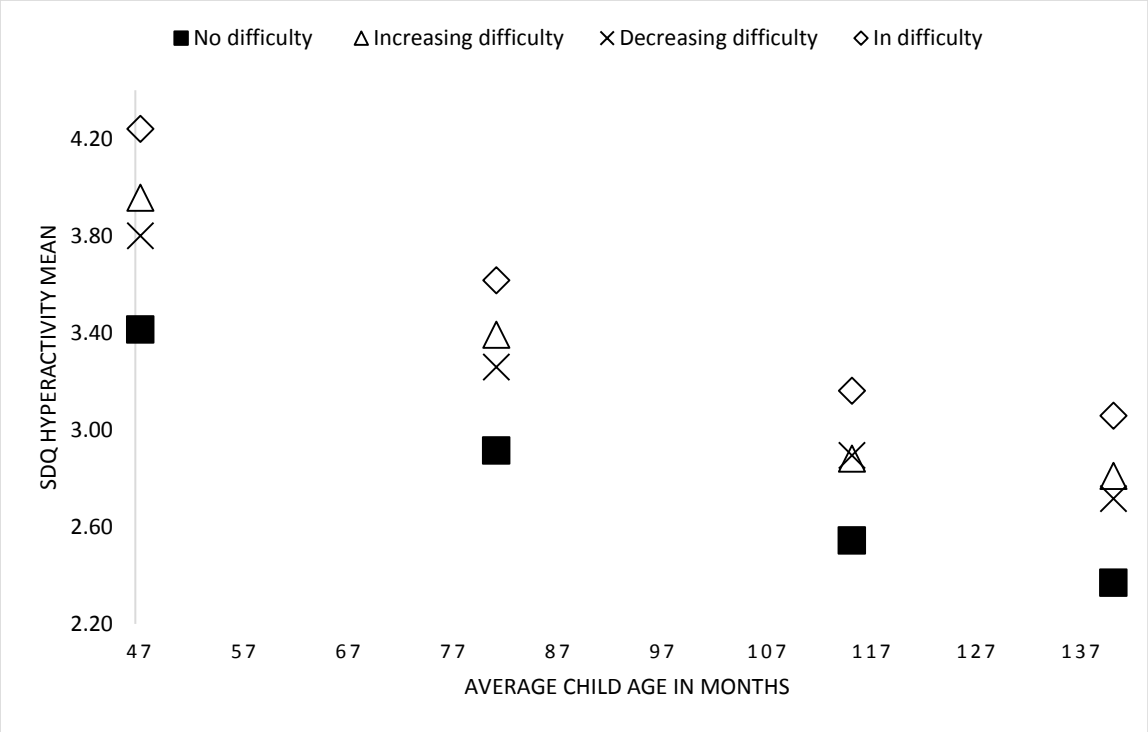
The trend for ADHD symptom scores was found for the other thresholds for financial difficulty, with in almost all cases there being the lowest coefficient for the *No difficulty* group, the changing trajectory groups not differing from each other, and the *In difficulty* group having a significantly higher coefficient than all other groups (see Table 3). The mean difference between the changing trajectory groups and the reference group (*No difficulty)* was lower than the mean difference between the reference group and the *In difficulty* group (Figure 2). Supplementary graphs 1 and 2 show this for the other thresholds. Increasing the stringency of the threshold results in no changes to the results, other than that the average SDQ hyperactivity scores for each SES change group are higher as “low” SES is defined more stringently. For example, the *In difficulty* SES group mean hyperactivity scores were 3.51 (95% CI 3.46, 3.57) for threshold ≥1 (primary analysis), 3.72 (95% CI 3.62, 3.81) for threshold ≥5

(moderate threshold for low SES) and 3.81 (95% CI 3.63, 4.01) for threshold ≥10 (severe threshold for low SES).

Linear regression models at different points through childhood

Multivariable regression models at each time point find similar results to those reported above. Those in the *No difficulty* SES group had the lowest ADHD symptom scores at each analysis point. The *Increasing* and *Decreasing* difficulty groups had intermediate values, significantly higher than the *No difficulty* group and significantly lower than the *In difficulty* group, which had the largest coefficient. Figure 2 shows the mean SDQ hyperactivity scores by group at each analysis point. Results from the four models are reported in supplementary information Table 4.

Figure 2: Mean SDQ hyperactivity scores by SES change group at each analysis A-D



Discussion

Different trajectories of SES are associated with different levels of ADHD symptoms

We evaluated SES trajectory four times over the course of childhood in relation to a subsequent measurement of ADHD symptoms as measured by the parent-report SDQ hyperactivity subscale. In a mixed effects model combining all four repetitions of measures, we found that those who had a stable trajectory of no financial difficulty had a lower average symptom score than all other groups. We also found that those children who are consistently in financial difficulty had a higher mean score than all other groups. The two groups defined by change in SES: the increasing and decreasing SES groups, had mean hyperactivity scores which sit in an intermediate position: being significantly different from each of the stable groups. Of interest, there is negligible difference between the coefficient sizes of the two changing SES trajectories, often within 0.03 points of each other.

Any experience of low SES is associated with increased ADHD symptoms

The implications of our findings are that any experience of low SES is associated with increased hyperactivity scores of around 0.2 - 0.4 SDQ points. This value increases as you adopt more stringent thresholds to define low SES, with those analysed with the severe threshold for low SES having an increase of around 0.3 – 0.5 SDQ points. This is suggestive of a trend where those who are the most disadvantaged have larger associations between SES and ADHD symptoms. Our results also suggest that the experience of any financial difficulty at any time is associated with increased ADHD symptoms. This demonstrates that regardless of the mechanisms by which this association occurs, there is a small but significant longitudinal relationship between change in SES and symptoms of ADHD.

The clinical significance of 0.4 SDQ points is debateable: the hyperactivity scale is scored from 0-10. It is often used as part of a multi-dimensional assessment of ADHD (Goodman et al., 2003, Carballo et al., 2014, Huss et al., 2008), and correlates with other measures of ADHD symptoms (Muris, Meesters and van den Berg, 2003, Huss et al., 2008). The parent-report version of the SDQ has a specificity of 92% and sensitivity of 74% for a

diagnosis of ADHD, although these figures were calculated using the impact supplement of this questionnaire, which data were not collected in ALSPAC (Goodman et al., 2003). Increased scores on the SDQ are related to an increased risk of meeting diagnostic criteria for ADHD, especially for those already close to thresholds.

Our findings in the context of social selection

In order to draw inferences from our findings in line with theories of social selection, we need to consider what level of ADHD symptoms you would expect to find if the relationship between SES and ADHD was entirely due to fixed genetic effects. Symptoms of ADHD would be expected to be stable regardless of changes in SES, so those born into high SES families at birth would have consistently lower mean ADHD symptoms than those born into lower SES families. A change in SES would not exert an effect on ADHD symptoms: thus those experiencing decreasing financial difficulty would have symptoms corresponding to their initial low SES, and those in increasing difficulty would have symptom levels corresponding to their initial high SES throughout childhood.

We did not find this, instead we found those in the changing SES groups had ADHD symptom levels that lay between those of the stable SES children. There are three potential explanations:

1. Symptoms of ADHD are temporally associated with SES, but due to constraints of measurement occasions the trajectory of change was not observed. The changing SES trajectory groups are in the process of changing levels of ADHD symptoms which is crudely reflected as both having an intermediate level of ADHD symptoms relative to the high and low stable SES groups.
2. The results could illustrate a ‘dose-response’ relationship where any experience of low SES leads to an increase in ADHD symptoms, with higher levels of exposure having an additive effect on the association with symptoms. Those in the high SES group have low SES on zero out of two occasions, changing SES groups will have low SES at one out of the two measurement points, and those in the constant difficulty group have low SES at two out of two occasions.

3. There is a difference in genetic susceptibility to ADHD symptoms between those of low, changing and high SES: those in constant low SES having the highest genetic risk for ADHD; changing SES families having a moderate genetic risk and some ADHD traits that lead to them being unable to provide a stable environment for their child, whose symptom levels reflect this. Those constantly of high SES would therefore represent those with the least genetic risk, and in each case genetic risk would be associated both with ADHD traits and SES.

Overall our study did not provide conclusive evidence to discount selection effects, but greater and consistent socioeconomic disadvantage was shown to be associated with a negative impact on symptoms of ADHD, and consistent family stability was associated with lower levels of ADHD symptoms. The mechanisms of this effect can only be disentangled further with studies that account for parental ADHD traits and have sufficient data to closely track changes in the variables of interest.

SES as a complex concept that may exert effects through a range of mechanisms

This study purposely did not control for many potential confounders, as many that we identified as commonly controlled for are heavily associated with SES, for example birthweight and maternal smoking during pregnancy (Bradley and Corwyn, 2002). Our aim was to identify the conceptual relationship between SES change and ADHD symptoms. This has implications for understanding the course and exacerbation of ADHD symptoms.

Our findings, if replicated, have implications for policy and health and special educational service delivery as we found that experiencing financial stress is at the very least associated with a small increased risk of ADHD symptoms in children. ADHD symptoms have been shown to be associated with substantially lower academic achievement in the ALSPAC (Washbrook, Propper and Sayal, 2013). The SES-ADHD association could translate to poorer health and educational outcomes for children growing up in disadvantaged socioeconomic circumstances, which is increasing during these austere times. The use of the subjective measure of financial difficulty as a measure of SES reflects whether the mother feels that she struggles to afford food, housing,

heating, clothing and necessities for the child: all acknowledged to be essential for basic living standards in 21st Century Britain. The measure has no objective standard, however at all times the majority of participants reported that they experienced no financial difficulty at all, as may be expected based on the ALSPAC sample demographics: suggesting that those who report difficulty experience a real difference in financial stress (Boyd et al., 2013, Wolke et al., 2009).

Strengths and Limitations

Whilst we did find evidence that different trajectories of SES are associated with different trajectories of ADHD symptoms, this is somewhat difficult to interpret as both the groups representing changing SES (rather than stable SES) had similar coefficient values. This may be due to the limited range of measurement occasions: depending on when a family's circumstances change and the amount of time before there is a change in the child's behaviour, children will have different trajectories of change. The longitudinal design of the study was a strength, and repeated measures allowed us to draw conclusions across childhood rather than only at individual time points. In addition, using a variety of thresholds to define low SES allowed us to test whether the association was robust when more stringent thresholds were used, and the results showed that if anything those that are more disadvantaged have higher symptom levels.

Future Directions

Our study indicates that increasing financial difficulty has a negative impact on symptoms of ADHD, and that consistent higher SES is associated with lower levels of ADHD symptoms. However, as the mechanisms by which this association operates have not been elicited, further research needs to determine mediators of the aetiological mechanisms before consideration of implications for policy and practice. Observational studies should explore whether socioeconomic changes in a family lead to changes in family environment or reduce biological markers of stress. These should be complemented by studying the relation between these social and environmental factors and symptoms of ADHD, of which some research already exists (Banerjee, Middleton and Faraone, 2007). Our findings could not provide conclusive evidence around whether impacts of SES changes are in addition to or interact with the complex genetic heritability of ADHD.

Recent research exploring interaction between genotypes and environmental exposures is beginning to allow us to tease apart the interrelation between these factors (Nikolas, Klump and Burt, 2015). It may be that a combination of genetic predisposition and social/environmental adversity interact to exacerbate or ameliorate ADHD symptoms in a differential manner across childhood. Future studies with more detailed data on SES and more frequent measures could address whether children in families that have changing SES do show linear trajectories of improvement or exacerbation of symptoms, and the extent to which symptoms can fluctuate.

Conclusion

This study demonstrates an association between SES and childhood symptoms of ADHD that was robust to changes in the threshold used to define SES and timing of the measurements. Our findings add to the building evidence that SES may influence the severity and / or impairment associated with the symptoms of ADHD.

Acknowledgements*:*

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We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. This publication is the work of the authors and Abigail Russell, Tamsin Ford and Ginny Russell will serve as guarantors for the contents of this paper. This research was specifically funded by a PhD studentship from the University of Exeter Medical School.

Supplementary Material

Supplementary Figure 1: Measurement occasions and analysis groupings (not to scale) for the predictor: change in financial difficulties, and outcome: ADHD symptoms from the Hyperactivity subscale of the Strengths and Difficulties Questionnaire

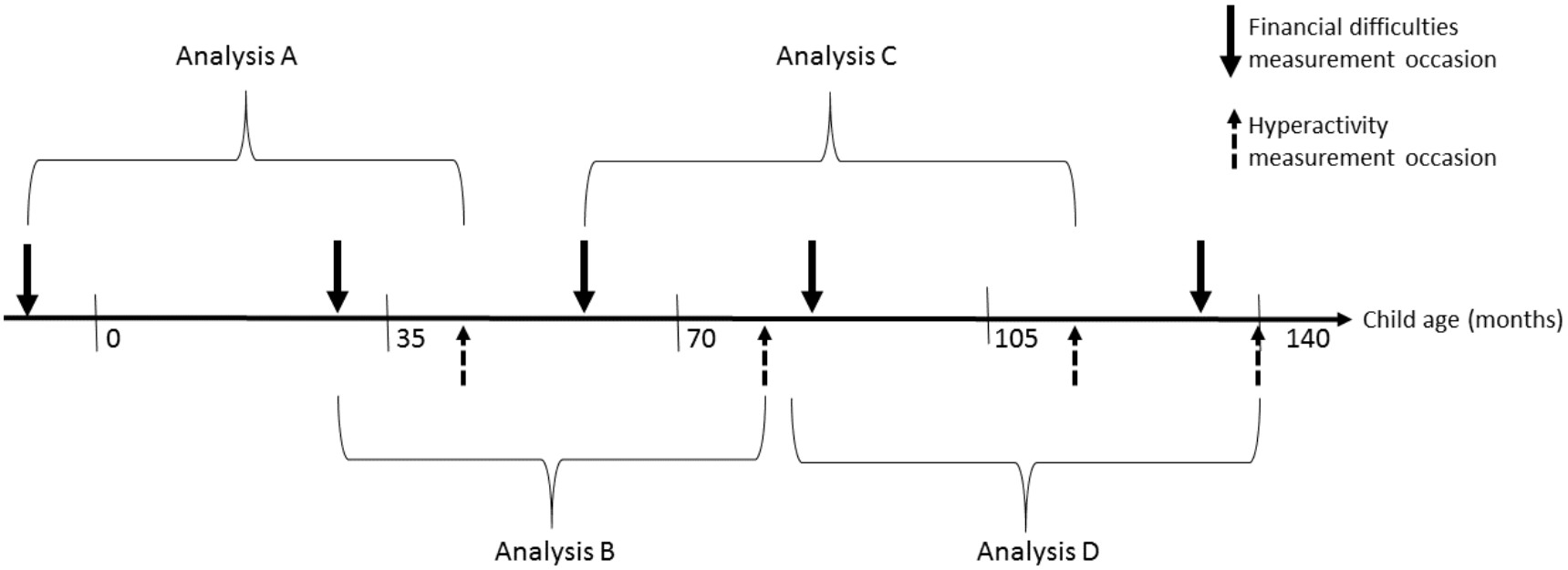


Figure 1. Illustration of measurement occasions across time for financial difficulties and hyperactivity. Each analysis includes two subsequent financial difficulties measurements (in order to group by trajectory) and one hyperactivity outcome. Not to scale.

Supplementary Table 1: Descriptive statistics by analysis A-D

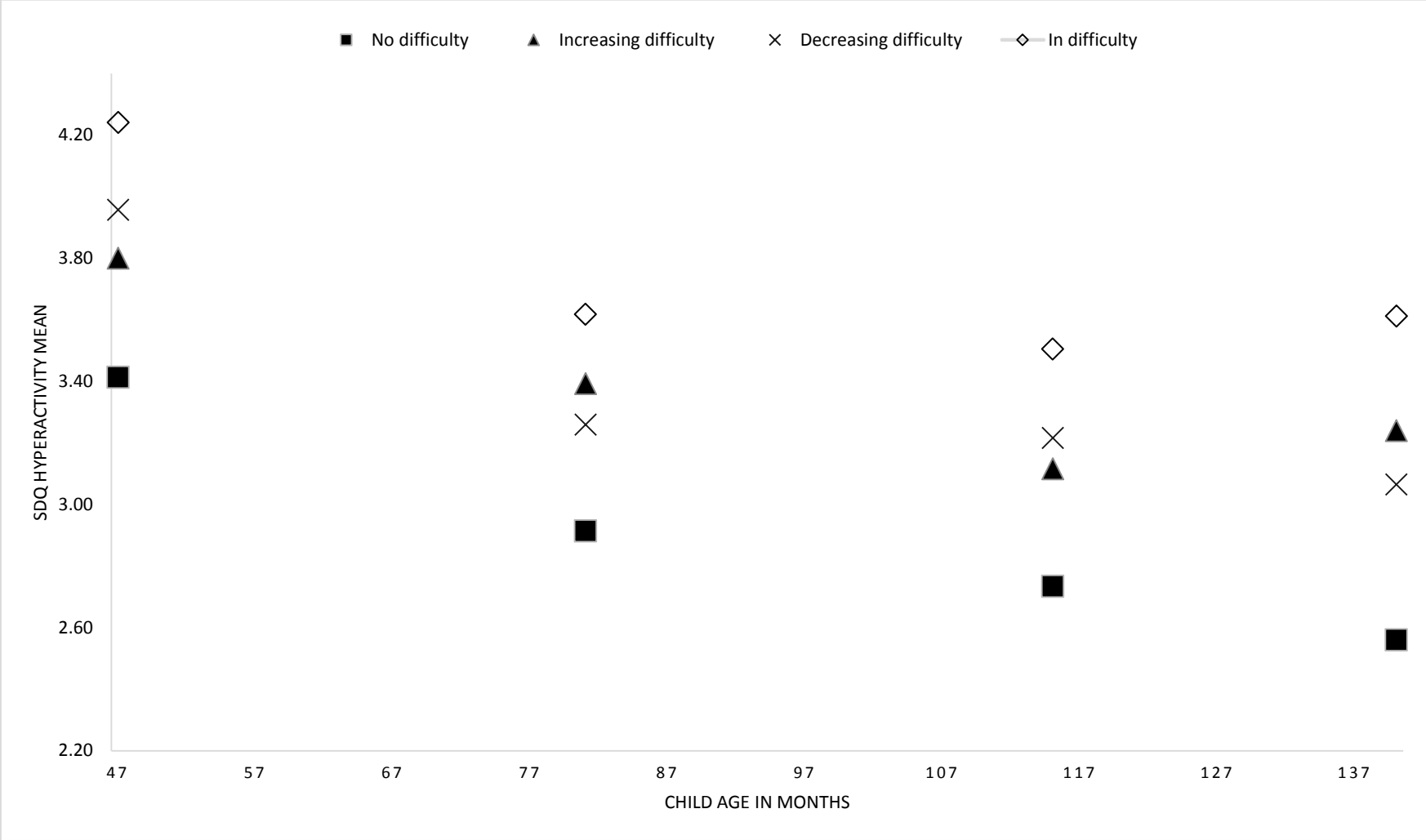
	Descriptive statistics							
	Analysis A (N=7565)		**Analysis B (N= 6188)**		**Analysis C (N= 5285)**		**Analysis D (N=4399)**	
	Frequency (n)	**%**	**Frequency (n)**	**%**	**Frequency (n)**	**%**	**Frequency (n)**	**%**
or	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
SES Trajectory Group (threshold ≥1)	*N=9035*		*N=6480*		*N= 5377*		*N= 4466*	
No difficulty	2,139	23.67	1,893	29.21	2,085	38.78	2,060	46.13
Increasing difficulty	1,332	14.74	536	8.27	384	7.14	451	10
Decreasing difficulty	1,068	11.82	994	15.34	872	16.22	682	15.27
In difficulty	4,496	49.76	3,057	47.18	2,036	37.86	1,273	28.5
SES Trajectory Group (threshold ≥5)	*N=9035*		*N=6480*		*N=5377*		*N=4466*	
No difficulty	5,727	63.39	4,400	67.9	4,191	77.94	3,814	85.4
Increasing difficulty	784	8.68	794	12.25	582	10.82	291	6.52
Decreasing difficulty	1,179	13.05	417	6.44	199	3.7	183	4.1
In difficulty	1,345	14.89	869	13.41	405	7.53	178	3.99
SES Trajectory Group (threshold ≥10)	*N=9035*		*N=6480*		*N=5377*		*N=4466*	
No difficulty	7,886	87.28	5,818	89.78	5,043	93.79	4,317	96.66
Increasing difficulty	374	4.14	325	5.02	203	3.78	76	1.7
Decreasing difficulty	536	5.93	178	2.75	75	1.39	50	1.12
In difficulty	239	2.65	159	2.45	56	1.04	23	0.52

Gender	*N=14665*		*N=6480*		*N= 5377*		*N= 4466*	
Male	7,531	51.35	3,319	51.22	2,724	50.66	2,222	49.75
Female	7,134	48.65	3,161	48.78	2,653	49.34	2,244	50.25
Parity	*N=12952*		*N=6359*		*N= 5285*		*N=4399*	
0	5,812	44.87	2,949	46.38	2,470	46.74	2,080	47.28
1	4,515	34.86	2,285	35.93	1,919	36.31	1,586	36.05
2	1,856	14.33	856	13.46	680	12.87	560	12.73
3	540	4.17	208	3.27	174	3.29	140	3.18
4	162	1.25	47	0.74	31	0.59	24	0.55
5+	67	0.52	14	0.22	11	0.21	9	0.2
Age at financial difficulties measurement 1 (months)	*N=11807*		*N=6360*		*N= 5377*		*N=4466*	
	-1.67	*0.6*	*33.59*	*1.3*	*61.36*	*0.91*	*85.47*	*1*
Age at financial difficulties measurement 2 (months)	*N=9452*		*N=6480*		*N= 5377*		*N=4466*	
	33.72	*1.44*	*61.42*	*0.99*	*85.52*	*1.08*	*134.36*	*1.19*
Age at hyperactivity measurement (months)	*N=9305*		*N=6419*		*N= 5377*		*N=4466*	
	47.88	*1.74*	*81.33*	*1.17*	*115.62*	*1.33*	*140.47*	*1.41*

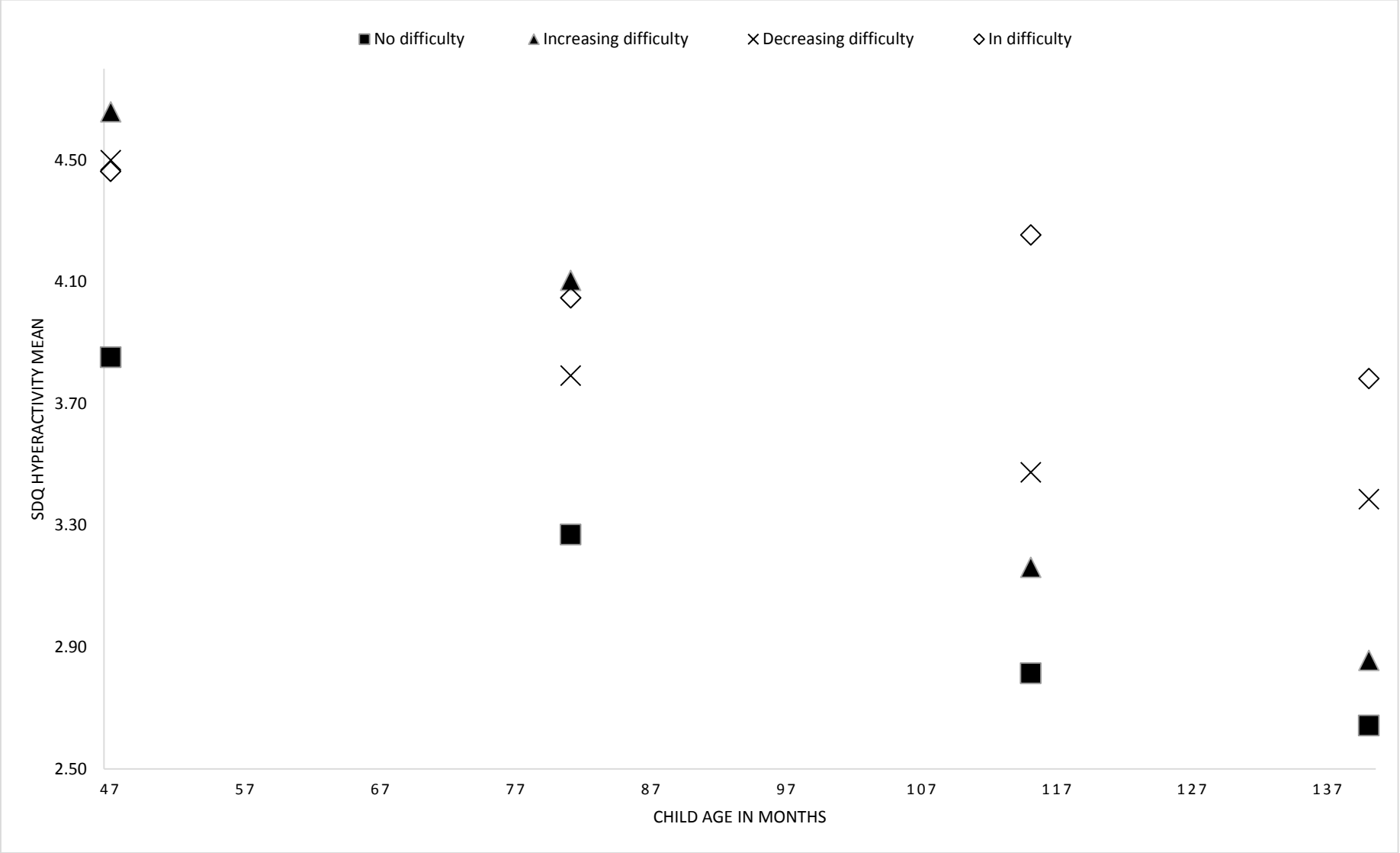
Supplementary Table 2: Hyperactivity descriptive statistics by analysis A-D

	SDQ Hyperactivity							
	Analysis A (N=7565)		**Analysis B (N= 6188)**		**Analysis C (N= 5285)**		**Analysis D (N=4399)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Overall	3.94	2.32	3.34	2.37	2.86	2.22	2.66	2.17
SES Trajectory Group (threshold ≥1)								
No difficulty	3.41	2.24	2.91	2.25	2.54	2.09	2.37	2.06
Increasing difficulty	3.96	2.30	3.39	2.33	2.88	2.25	2.81	2.19
Decreasing difficulty	3.80	2.26	3.26	2.30	2.89	2.21	2.72	2.16
In difficulty	4.24	2.34	3.62	2.42	3.16	2.3	3.06	2.27
SES Trajectory Group (threshold ≥5)								
No difficulty	3.41	2.24	2.91	2.25	2.73	2.14	2.56	2.12
Increasing difficulty	3.80	2.26	3.39	2.33	3.12	2.54	3.24	2.24
Decreasing difficulty	3.96	2.30	3.26	2.3	3.22	2.31	3.07	2.34
In difficulty	4.24	2.34	3.62	2.42	3.51	2.49	3.61	2.43
SES Trajectory Group (threshold ≥10)								
No difficulty	3.85	2.28	3.27	2.34	2.81	2.19	2.64	2.16
Increasing difficulty	4.66	2.57	4.11	2.51	3.16	2.23	2.86	2.42
Decreasing difficulty	4.50	2.45	3.79	2.55	3.47	2.44	3.39	2.24
In difficulty	4.46	2.51	4.05	2.61	4.25	2.99	3.78	3.09

Supplementary Graph 1: Graph showing SDQ hyperactivity mean at each analysis point by SES trajectory group, threshold ≥5 (moderate financial difficulty)



Supplementary Graph 2: Graph showing SDQ hyperactivity mean at each analysis point by SES trajectory group, threshold ≥10 (severe financial difficulty)



Supplementary Table 3: Results from multilevel mixed-effects linear regression model exploring association between SES trajectory and SDQ Hyperactivity: coefficients and standard errors

Predictor	Threshold ≥1 Coefficient (SE)	p	Threshold ≥5 Coefficient (SE)	p	Threshold ≥10 Coefficient (SE)	p
Financial Difficulties Trajectory						
No difficulty	reference group		reference group		reference group	
Increasing difficulty	0.20 (0.042)		0.26 (0.046)		0.33 (0.069)	
Decreasing difficulty	0.23 (0.037)		0.26 (0.040)		0.31 (0.061)	
In difficulty	0.41 (0.037)	<0.001	0.48 (0.049)	<0.001	0.52 (0.099)	<0.001
Male gender	0.73 (0.043)	<0.001	0.73 (0.043)	<0.001	0.73 (0.044)	<0.001
Age at SES measurement 1	-0.02 (0.001)	<0.001	-0.02 (0.001)	<0.001	-0.02 (0.001)	<0.001
Age at SES measurement 2	0.01 (0.001)	<0.001	0.01 (0.001)	<0.001	0.01 (0.001)	<0.001

In all cases the No difficulty trajectory coefficient is significantly lower than for all other groups (p<0.001), the In difficulty trajectory coefficient is significantly higher from all groups apart from for the highest threshold (≥10) and the two change groups (increasing and decreasing) do not differ significantly from each other and sit in between the In and No difficulty values. N=8,036. Thresholds refer to the cutoff for calculating change in financial difficulty on a scale from 0 to 15. SES: socioeconomic status SE: standard error

Supplementary Table 4: Results for multivariable linear regression evaluating mean SDQ hyperactivity score by SES trajectory group

	Analysis A (N=7565)		Analysis B (N= 6188)		Analysis C (N= 5285)		Analysis D (N=4399)	
	Coefficient (95% CI)	**p**	**Coefficient (95% CI)**	**p**	**Coefficient (95% CI)**	**p**	**Coefficient (95% CI)**	**p**
Financial difficulty group								
No difficulty	*reference*		*reference*		*reference*		*reference*	
Increasing difficulty	**0.40 (0.23 - 0.56)**	**<0.001**	**0.45 (0.23 - 0.68)**	**<0.001**	**0.31 (0.07 - 0.55)**	0.012	**0.43 (0.22 - 0.65)**	**<0.001**
Decreasing difficulty	**0.51 (0.33 - 0.69)**	**<0.001**	**0.35 (0.17 - 0.53)**	**<0.001**	**0.32 (0.15 - 0.49)**	**<0.001**	**0.36 (0.17 - 0.54)**	**<0.001**
In difficulty	**0.81 (0.69 - 0.94)**	**<0.001**	**0.69 (0.56 - 0.83)**	**<0.001**	**0.61 (0.48 - 0.74)**	**<0.001**	**0.67 (0.52 - 0.82)**	**<0.001**
Gender (male)	**0.58 (0.48 - 0.68)**	**<0.001**	**0.80 (0.69 - 0.92)**	**<0.001**	**0.83 (0.71 - 0.95)**	**<0.001**	**0.91 (0.78 - 1.03)**	**<0.001**
Parity: 0	*reference*		*reference*		*reference*		*reference*	
1	**0.27 (0.16 - 0.39)**	**<0.001**	-0.05 (-0.18 - 0.08)	0.451	-0.05 (-0.18 - 0.08)	0.416	-0.02 (-0.16 - 0.12)	0.783
2	-0.05 (-0.21 - 0.01)	0.509	-0.21 (-0.39 - -0.03)	0.019	0.02 (-0.17 - 0.20)	0.850	0.11 (-0.08 - 0.31)	0.252
3	0.06 (-0.23 - 0.34)	0.696	-0.15 (-0.48 - 0.18)	0.370	-0.23 (-0.57 - 0.10)	0.171	0.05 (-0.31 - 0.41)	0.786
4	-0.25 (-0.82 - 0.33)	0.398	-0.25 (-0.93 - 0.42)	0.466	-0.08 (-0.85 - 0.69)	0.844	-0.27 (-1.12 - 0.57)	0.528
5+	-0.65 (-1.70 - 0.41)	0.229	-0.78 (-2.15 - 0.59)	0.264	-0.58 (-1.86 - 0.71)	0.378	0.10 (-1.28 - 1.48)	0.888
Age at SES measurement 1	-0.01 (-0.10 - 0.08)	0.803	-0.00 (-0.05 - 0.04)	0.880	-0.01 (-0.08 - 0.06)	0.814	0.02 (-0.05 - 0.08)	0.614
Age at SES measurement 2	-0.01 (-0.05 - 0.03)	0.604	-0.01 (-0.07 - 0.05)	0.774	0.03 (-0.03 - 0.09)	0.340	-0.01 (-0.06 - 0.05)	0.795
Age at hyperactivity measurement	0.03 (-0.01 - 0.06)	0.094	**0.09 (0.04 - 0.14)**	**0.001**	0.02 (-0.03 - 0.07)	0.412	0.04 (-0.01 - 0.08)	0.125
constant	2.06 (0.26 - 3.86)	0.025	-3.87 (-8.99 - 1.24)	0.138	-2.14 (-8.77 - 4.48)	0.526	-3.64 (-12.56 - 5.28)	0.424

Notes: SES socioeconomic status. Bolded font: p≤0.001

Chapter Nine: Associations of early life socio-economic position in DNA methylation throughout childhood (study 6)

Abigail Emma Russell, Matthew Suderman

This study was conducted and written in collaboration between myself and Matthew Suderman at the University of Bristol. We designed the study in collaboration, Matt carried out the analysis due to the financial constraints of accessing the epigenetic data and wrote the corresponding sections of the methods and the results. We intend to submit this chapter for publication in a journal, and had hoped to do so prior to submission of my thesis, however due to a family emergency we were delayed in finalising the paper.

This chapter consists of the manuscript prior to comments from senior authors and submission for publication. We anticipate this will be submitted in summer 2016 and will have the following order of authors, comprising myself, Matt and our two supervisory teams:

Abigail Russell*, Matthew Suderman*, Jonathan Mill, Ginny Russell, Caroline Relton and George Davey Smith
*Joint first authors

Abstract

Background. Low socioeconomic status (SES) particularly during childhood is associated with increased risk of a wide range of negative health outcomes in adulthood. Though the biological mechanism behind this association is largely unknown, recent studies have uncovered associations between molecular profiles and both early life SES and related health outcomes. These studies however have important limitations leading to weak findings and little agreement between them. We aim to extend the literature on this topic by first examining epigenome-wide differential DNA methylation in the ARIES subsample of the Avon Longitudinal Study of Parents and Children (ALSPAC) by a variety of SES measures. We also aim to explore whether the findings of previous studies are replicated in our sample. **Methods.** We obtained DNA methylation profiles

using the Infinium HumanMethylation450 BeadChip from cord blood (i.e at birth) and peripheral blood at ages 7 and 15-17 years old in the same children from the ALSPAC (n ~1,000). Based on questionnaire data collected from the mothers before and shortly after birth of the study child, we defined 14 measures of SES for each child and tested each for association with the methylation levels of the 485,000 CpG sites included in the DNA methylation profiles at each time point. **Results.** One association survived adjustment for multiple tests at a false discovery rate (FDR) below 5% (p-value = $4.6x10^{-8}$) and 15 CpG sites below 20%; however, these false discovery rates took into account only the tests of association between a single SES measure and 485K CpG sites, not the tests for all SEP measures considered. There were no CpG sites with FDR < 20% for multiple SES measures or multiple methylation time points. We also identified evidence for eight differentially methylated regions associated with SES (Bonferroni adjusted p < 0.05 for all tests). We obtained evidence for replication of only one CpG previously reported to be associated with SES. **Conclusions.** We found little evidence for an extensive epigenetic signature of poor SES during childhood in whole blood samples, although we did find evidence for 15 differentially methylated positions and eight differentially methylated regions in relation to a range of SES measures. While it is possible that some associations tested were true positives, we have uncovered very little evidence of this and found little consistency between individual SES measures and epigenetic differences over childhood. Large consortium studies may be needed to identify signatures of SES in childhood blood samples.

Introduction

In most societies there is a substantial gap between the wealthiest and the most disadvantaged, both in terms of income and health. Those who are most disadvantaged are at increased risk of a wide range of negative health outcomes (Galobardes, Lynch and Smith, 2007, Borghol et al., 2012, Bradley and Corwyn, 2002). Socioeconomic status (SES) is a term used to describe where in a society an individual is placed in terms of their social and economic wealth. These links between SES and health have been observed for numerous physical and mental health outcomes (Reiss, 2013, Roy, 2004, Miech and Hauser, 2001), and associations between socioeconomic disadvantage (SED)

and poor health begin from birth or even prior- during gestation. SES is a complex concept, and is commonly measured in a variety of ways (Braveman et al., 2005). In studies of child development this often includes parental education, income, occupation, housing tenure, and family composition (Russell et al., 2015, Hauser, 1994).

One core focus for researchers in the field of health inequalities has been on the mechanisms of the SES-health association. Many of the negative health outcomes associated with SED are thought to have a biological basis, yet molecular studies have failed to identify suitable mechanisms (Lundborg and Stenberg, 2010). A few recent studies have linked SED to epigenetic differences, mainly differences in the DNA methylation of cytosine residues in the context of CpG dinucleotides (Murgatroyd and Spengler, 2011). The presence of DNA methylation at the beginning of a gene typically marks an inactive gene. Although extremely stable, DNA methylation can be influenced by environmental exposures, particularly during sensitive periods of development (Lévesque et al., 2014), resulting in long-term changes in gene expression. Thus, DNA methylation provides an attractive mechanism to explain the increased disease risk of SED-exposed individuals.

The precise findings of previous studies are varied, these are summarised in Table 1, but all find some association between SES and DNA methylation. Most prior studies find a small number of differentially methylated positions (DMP's) in specific genes (King, Murphy and Hoyo, 2015, Perng et al., 2012, Obermann-Borst et al., 2012, Appleton et al., 2013, Tehranifar et al., 2013, Lam et al., 2012, Stringhini et al., 2015, Needham et al., 2015) whereas two studies find hundreds of DMP's in adolescent and adult populations (Borghol et al., 2012, Beach et al., 2016). One study finds global hypomethylation in those from SED backgrounds (McGuinness et al., 2012). We aim to extend the literature on this topic by examining epigenome-wide differential DNA methylation in the Accessible Resource for Integrated Epigenomic Studies (ARIES) subsample of the Avon Longitudinal Study of Parents and Children (ALSPAC) by a variety of SES measures. We also aim to explore whether the findings of previous studies are replicated in our sample.

Table 1: Findings from previous studies on SES and DNA methylation

Author (year)	SES measure	Population	Gene/site differentially methylated	Further details if available	Method
Childhood SES and childhood DNA methylation					
King, Murphy and Hoyo (2015)	household income	cord blood, 619 infants	*IGF2, H19, MEG3*	all significantly associated with SEP	Pyrosequencing (Qiagen PyroMark Q96 MD Pyrosequencer)
	maternal education		*IGF2, MEEG3*		
Perng (2012)	Maternal education	568 boys, age 5-12	*LINE-1*	children in highest stratum had hypermethylation compared with other 3 groups	PCR with primers, PyroQ-CpG (Qiagen) to estimate methylation
Obermann-Borst (2012)	Maternal education	120 children, 17 months old	*INSIGF* CpG #2, 5, 6	hypermethylation if mother had low education level	Epityper, Sequenom
	Maternal education		*IGF2R* CpG #20, 21 *IGF2R* Cpg #8-10 (borderline)		
Appleton (2013)	Maternal education	444 newborn infants	*HSD11B2*	hypomethylation if lower education or higher risk score	PyroMark CpG
	Cumulative risk score (maternal education, poverty, marital status and dwelling crowding)		*HSD11B2*		

Adolescent SES and adolescent DNA methylation					
Beach et al. (2016)	Cumulative index based on presence of: being below federal poverty level, primary caregiver not completing high school, primary caregiver unemployment, single parent family, receipt of social welfare, income rated as inadequate to meet needs	398 adolescents, SES age 11, DNA methylation age 19	2,032 loci associated at FDR < .05	28,640 loci were associated at the $p < .01$ level of significance prior to FDR correction	Infinium HumanMethylation 450 BeadChip (Illumina)
Childhood SES and adult DNA methylation					
Tehranifar et al. (2013)	Maternal age at pregnancy	90 adult women	Sat2	hypomethylated in <25	MethyLight assay on ABI Prism 7900 sequence detection system
	Family income at birth			hypermethylated in lowest quartile	
	Maternal education at birth			hypermethylated <high school graduate	
	Family structure through age 13		Alu	hypermethylated single parent	
			Linoleic acid metabolism	hypomethylation in low childhood SEP	
			Sensory perception of smell and taste, hormone-mediated signalling	hypermethylation in low childhood SEP	
			DNA methylation machinery (MBD4, HEMK2), DICER1	hypermethylation in low childhood SEP	

Author (year)	SES measure	Population	Gene/site differentially methylated	Further details if available	Method
Borghol et al. (2012)	Father's occupation and lacking household amenities	40 adult males	*1252 gene promotor regions*	associated with childhood SEP	MeDIP
Stringhini et al. (2015)	household's highest occupation	857 adults	*41 signals: NFATC1 (20 probes) CXCL2 (4 probes), PTGS2, MAP2K5, MAP3K6 (3 probes), IL1A, GPR132, TNFRSF11A (2 probes), ADM, OLR1 (1 probe)*	survived adjustment for multiple testing	Infinium HumanMethylation 450 BeadChip (Illumina)
	SES trajectories		*12 signals: NFATC1 (5 probes) MAP3K6, IL1A (2 probes), GPR132, CXCL2, MAP2K5 (1 probe)*		
Needham et al. (2015)	maternal education	1264 adults	*AVP* *FKBP5* *OXTR* *CCL1* *CC1D*	variable detailed methylation patterns	Illumina HumanMethylation450 BeadChip and HiScan reader
Adult SES and adult DNA methylation					
McGuinness et al. (2012)	Index of Multiple Deprivation	239 adults		Global hypo-methylation in low SES group	Methylamp Global DNA Methylation Quantification Ultra Kit

Methods

Study population and sample acquisition

This study used DNA methylation data generated under the auspices of ALSPAC (Fraser et al., 2013, Boyd et al., 2013). In brief, all pregnant women living in a defined geographical area (Avon) in South-West England with an estimated delivery date between 1st April 1991 and 31st December 1992 were initially invited to enrol in the study, with supplementary recruitment taking place in two further phases. A subsample of 1,000 children and their mothers were enrolled in the ARIES project: this comprises the sample for the current study. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. DNA extracted from cord blood at birth and peripheral blood samples when the study children were aged 7 and 15-17 years were used along with a wide range of exposure and phenotypic data reported by the child's mother. DNA methylation analysis and data pre-processing were performed at the University of Bristol as part of the ARIES project (Relton et al., 2015) (http://www.ariesepigenomics.org.uk).

Measures of socioeconomic status

The following measures of SES were collected during routine questionnaires posted to ALSPAC participants and are all reported by the mother of the study child. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>.

Housing tenure: information on current housing tenure at 8-12 weeks gestation was collected, responses were classed as high SES if the mother reported owning or having a mortgage on the house, and low SES for other categories (i.e. private renting home or housing association)

Mother and father occupation: mothers reported at 32 weeks gestation on their present or most recent job, job status and type of industry worked in, for both themselves and their partner. Office of Population Censuses and Surveys occupation codes (ONS, 1990) were generated for each individual, classified within six ordered levels: I (professional, highest SES) II (managerial and technical), III (skilled occupations) III (manual skilled), IV (manual, partly skilled) or V (manual, unskilled, lowest SES).

Mother and father education: also at 32 weeks gestation mothers reported on the highest level of education they and their partner had completed. These were classified into five ordered levels: CSE (lowest SES); Vocational; O-level (currently known as GCSE: final exams at end of compulsory education in the UK age 16); A-level (age 18 pre-University qualifications) and Degree (highest SES).

Family adversity: This index, previously used in ALSPAC (Steer, 2004), compiles indicators of a range of social adversities that may be faced by a family. This includes marital status, financial difficulties, neighbourhood stress, living arrangements, home ownership, age of mother at birth, whether the father lives with the child, and the number of children in the home. This index was calculated in both a short and long form. We utilised the short and long versions during pregnancy and again at 0-2 years, and the short version at 2-4 years as SES indicators. Each item included in the adversity score was assigned a value of one if adversity was present and zero otherwise. Possible scores for the long index range from 0 (no adversity, high SES) to 18 (highest adversity, low SES) and for the short index from 0 to 15.

Crowding index: mothers reported on the number of people living in the home when the study child was two years nine months old. The crowding index was obtained by dividing this number by the number of rooms in the home. Responses were categorised into four ordered levels: ≤0.5, >0.5-0.75, >0.75-1, and >1 (numbers closer to 1 indicating more crowded conditions and lower SES).

Family income: when children were aged two years nine months, mothers were asked to report “on average, about how much is the take-home family income each week?” (and included social benefits). Responses were recorded in five ordered categories: less than £100, £100-£199, £200-£299, £300-£399, and £400 or more.

Equivalised household income: average weekly household disposable income was recorded when study children were age 3-4 years. It was then transformed by dividing it into quintiles and scaled to account for family size, composition and housing benefits (Gregg, Propper and Washbrook, 2008).

Socioeconomic status: Overall SES was calculated as described in a previous study with ALSPAC (Borghol et al., 2012). Briefly, mothers’ reports on father's occupation (as above) were combined with home crowding index,

whether or not the home had hot running water, and whether or not the household had sole use of hot running water and shower facilities when the child was aged two years nine months. The final score is a 12-point index derived from a weighted sum of each item. Higher scores indicate lower SES.

Covariates

Covariates included mother's age at birth of study child, child gender, whether they had been exposed to maternal smoking during pregnancy (yes or no), ethnicity (white or non-white), body mass index (BMI) of mother at 12 weeks gestation, birthweight, gestational age and parity. Missing values in covariates were replaced with the median for continuous variables and the mode for categorical variables.

DNA methylation profile generation

DNA was bisulphite converted using the Zymo EZ DNA Methylation^{TM} kit (Zymo, Irvine, CA). Infinium HumanMethylation450 BeadChips (Illumina, Inc.) were used to measure genome-wide DNA methylation levels at over 485,000 CpG sites. The arrays were scanned using an Illumina iScan, with initial quality review using GenomeStudio. This assay detects methylation of cytosine at CpG islands using two site-specific probes – one to detect the methylated (M) locus and one to detect the unmethylated (U) locus. Single-base extension of the probes incorporates a labelled chain-terminating ddNTP, which is then stained with a fluorescence reagent. The ratio of fluorescent signals from the methylated site versus the unmethylated site determines the level of methylation at the locus. The level of methylation is expressed as a "Beta" value (β-value), ranging from 0 (no cytosine methylation) to 1 (complete cytosine methylation). β-values are reported as percentages.

Quality control

During the data generation process a wide range of batch variables were recorded in a purpose-built laboratory information management system (LIMS). The LIMS also reported quality control metrics from the standard control probes on the 450K BeadChip. Samples failing quality (samples with >20% probes with p-value ≥ 0.01) were repeated. Samples from all three time points in ARIES were randomized across arrays to minimise the potential for batch effects. As

an additional quality control step, genotype probes on the 450K BeadChip were compared between samples from the same individual and against SNP (single nucleotide polymorphism)-chip data to identify and remove any sample mismatches.

Methylation profile normalisation

Raw β-values were pre-processed using R (version 3.0.1) with background correction and sub-set quantile normalisation performed using the pipeline described by Touleimat and Tost (2012) and implemented in the watermelon R package (Pidsley et al., 2013). Finally, to reduce influence of outliers in regression models, normalized β-values were 90%-Winsorized.

Cell type heterogeneity

Blood is composed of many cell types and composition ratios can vary over time within a given individual as well as between individuals. DNA methylation differs significantly between blood cell types so it is necessary to adjust for cell type variance in methylation analyses to avoid confounding. Cell type proportions per individual were estimated from DNA methylation profiles using the method described by Houseman et al. (2012) using the ‘estimateCellCounts' function from the ‘minfi' R package (Aryee et al., 2014). Cell types included CD8+ T cells, CD4+ T cells, CD56 natural killer cells, CD19 B cells, CD14+ monocytes and granulocytes. Some of these proportions are significantly associated with sex.

Genomic inflation

Genomic inflation was estimated as the ratio of the median of the observed test statistic divided by the expected median.

Statistical Analysis

Associations were tested using linear regression models with adjustments for child sex, DNA extraction method, estimated cell counts, maternal age at birth, parity, smoking during pregnancy, ethnicity, mother’s BMI, child birthweight, child gestational age, and independent surrogate variables to adjust for unknown confounders. In order to understand the effects of covariates on regression models, we in fact fit six different models:

1. basic: child sex and sample type (DNA extraction method).
2. counts: basic with estimated cell counts.
3. confounders: basic with maternal age at birth, parity, smoking during pregnancy, ethnicity and BMI and child birthweight and gestational age.
4. full: all of the above.
5. isva0: Independent Surrogate Variables (ISVs) derived from methylation data.
6. isva1: ISVs from ISV analysis applied to the methylation data along with all variables listed above.

Differentially methylated regions (DMR's) were identified using DMRcate (Peters et al., 2015). Briefly, t-statistics for each CpG site calculated as part of association tests were squared and then smoothed spatially using a Gaussian kernel. Models are then fit to the curves and p-values derived. A p-value threshold for statistical significance was calculated using permutation tests to obtain a null distribution. A specific EWAS (equivalised income in cord blood) was computed 100 times, each time with the variable of interest randomly permuted. DMRcate was applied to the resulting t-statistics of each instance and the minimum p-value obtained. The p-value threshold ($p = 2.9x10^{-14}$) was then selected as the 5^{th} percentile of these 100 minimum p-values. We note that this threshold is lower than a Bonferroni-adjusted threshold of $p < 0.05$ for all individual CpG site tests performed, i.e. 48500 CpG sites x 14 SEP variables x 3 time points x 6 regression models ~ 122 million or a p-value threshold of $0.05/122 \text{ million} = 4 \times 10^{-10}$).

Results

Associations between childhood SES and differentially methylated CpG sites across childhood

We tested associations between fourteen measures of socioeconomic position and DNA methylation from the same ~1,000 individuals at three different time points from birth to age 17. DNA methylation was measured in cord blood at birth, and in peripheral blood at seven years old and 15-17 years old. Socioeconomic measures included parental occupation, parental highest educational attainment, housing tenure, family income, equivalised family

income and crowding index. We also considered two composite measures: the family adversity index and a previously described SES index combining parental occupation and living conditions (Borghol et al., 2012). Participant characteristics are described in Table 2 and population characteristics in Table 3. Most SES measures were strongly but not perfectly associated with one another (Figure S1).

Associations were tested using several different sets of potential confounders and the quality of the overall model fit assessed by comparing resulting probe p-values against p-values expected if there were no true associations. Systematic deviation from expected p-values is measured using a statistic called genomic inflation which increases above one for p-values consistently lower than expected and decreases below one for p-values consistently higher than expected (see Methods). We found p-values to be closest to expected values (i.e. genomic inflation closest to 1) when fitting the model using the confounder set called *isva1* (Figure S2). We therefore use this model to identify potential associations between SES measures and DNA methylation.

Associations with false discovery rates below 20% are listed in Table 4. The top 50 associations from each analysis are provided in Supplementary Spreadsheet 1. Adjustment for multiple testing was applied per SES measure and ARIES time point, not across analyses of all SES measures and time points. Only one test yielded a false discovery rate less than 0.05 (FDR = 2.2%). CpG site cg15437874 was positively associated with crowding index in peripheral blood obtained at age 15-17 years (Figure 1). It was also weakly associated (at nominal $p < 0.05$) with three other SES measures: family adversity index (short and long, 0-2y) and equivalised income. For each measure, it is positively associated with social disadvantage. Out of the 15 associations listed in Table 4, CpG site cg01347453 was associated (at nominal $p < 0.05$) with the largest number of SES measures: family adversity index (short and long index during pregnancy, 0-2y and 2-4y), equivalised income, family income, father and mother educational attainment, and father occupation. For each measure, DNA methylation at this site is positively associated with social disadvantage.

No CpG site appears more than one time in the top 15 associations (Table 4) indicating few if any stable associations with SES throughout

childhood. However, CpG site cg01470456 near the *RALYL* gene is most strongly negatively associated with crowding index at age 7 ($p = 3.4x10^{-7}$; coefficient = 0.033) and somewhat less so at birth and at age 15-17 (at birth: p = 0.00016 and coefficient = -0.025; at age 15: p = 0.00039 and coefficient = -0.022) (Figure 2a). Although it does coincide with SNP rs77381455, the minor allele frequency is quite low (~ 1.5% in dbSNP, the database of SNP's) so the association is unlikely to be driven by a SNP. The association of another CpG site cg14215309 with fathers' occupation appears to become stronger throughout childhood (Figure 2b). At birth there appears to be no association (p = 0.37) but by age seven there is some evidence of a positive association (p = 0.0019; coefficient = 0.0025) that has doubled by age 15 ($p = 3x10^{-7}$; coefficient = 0.0049).

Associations between childhood SES and differentially methylated regions

The absence of any convincing associations may be the result of low power due to a large number of tests (~485,000) applied to a relatively small number of samples (~1000). In fact, CpG sites in close proximity tend to have highly correlated DNA methylation levels so the assumption of multiple tests, that each test is independent, may yield overly conservative significance thresholds. We therefore effectively reduced the number of tests by testing small genomic regions containing multiple CpG sites for associations with SEP measures (Peters et al., 2015). Using this approach, we identified eight genomic regions associated with various SES measures and time points (Table 5). In contrast to the strongest individual CpG site associations, most of the regions (5 out of the 8) are quite strongly associated with the SES measure throughout childhood (see Figure 3 for an example), and cover measures of parent education, income and the index measure of SES.

Table 2: Distributions of SES measures in ALSPAC and ARIES sample at each time point

	SES measure	Sample							
		ALSPAC (n=14676)		ARIES cord (n=914)		ARIES 7y (n=973)		ARIES 15-17y (n=974)	
		N	%	N	%	N	%	N	%
	Father occupation	**11010**		**845**		**901**		**902**	
low SES	V	316	2.9	20	2.4	19	2.1	20	2.2
	IV	1078	9.8	63	7.5	66	7.3	66	7.3
	III (manual)	3463	31.5	223	26.4	238	26.4	237	26.3
	III (non-manual)	1199	10.9	118	14	120	13.3	121	13.4
	II	3749	34.1	284	33.6	309	34.3	307	34
high SES	I	1205	10.9	137	16.2	149	16.5	151	16.7
	Mother occupation	**10111**		**803**		**854**		**856**	
low SES	V	221	2.2	7	0.9	8	0.9	8	0.9
	IV	997	9.9	70	8.7	72	8.4	73	8.5
	III (manual)	791	7.8	36	4.5	42	4.9	39	4.6
	III (non-manual)	4326	42.8	315	39.2	339	39.7	342	40
	II	3180	31.5	298	37.1	310	36.3	307	35.9
high SES	I	596	5.9	77	9.6	83	9.7	87	10.2
	Family income	**8842**		**772**		**828**		**825**	
low SES	<100	770	8.7	33	4.3	34	4.1	34	4.1
	100 - 199	1561	17.7	100	13	107	12.9	109	13.2
	200 - 299	2513	28.4	213	27.6	229	27.7	230	27.9
	300 - 399	1879	21.3	191	24.7	202	24.4	199	24.1
high SES	>400	2119	24	235	30.4	256	30.9	253	30.7
	Crowding index	**9505**		**814**		**872**		**871**	
low SES	> 1	739	7.8	39	4.8	44	5	42	4.8
	>0.75 - 1	3434	36.1	276	33.9	294	33.7	298	34.2
	>0.5 - 0.75	3571	37.6	341	41.9	363	41.6	363	41.7
high SES	<= 0.5	1761	18.5	158	19.4	171	19.6	168	19.3

	SES measure	ALSPAC (n=14676)		ARIES cord (n=914)		ARIES 7y (n=973)		ARIES 15-17y (n=974	
		N	%	N	%	N	%	N	%
	Mother education	**12482**		**894**		**953**		**953**	
low SES	CSE	2521	20.2	82	9.2	83	8.7	83	8.7
	Vocational	1228	9.8	69	7.7	71	7.5	70	7.3
	O level	4323	34.6	299	33.4	325	34.1	323	33.9
	A level	2803	22.5	260	29.1	279	29.3	281	29.5
high SES	Degree	1607	12.9	184	20.6	195	20.5	196	20.6
	Father education	**12001**		**882**		**939**		**940**	
low SES	CSE	3133	26.1	137	15.5	146	15.5	144	15.3
	Vocational	1014	8.4	67	7.6	69	7.3	70	7.4
	O level	2552	21.3	189	21.4	205	21.8	206	21.9
	A level	3121	26	262	29.7	275	29.3	273	29
high SES	Degree	2181	18.2	227	25.7	244	26	247	26.3
	Housing tenure	**12711**		**927**		**927**		**926**	
low SES	rented	3051	24	92	9.9	92	9.9	93	10
high SES	owned	9660	76	835	90.1	835	90.1	833	90
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	Equivalised income	5.3	0.5	5.4	0.4	5.4	0.4	5.4	0.4
	Index of SEP	5.2	2.7	4.8	2.7	4.8	2.7	4.8	2.7
	FAI (short, pregnancy)	1.1	1.3	0.8	1.1	0.8	1.1	0.8	1
	FAI (long, pregnancy)	1.3	1.6	0.9	1.3	0.9	1.3	0.9	1.3
	FAI (short, 0-2y)	1.5	1.6	1.2	1.4	1.2	1.4	1.2	1.4
	FAI (long, 0-2y)	2	2	1.6	1.9	1.6	1.9	1.6	1.8
	FAI (2-4y)	1.3	1.4	1.1	1.3	1.1	1.3	1	1.3

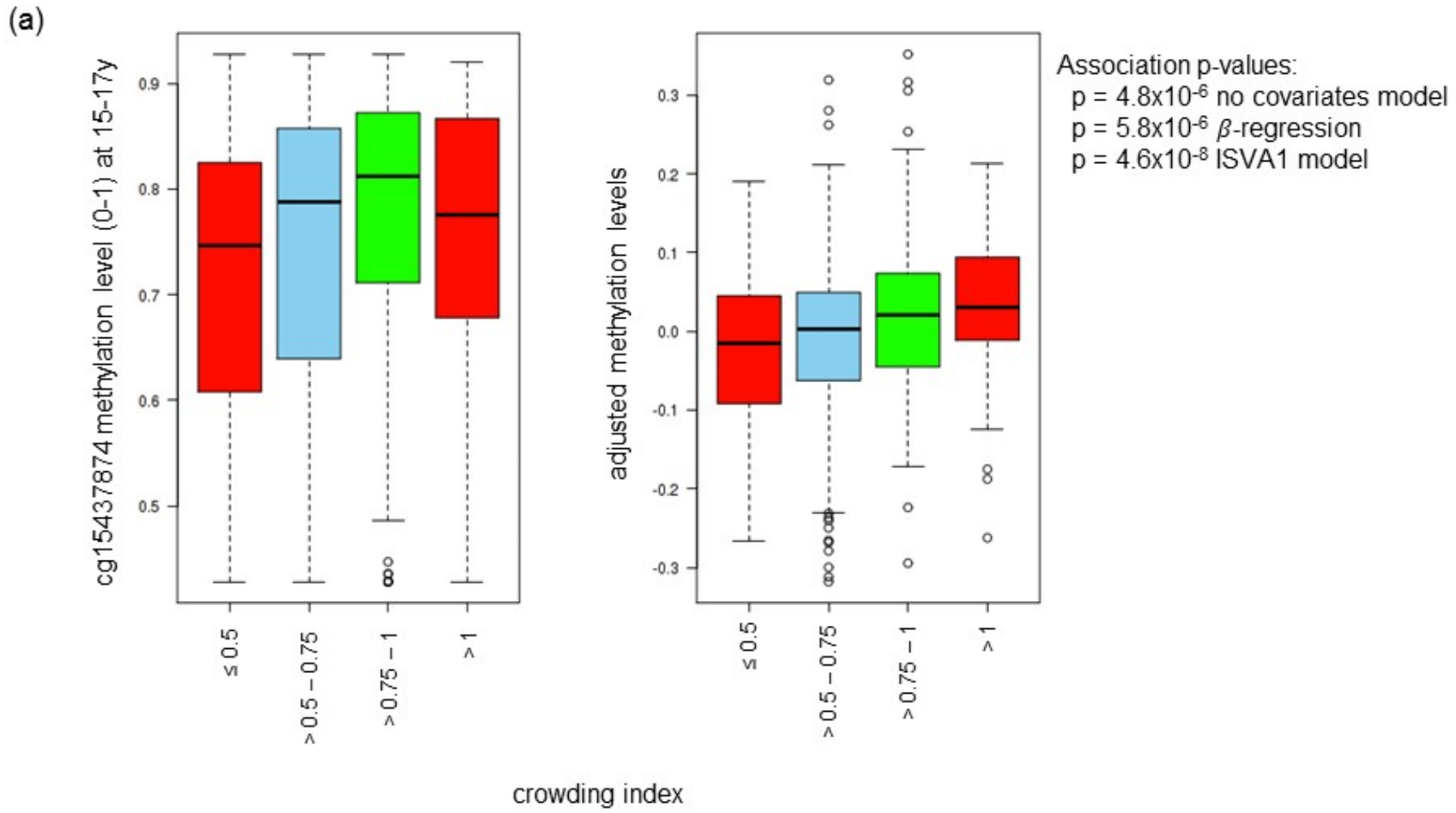
Notes: FAI Family adversity index. SES socioeconomic status

Table 3: Population Characteristics

	ALSPAC (n=19467)		ARIES cord (n=914)		ARIES 7y (n=973)		ARIES 15-17y (n=974)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex	**19,467**		**914**		**973**		**974**	
female	9,390	48.2	469	51.3	488	50.2	500	51.3
male	10,077	51.8	445	48.7	485	49.8	474	48.7
Smoking during pregnancy	**19,467**		**914**		**973**		**974**	
no	15,793	81.1	785	85.9	836	85.9	840	86.2
yes	3,674	18.9	129	14.1	137	14.1	134	13.8
Maternal ethnicity	**19,467**		**914**		**973**		**974**	
non-white	611	3.1	26	2.8	26	2.7	26	2.7
white	18,856	96.9	888	97.2	947	97.3	948	97.3
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Maternal BMI	22.63	2.98	22.8	3.6	22.8	3.6	22.7	3.5
Birthweight	3389.65	490.99	3483.4	482.1	3486.9	483.8	3490.8	484.7
Gestational age	39.46	2.13	39.6	1.5	39.6	1.5	39.6	1.5
Parity	0.89	0.78	0.7	0.8	0.8	0.8	0.7	0.8
Maternal age at birth	339.7	54.54	359.5	53.3	360	53	360	53

Notes: BMI- body mass index

Figure 1: Two of the strongest associations with SES. 1a- crowding index, 1b- (overleaf) family adversity index



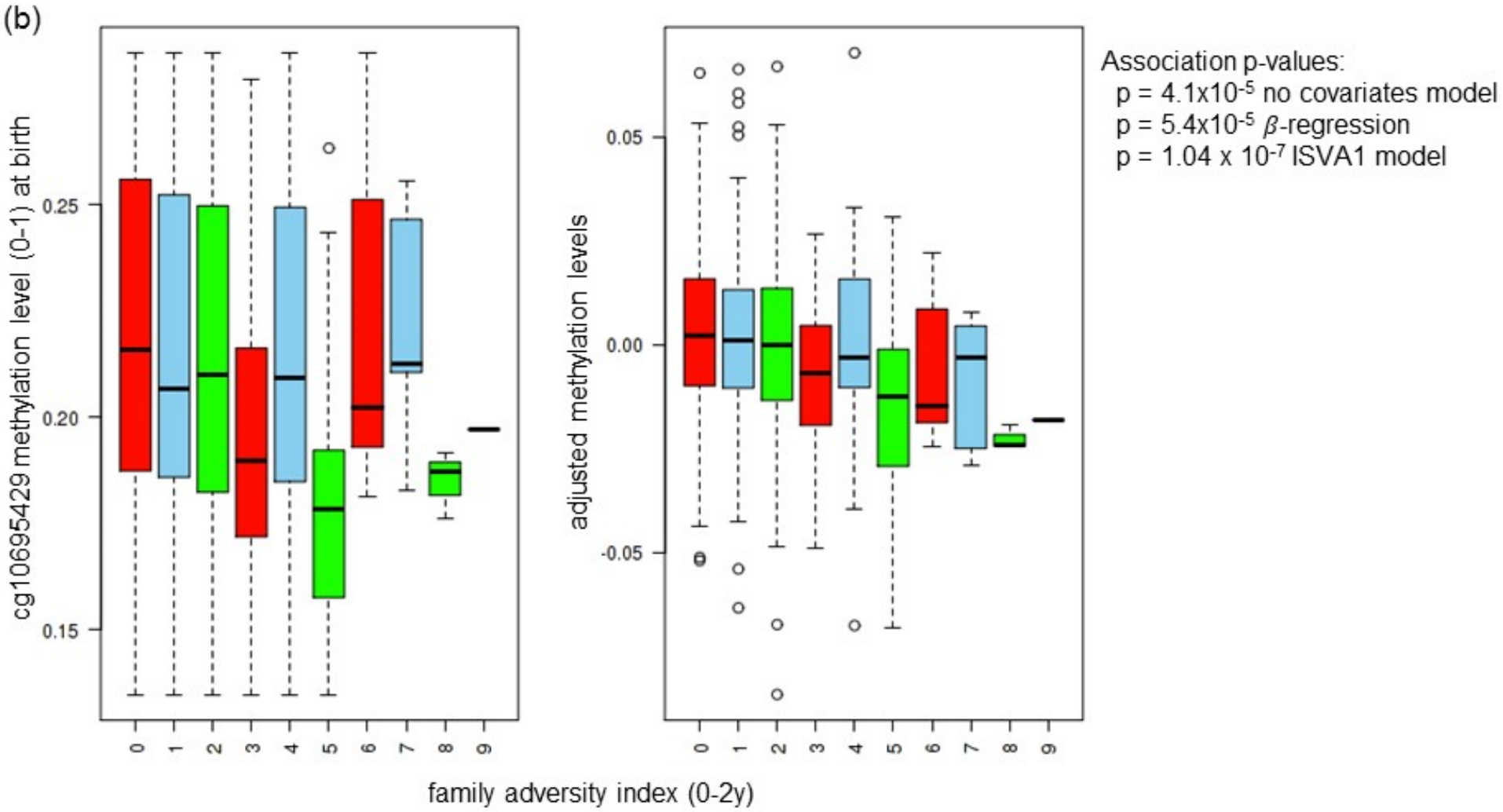

(b)
cg10695429 methylation level (0-1) at birth
0.25
0.20
0.15
adjusted methylation levels
0.05
0.00
-0.05
0 1 2 3 4 5 6 7 8 9
family adversity index (0-2y)
Association p-values:
p = 4.1x10-5 no covariates model
p = 5.4x10-5 β-regression
p = 1.04 x 10-7 ISVA1 model

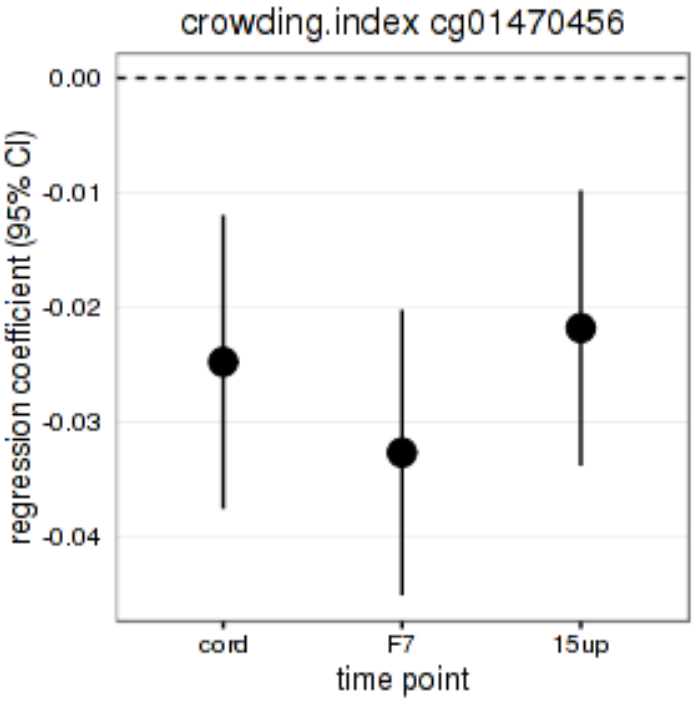
Table 4: 15 strongest associations across all SES measures and ARIES time points.

Child age (years)	Variable	CpG	Gene	Location	p-value [1]	FDR[2]	coefficient	max p-value[3]	SEP measures[4]
15-17	Crowding index	cg15437874	LOC100507443 (non-coding)	chr2:208976637	4.60E-08	0.022342	0.0230382	0.0000019	4
birth	FAI, short, 0-2	cg10695429	IGF2BP2	chr3:185542769	1.04E-07	0.0505498	-0.0026538	0.0000148	8
birth	FAI, 2-4	cg01347453	LOC100131060 (non-coding)	chr1:59369309	1.43E-07	0.0692017	-0.0004044	0.0000052	10
7	FAI, long, pregnancy	cg21645973	ARHGEF10L	chr1:17914070	1.78E-07	0.085222	0.0044391	0.0152722	4
birth	FAI, short, 0-2	cg08202494	OSR2	chr8:99961545	2.17E-07	0.0527217	0.0018124	0.0011082	6
7	Mother occupation	cg13730736	KCNT1	chr9:138653071	2.86E-07	0.1386632	-0.0165699	0.0000219	3
15-17	Father occupation	cg14215309	BAIAP2L1 (70Kb upstream)	chr7:98099806	2.98E-07	0.1448224	0.0048784	0.0000106	7
7	Crowding index	cg01470456	RALYL	chr8:85787158	3.35E-07	0.162561	-0.0326878	0.0001091	5
7	FAI, long, pregnancy	cg08968329	PIEZO1	chr16:88844499	3.51E-07	0.085222	0.0011459	0.0082475	3
15-17	FAI, short, pregnancy	cg08506606	LOC101929574 (non-coding)	chr10:82295502	3.75E-07	0.1818825	0.0033493	0.0000185	2
7	FAI, long, pregnancy	cg23658354	PTPRO	chr12:15698695	8.00E-07	0.1296004	-0.0066589	0.0102466	8
birth	FAI, short, 0-2	cg03928384	CCR2	chr3:46395191	1.20E-06	0.1609191	0.0053413	0.0000232	7
birth	FAI, short, 0-2	cg04206417	EMID1	chr22:29601559	1.30E-06	0.1609191	0.0015691	0.0000049	7
7	FAI, long, pregnancy	cg16975614	CBLB (14Kb upstream)	chr3:105601834	1.60E-06	0.1972193	0.0179954	0.0000738	7
birth	FAI, short, 0-2	cg12459932	RUNX3	chr1:25292018	2.00E-06	0.1901391	0.0050726	0.0004832	5

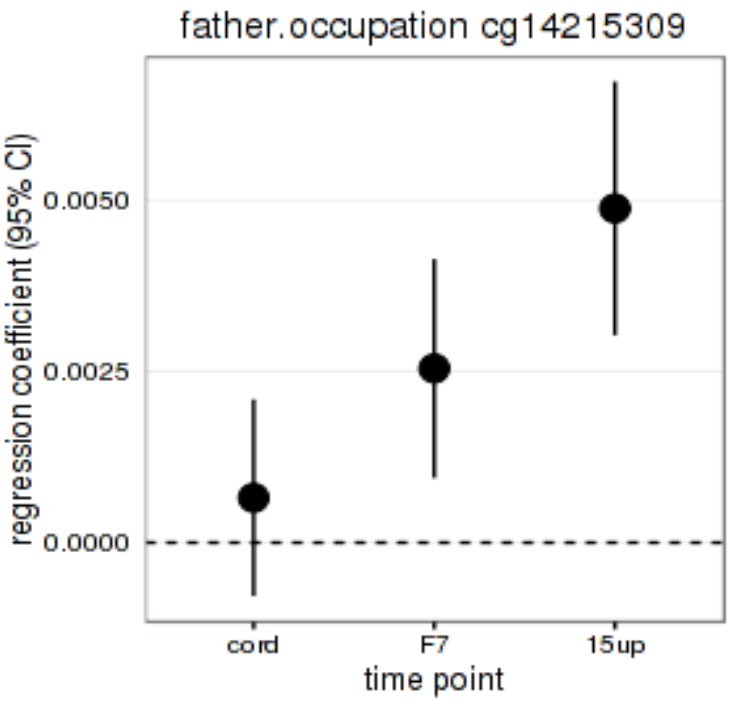
Notes for Table 4. 1. Table shows all associations with FDR < 0.2. 2. Adjustment for multiple testing applies to the analysis of each SES measure individually, not across all SES measures. 3. The maximum p-value across all regression models defined by different sets of covariates. 4. Number of SES measures with nominal association $p < 0.05$. FAI: family adversity index

Figure 2: Regression coefficients for two of the top CpG site associations at three time points, birth, age 7 and age 15-17 years

2a)



2b)



Notes: In (a), CpG site cg011470456 near the *RALYL* gene is most strongly negatively associated with crowding index at age 7y ($p = 3.4x10^{-7}$; coefficient = 0.033) and somewhat less so at birth and at age 15y (at birth: p = 0.00016 and coefficient = -0.025; at age 15y: p = 0.00039 and coefficient = -0.022). In (b), CpG site cg14215309 appears to become more strongly associated with father's occupation throughout childhood. At birth there appears to be no association (p = 0.37) but by age 7 there is some evidence of a positive association (p = 0.0019; coefficient = 0.0025) that has doubled by age 15y (p = 3x10-7; coefficient = 0.0049)

Replication of previously reported SES-DNA methylation associations

We also tested individual loci previously linked to SES. If specific CpG sites reported in previous studies were not on the microarray, we looked for associations between CpG sites within 1,000 base pairs of the site previously reported. We found evidence to replicate the findings of only two of the previously published studies (outlined in Table 1): in other cases, either p-values of CpG sites were >0.1 (Obermann-Borst et al., 2012) or false discovery rates were >0.2 (Stringhini et al., 2015, Needham et al., 2015, Appleton et al., 2013, King, Murphy and Hoyo, 2015).

The first replication was an association with maternal education: CpG site cg02719427, one of four CpG sites within 200bp of the CpG site in *IGF2* that King, Murphy and Hoyo (2015) found was associated with maternal education in cord blood. In our sample this CpG site was associated with maternal education at age 15-17 ($p = 0.009$, FDR = 0.11, change in methylation = 0.05% per educational level increase).

The second replication was an association with parental occupation. Lam et al. (2012) identified three CpG sites associated in adult peripheral blood with parental occupation: cg01033160, cg06623268 and cg16137862. Of these, father occupation was weakly associated with cg16137862 methylation at age 15-17 (nominal $p = 0.01$), however direction of methylation difference was inverted in our dataset. Father occupation but not mother occupation was associated with cg06623268 methylation at age seven (nominal $p = 0.09$ and 0.1, respectively).

Table 5: Eight differentially methylated regions.

5a: Region information

	Child age (years)	Variable	Chromosome	Start	End	Gene	p-value	t-statistic	Number of probes
1	birth	Mother occupation	6	32120584	32120955		1.68E-15	2.43	14
2	birth	Mother Education	22	51016899	51017019		2.57E-14	-1.99	4
3	birth	Equivalised income	5	135415948	135416029		1.45E-14	2.47	2
4	birth	Father education	7	27183133	27184188	HOXA5	2.74E-14	-2	32
5	birth	FAI, long form, 0 to 2	1	92946187	92947035	GFI1	1.85E-14	-3.93	4
6	7	SEP Index	22	51017067	51017432		1.83E-14	2.75	5
7	7	FAI, short, pregnancy	11	368351	369192	B4GALNT4	1.40E-17	2.57	24
8	15-17	Equivalised income	5	135415693	135416613	VTRNA2-1	1.16E-16	2.91	16

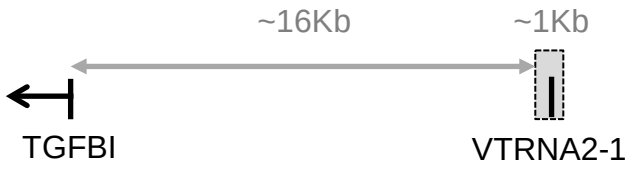
Note. FAI: family adversity index

5b: Associations across childhood for each differentially methylated region

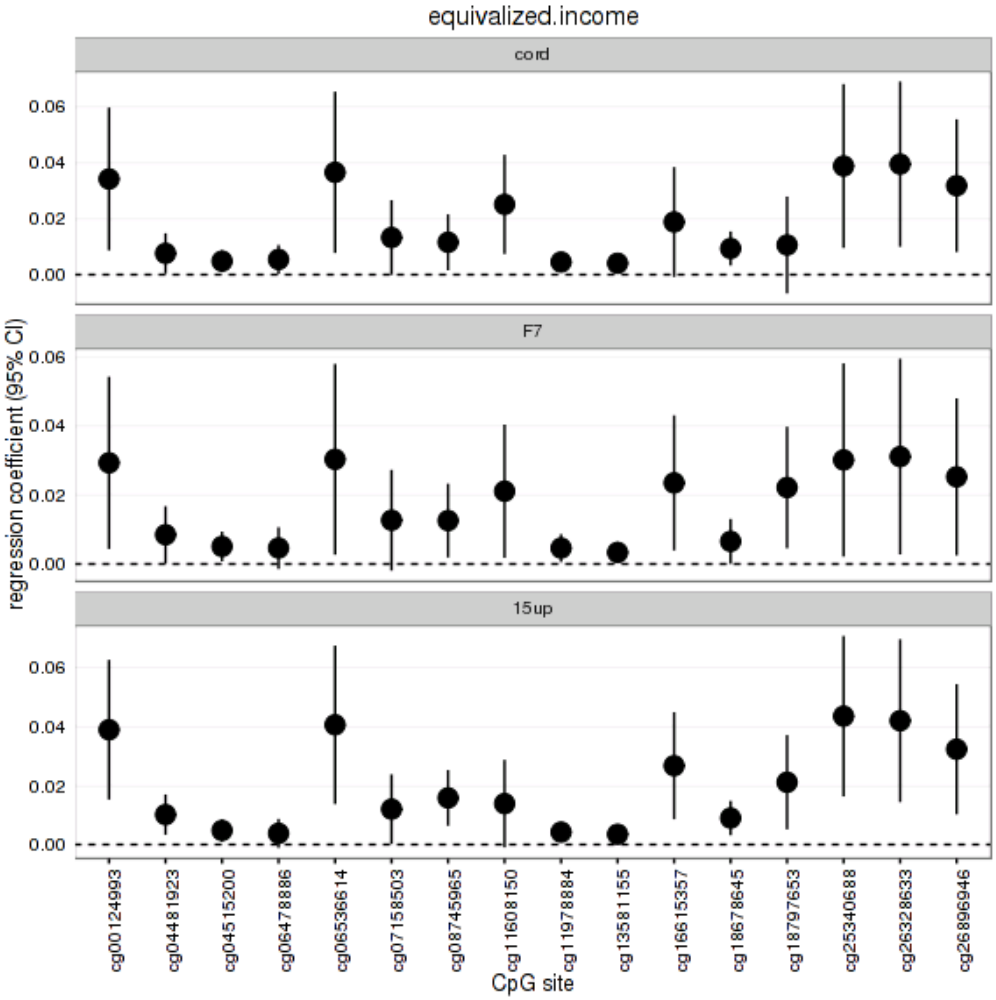
	birth		7 years		15-17 years	
	p-value	**t-statistic**	**p-value**	**t-statistic**	**p-value**	**t-statistic**
1	1.68E-15	2.425709	0.009588	-0.12181	0.170176	-0.14194
2	**2.57E-14**	**-1.99063**	**3.07E-07**	**-1.7928**	**2.80E-08**	**-2.15336**
3	**1.45E-14**	**2.474622**	**2.84E-08**	**1.784794**	**7.73E-19**	**1.741715**
4	**2.74E-14**	**-1.99669**	**5.37E-08**	**-1.48234**	**5.01E-07**	**-1.61602**
5	1.85E-14	-3.93004	0.071645	-1.5607	0.774049	-0.85902
6	**3.69E-11**	**2.850261**	**1.83E-14**	**2.749943**	**9.87E-05**	**2.069476**
7	0.145503	1.035555	1.40E-17	2.573112	0.000104	1.185884
8	**1.82E-11**	**2.576219**	**8.17E-07**	**2.140723**	**1.16E-16**	**2.906109**

Figure 3: A genomic region positively associated with equivalised income in each of the three time points.

3a



3b



Notes: Part (a) shows that the approximately 1Kb region contains the *VTRNA2-1* gene which is ~16Kb upstream of the *TGFBI* gene. Part (b) shows the regression coefficients of each CpG site that was measured in the region. For the most part, the coefficients are consistently positive and a similar pattern of magnitudes is maintained within each time point.

Discussion

Findings

In the current study we explored whether a wide variety of measures of SEP were associated with DNA methylation in blood in just under 1,000 individuals at birth, age seven and age 15-17 years. We found little evidence for any stable associations between SES and DNA methylation, only one association test survived adjustment for multiple testing (Bonferroni $p < 0.05$) and only 15 CpG sites at FDR < 20%. This is consistent with most previous epigenome-wide studies that report only a small number of associations between SES and DNA methylation.

Although we identified one CpG site that was associated with a large range of SEP measures (cg01347453), we cannot conclude that these are indeed true effects as the associations did not survive adjustment for multiple testing. In addition, we were also largely unable to replicate results of previous studies on SES and DNA methylation, with minor exceptions. While it is possible that some associations tested in this study were true positives, we have uncovered very little evidence of this. Large consortium studies may be needed to identify signatures of SES in peripheral tissues, utilising larger samples with a wider range of socioeconomic circumstances. In addition, the sample in ARIES had a smaller proportion of low SES individuals than the wider ALSPAC population: studies reporting a large number of associations between SES and DNA methylation tend to have a high proportion of participants from severely deprived SEP backgrounds (Borghol et al., 2012, Beach et al., 2016).

Using the GeneCards database (www.genecards.org) we explored the functions of the genes these CpG sites were located in or closest to, as well as scanned publication lists for each gene for relevant findings. These genes were linked to a variety of specific functions but with little similarity between them, and no previously reported associations of interest. Details are provided in Supplementary Spreadsheet 2.

We also found evidence for eight differentially methylated regions associated with a variety of SES measures: most of these associations were between SES and methylation in cord blood samples. Equivalised income was associated with two overlapping regions on chromosome 5, one region was associated with cord blood and the other at age 15-17. This result possibly

indicates that there are associations between SES and DNA methylation but that our study may have been underpowered.

Strengths

The current study has many strengths. Because we utilised a well-characterised cohort providing multiple measures of early life SES, we were able to explore whether specific or multiple SES facets were associated with DNA methylation. We were also able to explore potential associations longitudinally, as we had data from the same individuals at three time points during childhood. The fact that methylation was measured from birth and into adolescence as opposed to only in adulthood allows us to at least partially test the hypothesis that DNA methylation mediates the effect of early life SES has on later health outcomes. Our study is also methodologically rigorous: we utilised a variety of regression models that adjusted for a range of confounders as well as surrogate variables. The lack of agreement between findings in our study and between previous studies of SES is possibly influenced by a lack of rigorous methodology applied consistently across all studies.

Limitations

Our failure to replicate previous findings may also be due in part to the wide variety of DNA methylation profiling methodologies used in different studies as well as differences in sample populations, with most of the previously published studies using samples collected in adulthood rather than childhood. Our study however is consistent with previous studies in that there is little consistency between studies.

Our study may lack sufficient variation in SES measures because of selection bias: participants with the most complete phenotypic and exposure profiles were selected for DNA methylation profiling. Comparisons of the whole ALSPAC sample with the ARIES subsample shows that those in ARIES were less likely to be in the lower SES groups, for example 8.7% of the ALSPAC sample earned <£100 per week and in the ARIES sample only 4.3% were in this low income category. In addition, the relatively small sample size of ARIES meant that, in some instances, the number of individuals in a given SEP category was quite small. For example, there were only eight individuals in the lowest category of mothers' occupation. Fortunately, in most cases there were at least 50 individuals in each category.

Like most previous studies, we tested associations in DNA methylation profiles obtained from an easily accessible peripheral tissue, whole blood. DNA methylation levels and responses are often highly tissue specific (Provençal et al., 2012, Davies et al., 2012). For example, in a study of rearing in rhesus macaques, 1357 associations with rearing were reported in prefrontal cortex DNA methylation compared with only 122 associations reported in T-cells (Provençal et al., 2012). This finding supports the reasonable hypothesis that the brain is more responsive to social stress than blood.

Future directions

Ours is the most comprehensive study of DNA methylation and SES in childhood. It is surprising that all previous studies report stronger although unreplicated associations. This may indicate publication bias against null findings. Whatever the case may be, it does appear that DNA methylation in peripheral tissues has little or no role in mediating the effects of early life social disadvantage on later health outcomes. We cannot say that it has no role because our study may be underpowered to identify weak yet true associations. The number of different SES measures considered in our study highlights the complexity of SES exposures. It is possible that our EWAS regression models and small sample sizes are incapable of handling this complexity.
To determine which of these possibilities are true, future research will need to be methodologically rigorous, be consistent in the measures of SES, populations, methods of measuring DNA methylation and tissue types used, include larger numbers of individuals at the extremes of SES.

Acknowledgements

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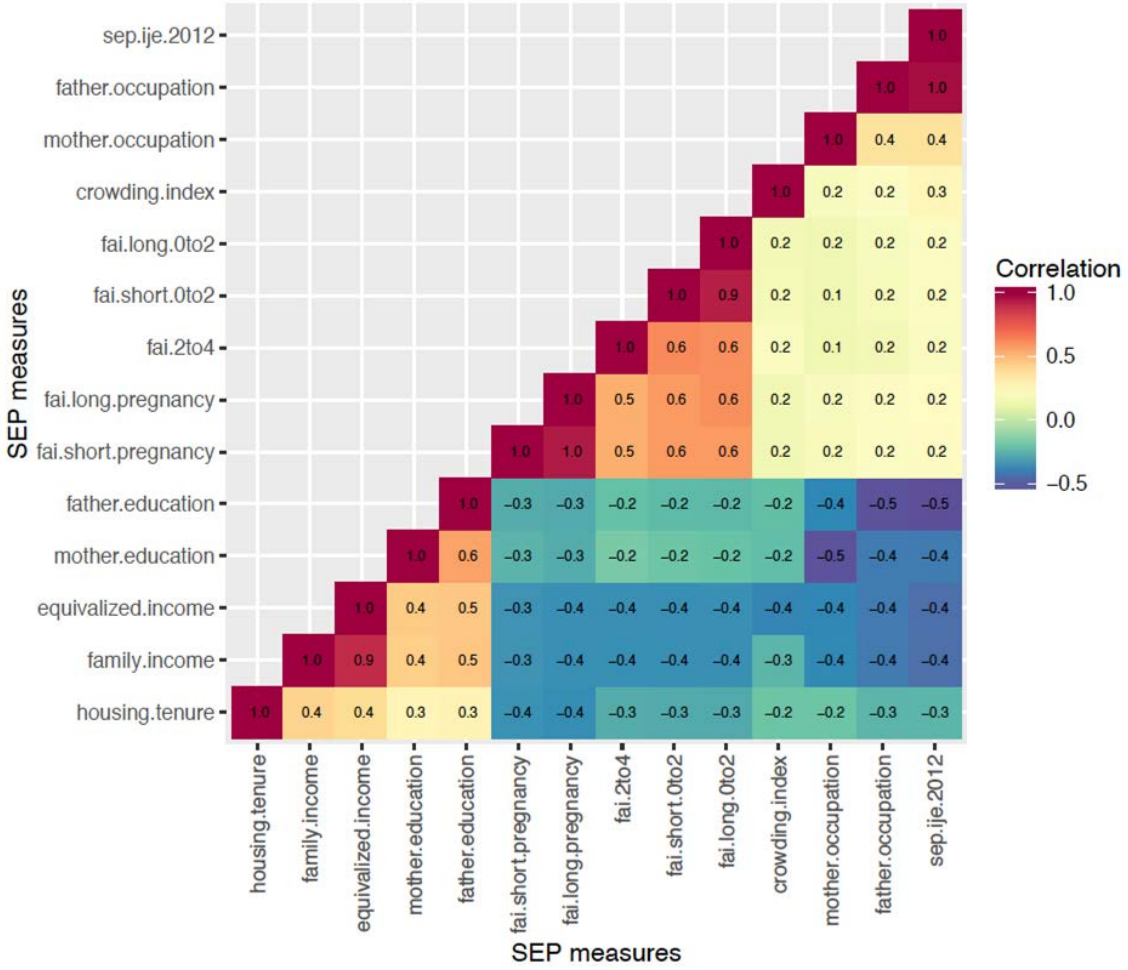
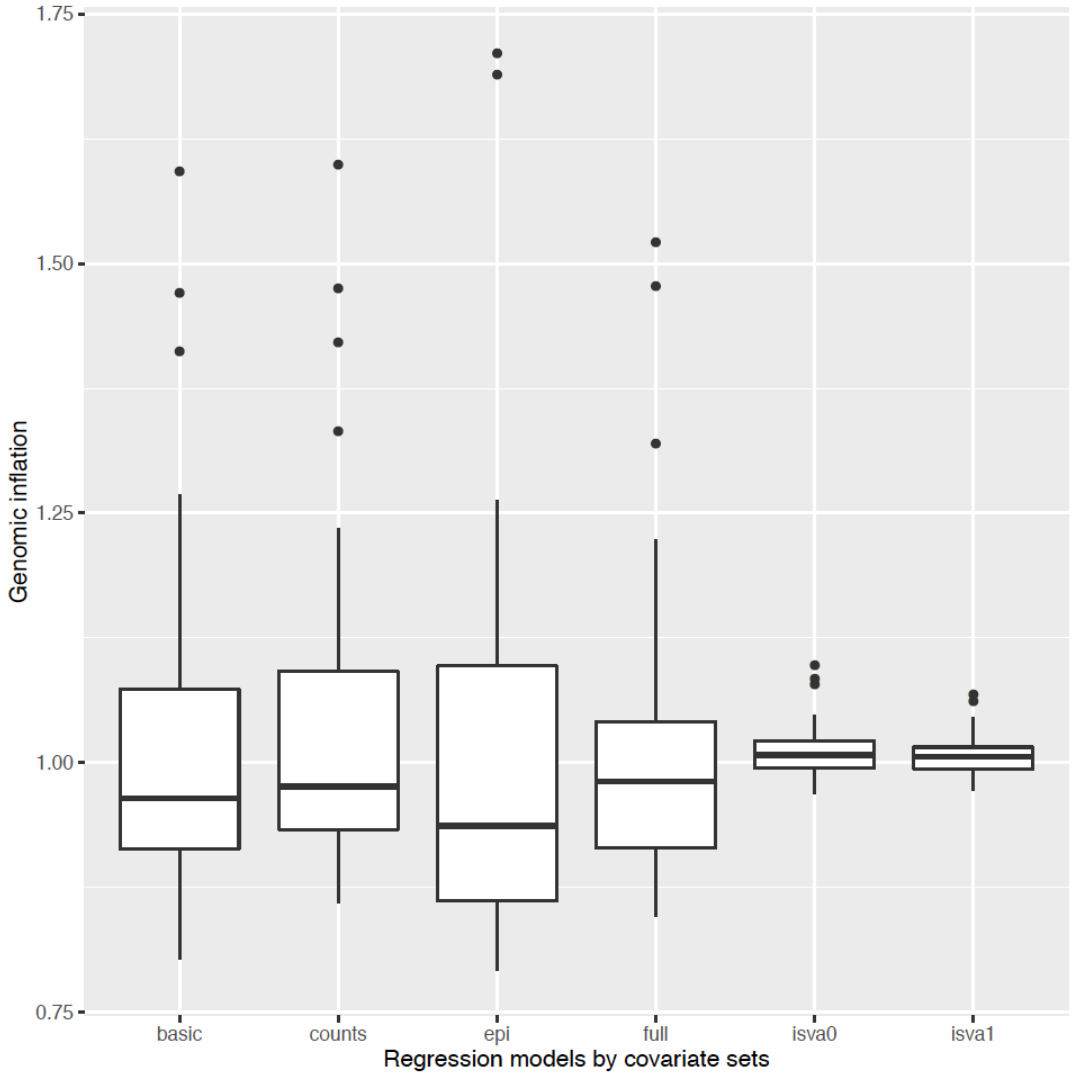
Supplementary Material

Figure S1: Correlation (Spearman's rho) between SES measures in all of ALSPAC.



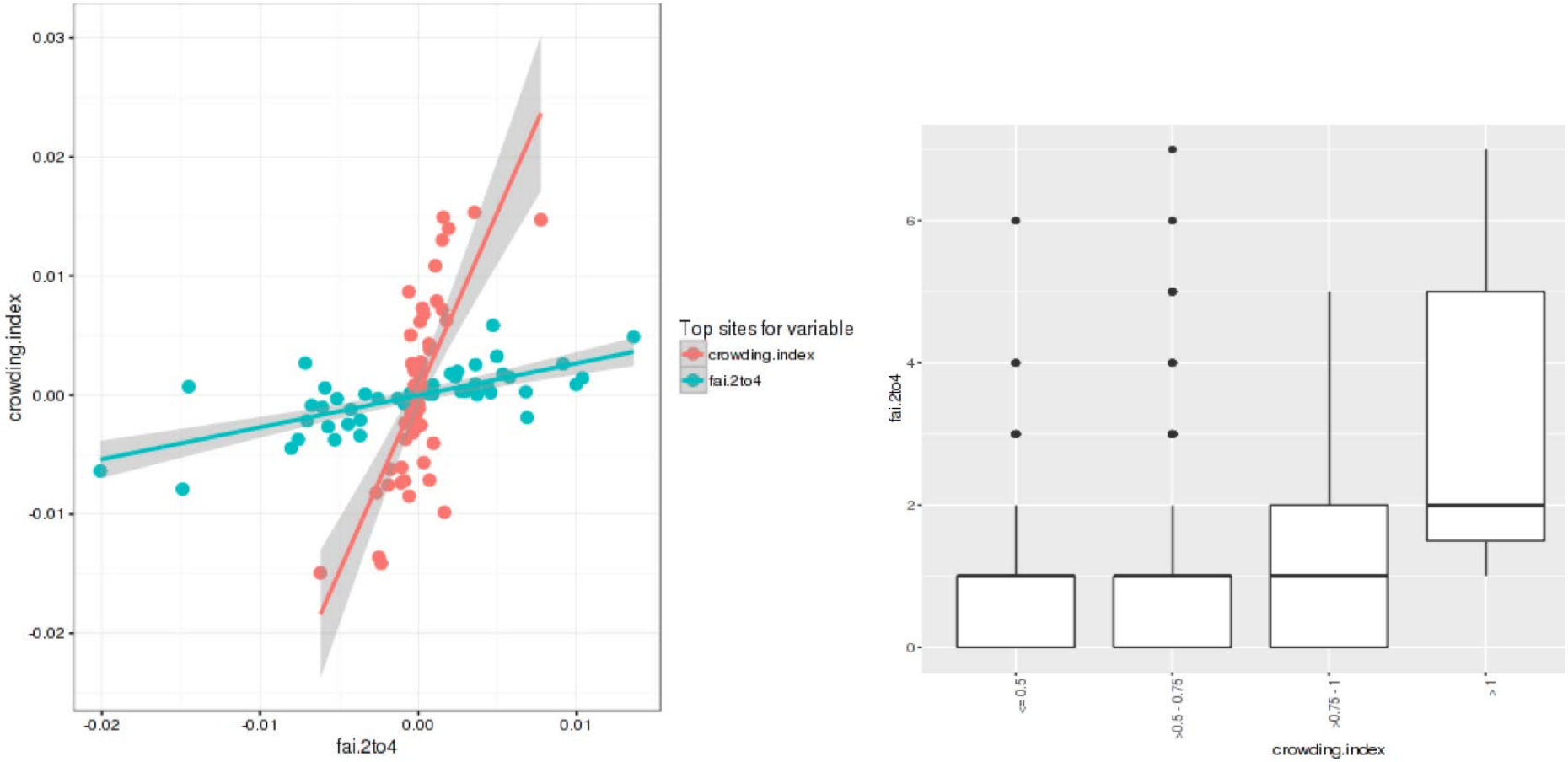
Correlations are identical for each subset corresponding to a time point in the ARIES DNA methylation dataset.

Figure S2: Genomic inflation distributions by model.



Under the assumption that most CpG sites are not associated with an SEP exposure, genomic inflation should be equal to 1, that is no inflation or deflation of significance levels.

Figure S3: Correlation of effect sizes for the top 50 associations for two SES measures: crowding index and family adversity index (2-4y).



Spearman's rho for each set of 50 associations is 0.68 between SES measures whereas the correlation between the measures is only 0.17.

Figure S4: Correlation between effect size correlations and SES measure correlations.

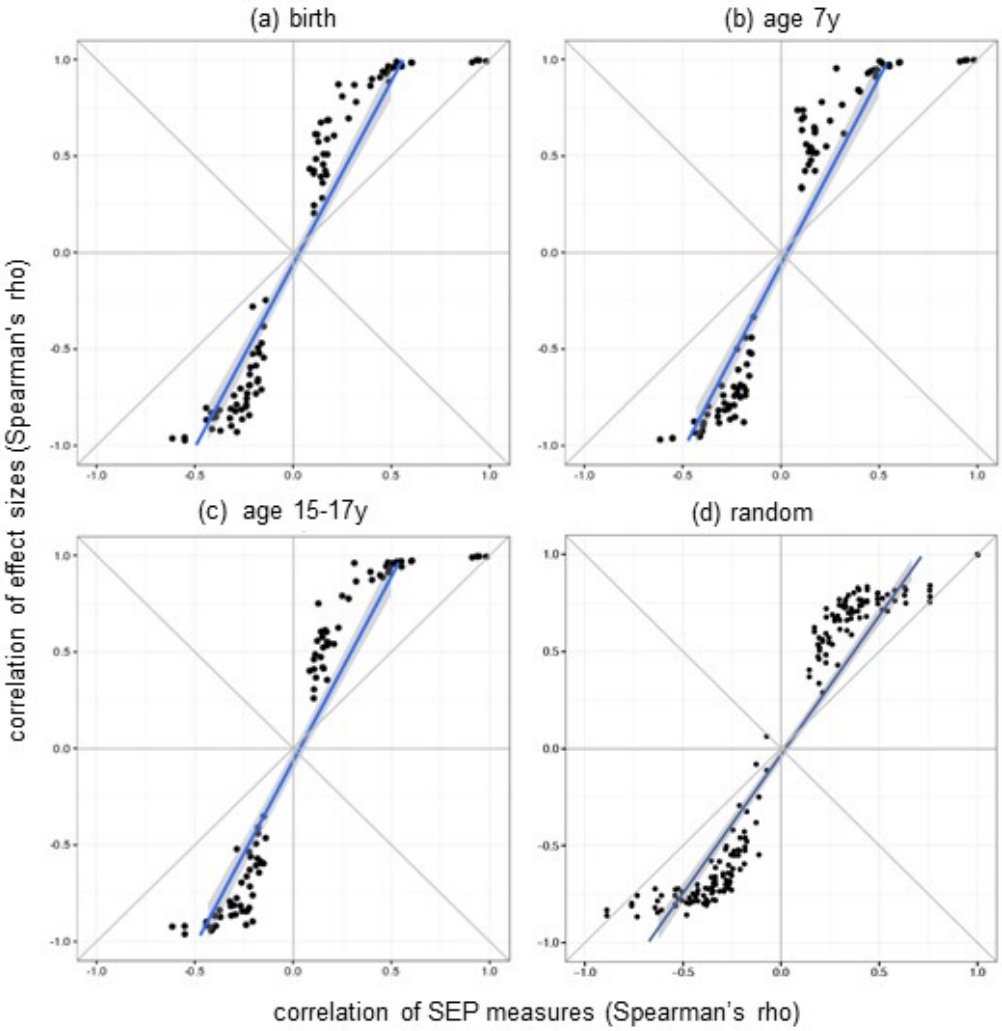


Figure S4

Notes for Figure S4. Each pair of SES measures is represented by a point in the scatter plot. The position of a point horizontally denotes the correlation (Spearman's rho) between the two SEP measures. The position of the point vertically denotes the correlation between the effect sizes of 50-100 CpG sites. The 50-100 CpG sites is the union of the 50 most strongly associated with each SEP measure in the pair. Each set of points is fit with a regression line contained within the 95% confidence interval. Plots (a)-(c) are derived from the blood DNA methylation collected at birth (cord blood), age 7y and age 15-17y. Plot (d) is derived from randomly generated data, DNA methylation from a uniform distribution between 0 and 1 and SEP measures from a standard normal distribution with random noise added to reduce correlation between measures.

Chapter Ten: Discussion

10.0 Chapter overview

This chapter brings together the findings from the studies in the prior six chapters. The aim of my thesis was to explore evidence for the association between socioeconomic disadvantage and ADHD. The findings of my studies contribute to the theory around both SES and ADHD as well as the links between them. In this chapter I will discuss the contribution of my findings to the conceptualisation and measurement of SES, as well as to the elucidation of mechanistic links between SES and ADHD. I go on to discuss how my findings add to the discussion of aetiology and nosology of ADHD. I will then discuss implications for clinical practice and social policy, an evaluation of the strengths and limitations of the PhD, and suggest avenues for future research.

10.1 Contribution to understanding the association between socioeconomic disadvantage and childhood ADHD

It is likely that SES is associated with ADHD through several of the putative pathways illustrated in Figure 1 in Chapter 3 (Russell et al., 2013). My mediation analysis showed that SES could potentially be mediated by exposure to cumulative adversities over childhood as well as parental involvement. These home and family environmental mediators are congruent with existing studies of the home environment and ADHD, particularly those focussing on enriched home learning environments for the child (Boe et al., 2012, Mulligan et al., 2013, Schmiedeler, Niklas and Schneider, 2013). It may be that providing a stimulating home environment and involved and educationally-focussed parenting protects children against some of the host of risk factors linked to low SES. My mediation analysis did not find maternal depression mediated the SES-ADHD association. This finding is inconsistent with previous literature that finds significant associations between maternal depression and ADHD (Kiernan and Mensah, 2009, Batenburg-Eddes et al., 2013). These studies however explore the role of maternal depression during pregnancy or close to birth: in my study I investigated exposure to maternal depression between the ages of two and six. It may be that, similar to my findings for SES, maternal depression exerts an impact on child development during a sensitive period, only in this case the period is earlier in the child's life than the sensitive period for exposure

to low SES. An alternate explanation is that maternal depression is closely tied to other indicators of psychosocial stress and therefore it is not predictive of ADHD over and above accounting for psychosocial stress as measured by financial difficulties, and a cumulative index of adversity (which does include one indicator of maternal mental health).

The findings from my studies do not rule out that the SES-ADHD association operates due to increased exposure to risk factors that mediate it. My mediation model only accounted for approximately 30% of the association between SES and ADHD in the ALSPAC and therefore other factors related to financial difficulty are likely to account for the remaining association. It is also likely that exposure to low SES in severe cases leads to altered neurological development. In addition, research has begun to show evidence for interactions between SES and genotypes that lead to an increased risk of symptoms of ADHD: much more work is needed before the extent of this relationship will be made clear. What is apparent is that SES is associated with the aetiology of ADHD through a host of mechanisms, and there is likely to be substantial heterogeneity between individuals with different genetic makeup and mixes of risk and protective factors.

The results of my studies utilising ALSPAC data provide interesting evidence that measures reflecting subjective financial stress (financial difficulties), instability (housing tenure) and likelihood of other common measures that comprise SES (younger maternal age, single parent status) are associated with an increased risk of ADHD. Furthermore, this SES-ADHD association operates differentially depending on the timing of exposure to low SES (birth to age seven), duration (a high proportion of time in low SES is related to higher ADHD symptom levels) and changing exposure to SES (those consistently out of difficulty having the lowest mean symptoms, those in either increasing or decreasing difficulty having higher mean symptoms and those consistently in difficulty having the highest mean symptoms).

My epigenetics study did not find evidence that experiences of low SES in a subsample of the ALSPAC were associated with substantial epigenetic differences in children. With exponential increases in the publication of epigenetics research, studies exploring the epigenetic profiles of children with ADHD may help to elucidate candidate areas of the epigenome that could be evaluated for their association with SES in order to draw a theoretical link.

Epigenetic markers on genes implicated in SES-gene interactions will also be relevant candidates to study.

The next step in further understanding this association would be to account for causal influences of parental ADHD, however this needs to be done in prospective, multi-generational studies. The Swedish health registers and linked cohorts may provide appropriate data through which this could be investigated, as they contain diagnostic and socioeconomic characteristics for individuals as well as links between parents and children: studies are already emerging from this group using sibling or cousin control designs to account for aspects of shared environment and heritability estimates (Larsson et al., 2013).

10.2 Contribution to discussion of conceptualising and measuring SES

My systematic review demonstrated that there is evidence for an association between low SES and ADHD, confirming the findings of Reiss (2013) in her more general review on SES and child mental health. My review revealed complexity in understanding this association: as SES is not a homogeneous concept and is commonly measured in a range of ways, a more detailed consideration of measures of SES that are associated with ADHD is needed. This will enable researchers to begin to understand the mechanisms by which the two might be associated

There is a body of literature (as reviewed in Chapter 2 of the Introduction), that focusses on measuring SES in health research, and the findings of my systematic review contribute to this (Hauser, 1994, Galobardes, Lynch and Smith, 2007, Braveman et al., 2005, Shavers, 2007). Galobardes, Lynch and Smith (2007) suggest that the choice of SES facet to include in a particular study should depend on the research question / hypothesis. Shavers (2007) discusses how the use of measures of SES in health research often depends on the data available rather than careful consideration of the facet to be measured. She also reports inconsistent results across the field of health disparities in relation to SES and that one explanation for this is the lack of precision and reliability of measures: something that I found in my systematic review. Shavers (2007) suggests that the choice of SES facet in individual studies should be based upon their hypothesised meaning and relation to the outcome being investigated, considering where and how SES may lie on the causal pathway. It is for this reason that I conducted one study with a broad

range of SES measures, then used the measure most strongly associated with ADHD in order to conduct more in-depth analysis of the SES-ADHD association.

Braveman et al. (2005) take this nuanced understanding of the complexity of SES one step further by bringing timing into the picture: they argue that different facets of SES affect different health outcomes at different points across the life course. They suggest this is commonly unacknowledged in studies that measure one indicator of SES at one point in time. Other studies are flawed as they do not detail the theory behind the choice of SES measure. I found this to be the case in studies included in my systematic review: measurement of SES was often ad-hoc and many studies had to be excluded because of the poor level of detail in reporting SES (either not saying what facet was measured or not reporting the breakdown of SES across the study sample). My study investigating the timing and duration of exposure to low SES contributes to understanding the impact of timing of SES in childhood and found that low SES in early childhood had a stronger influence on symptoms of ADHD across childhood than low SES in later childhood.

Galobardes, Lynch and Smith (2007) do however discuss that no single SES indicator will ever be considered “best”, as each have different meanings and are relevant to different health outcomes. In addition to this they argue that all measures of SES are inter-correlated and represent the same underlying concept: social stratification. Bradley and Corwyn (2002) published a discussion of measuring SES in child development. They introduce other facets of SES likely to be associated with child development: housing tenure and single parent status (although they consider this to be a risk factor that often co-occurs with low SES). Bradley and Corwyn discuss measures of SES within the framework of understanding the mechanisms or causal pathways that SES may be on. In the case of child development, these pathways may involve nutrition, maternal behaviours during pregnancy, and the differences between material and social resources (Bradley and Corwyn, 2002). In the studies that I conducted where I considered multiple measures of SES, I found evidence that a variety of SES facets have independent associations with ADHD. In addition, I found evidence that the timing and duration of the experience of socioeconomic disadvantage did impact on the association, supporting the theories discussed above and implying that careful interrogation of SES-health associations needs to be

undertaken to draw out the mechanisms through which they operate, for individual outcomes. Based on the findings from my studies, I agree with the theoretical approach taken by other researchers in the field: that the choice of SES facet is important in determining the pathways between socioeconomic disadvantage and ADHD, and that taking forward a specific measure of SES to investigate its association with ADHD in more detail adds more to knowledge and theory than if SES is considered as one broad dimension.

10. 3 Contribution of findings to theory of mechanistic links between SES and ADHD

The complexity in the meaning and measuring of SES required careful consideration when planning my quantitative data analysis. My systematic review found associations broadly similar in magnitude to those reported in the literature between income, education and single parent status and ADHD, but there was substantial heterogeneity in these findings. As it was apparent from the theoretical literature that different facets of SES may be differentially associated with ADHD through different mechanisms, I decided to include a range of SES measures in my mediation study in order to draw out precisely the measures of SES that are associated with ADHD and to elucidate theory on the SES-ADHD association.

In my mediation analysis I explored different measures of family SES when the cohort children were born in relation to those that received a research diagnosis of ADHD at age seven. Four SES facets were significantly associated with an increased risk of ADHD: rented or council housing tenure, single parent status, younger maternal age at study child birth and mother-reported financial difficulties. I will discuss each of these in turn in terms of what each facet of SES may reflect with regards to underlying socioeconomic position and how they may be on the causal pathway for ADHD.

Housing tenure

I found that in the ALSPAC population, families living in rented or housing association accommodation (as opposed to owning or having a mortgage on a house when the study child was born) was associated with a univariate increased risk of ADHD when the child was aged seven of 1.84 (1.22, 2.76). This was no longer significant in a multivariable model including the other

SES measures detailed in this section. Hauser reports housing tenure, along with income and education, as a powerful measure of SES for studies of child development (Hauser, 1994). Kiernan and Huerta (2008) consider housing tenure to reflect the economic circumstances of the family, and others consider it to be a better and more stable indicator of cumulative wealth than income (Laaksonen et al., 2005). Graham and Blackburn (1998) however suggest that housing tenure is not a sufficiently sensitive measure to gain real insight into the material circumstances of a family. As three out of ten single mothers live with their extended families, they argue that housing tenure measures reflect the wider family circumstances as opposed to those of the mother herself.

If the mechanism through which housing tenure is associated with ADHD is related to the household environment around the child as they develop, then this may explain why it appears to be predictive of ADHD. For example, Haste et al. (1990) found that rented housing tenure was a risk factor for poor dietary nutrient intake in pregnant women, and there are well known links between poor maternal diet and poor foetal outcomes. With regards to Graham and Blackburn's argument, it may also be that single mothers who live with their wider family are less at risk of this lower nutritional intake because of the social support and stability offered by their network of relations. A further model of SES and child cognitive and emotional development was proposed by Conger and Elder (1994): that of family investment. This model posits that material wealth is directly related to parents' ability to purchase materials and services needed to ensure optimal child development, and those of lower SES are less able to provide this quantity of quality of investment in their child (Kiernan and Huerta, 2008).

The study that my thesis stems from, using the MCS cohort in the UK, found housing tenure to be strongly associated with ADHD (Russell et al., 2013), and this was supported by my findings in the ALSPAC. These cohorts were born ten years apart but are both representative of the UK population, which suggests that the housing tenure-ADHD association is not due to cohort effects and my findings are directly applicable to enhancing the understanding of environmental influences on ADHD in the UK. Some have posited that housing tenure is associated with ADHD through direct toxicological mechanisms: for example children living in rented housing being more likely to be exposed to inferior building quality and higher levels of heavy metals such as

lead, which in extreme exposures is associated with symptoms common in ADHD (Yolton et al., 2014). Other proposed mechanisms are more applicable to what measures of housing tenure currently reflect in the UK. In an ecological stress process model of child mental health, Mohammad et al. (2015) discuss how housing instability can be one of a wide variety of stressors that may lead to increased child mental health problems.

Bronfenbrenner's ecological process model emphasises that factors proximal to the child are most influential in their early development (Bronfenbrenner and Morris, 2006). These include both people and the physical environment. I suggest that housing tenure is likely to reflect both instability in material wealth and therefore the physical resources parents can provide for the child, but also to be related to the stability of the home environment and family income: psychosocial stressors on the parents due to this could be associated with parenting mechanisms that either promote resilience or increase the risk of behavioural symptoms of ADHD.

Single parent status

In a report for the department of work and pensions (DWP) in 2001 titled "Families, poverty, work and care", a comprehensive overview was conducted of family structure and its relation to poverty and stability for families in the UK at the time. Lone mothers are more at risk of a wide range of outcomes that would lead to them being classed as low SES. Among these are that lone mothers are more likely to be living in rented accommodation and have lower income than two-parent families. The same applies to lone fathers (Millar and Ridge, 2001). The report states the importance of two adults earning income in order to keep families out of poverty: this is of interest as in prior decades women were culturally expected to stay at home and raise children (if they had any), yet in the last 15 years policy-informing reports make it explicit that both parents need to be economically active just to avoid poverty. It may be therefore that single parent families are not only likely to suffer from lack of material and economic resources, even if the parent works, but also that there is likely a high burden of psychosocial stressors on the parent, related both to material circumstances and the stressors that they are likely to experience in raising a child alone.

Kiernan and Huerta (2008) draw a link between single parent status and increased risk of maternal depression that is then associated with child behavioural problems. I did not find evidence to support this proposed mechanism between SES and ADHD in my mediation study, although single parent status was associated with a univariate increased risk of ADHD of 1.70 (1.09, 2.66), this did not hold after adjusting for the other predictive SES measures. I conclude that because of this, and in line with the wide confidence intervals of the effect size, it is likely that single parent status is associated with ADHD through the increased likelihood of exposure to other facets of low SES, and probably represents a higher burden of psychosocial stressors. In my mediation analysis, I found that maternal depression when the child was age between two and six did not mediate the SES-ADHD association, in contrast to the mechanisms proposed above (Kiernan and Huerta, 2008, Millar and Ridge, 2001), however a cumulative psychosocial adversity measure did mediate the association. This leads me to consider this cumulative adversity model a likely pathway through which SES increases the risk of ADHD. This adversity index included measures of housing quality and crowding, parental education, financial difficulties, relationship indicators (such as partner cruelty), criminal behaviour, substance abuse and maternal mental health.

This cumulative risk model (multiple factors accumulate to promote or mitigate the risk of the outcome of interest) has been proposed as being of importance in child mental health, and presence of increasing risks is associated with stronger associations with child mental health problems (Rutter, 1977). This ties in to the theory around the impact of children's early social and physical circumstances having lasting consequences for brain development (Kreppner, O'Connor and Rutter, 2001, Taylor and Rogers, 2005).

Maternal age at child birth

I investigated maternal age at birth as a predictor in my study as it has been known for several decades that older maternal age is associated with an increased risk of ASD, but little is known about links between maternal age and ADHD (Gillberg, 1980, Durkin et al., 2008). Maternal age at child birth is also likely to reflect underlying differences in SES, as younger mothers are less likely to have completed educational qualifications or have stable housing (unless they live with wider family). I found that the association of maternal age at birth

with child ADHD was no longer significant after adjusting for other SES factors. It has been found however that after adjusting for educational level and marital status, younger mothers remain at an increased risk of giving birth prematurely, having lower birthweight infants and being born small for gestational age (Fraser, Brockert and Ward, 1995). Birthweight is known to be closely intertwined with SES (Aber et al., 1997, Aizer and Currie, 2014) and is considered a viable mechanism through which low SES may lead to poor neurodevelopmental outcomes, although I controlled for birthweight in my analysis (Kroenke, 2008).The association between birthweight and ADHD has not been consistently reported (Crea, Chan and Barth, 2013, Rice et al., 2010, Tarver, Daley and Sayal, 2014), although studies find an increased risk of ADHD medication prescription in children born prematurely and to younger mothers (Lindström, Lindblad and Hjern, 2011). The authors of such studies discuss the impact on brain development of premature birth as being a causal influence in the development of ADHD.

Financial difficulties

In my mediation study with the ALSPAC I found financial difficulties to be the measure of SES most strongly associated with a research diagnosis of ADHD: children whose mothers report being in financial difficulty and struggling to afford basic necessities are twice as likely to receive a research diagnosis at age seven. I took this measure forward to further explore the relationship between financial difficulties and SES. Financial difficulties as a measure asks about the subjective experience of financial struggle, and represents not necessarily material wealth (as it does not ask about the material possessions provided, just how difficult it is to afford them), but is likely to tap into the underlying consequences of low income or unstable finances. I believe that this is likely to be a measure sensitive to the burden of stress caused by poor socioeconomic circumstances.

One potential mechanism through which stress, exacerbated by low SES could contribute to risk of ADHD is through prenatal exposure to cortisol, as it is known to cross the placenta during pregnancy (Aizer and Currie, 2014, Dadds et al., 2015). However, although a substantial body of research exists, there is no clear evidence to substantiate the theory that maternal exposure to stress during pregnancy leads to abnormal cortisol levels in the child that are then

associated with ADHD (Dadds et al., 2015, Isaksson, Nilsson and Lindblad, 2013). Further biological mechanisms through which stress could impact on child development include monoamine oxidase A (MAOA) and its interaction with genotype, environmental adversity and stress (Enoch et al., 2010, Goldman and Rosser, 2014). These research fields are emerging and there are no well-substantiated biological mechanisms that currently link early psychosocial stress with ADHD. Evidence linking brain development, early adversity and ADHD will be presented, in line with the findings from my mediation analysis that almost 30% of the SES-ADHD association was mediated by parental involvement and cumulative exposure to adversity.

In the section above I have outlined a wealth of theoretical links between how the association between different measures of SES and ADHD operates. Although my systematic review is informative it sheds no light on the potential causal relationship between SES and ADHD. However, my first quantitative study (study 3) brings to light underlying commonalities between SES measures that were found to predict ADHD: instability, likelihood of cumulative risks and exposure to adversity, which are likely to cause psychosocial stress to the family. I now move on to discuss current theory around the aetiology of ADHD and how the findings reported in my thesis contribute to a discussion of the nosology of ADHD.

10.4 Contribution to aetiology and nosology of ADHD

Current understanding of ADHD is heavily focussed on heritable factors that are thought to account for the majority of its aetiology (Faraone et al., 2015, Thapar et al., 2013, Tarver, Daley and Sayal, 2014). Most of these overviews of ADHD include information on researched environmental exposures that may increase the risk of symptoms: SES is commonly included in this list and has not been shown to be causal. My qualitative study (study 2) reveals that this scientific conceptualisation and understanding of ADHD is known by many educational practitioners. It is only one of several causal models endorsed by practitioners in relation to the children and young people with ADHD that they have experienced working with.

Theories of two distinct aetiologies of ADHD

Educational practitioners spontaneously put forward theories of the cause of ADHD that were clearly based on beliefs that factors associated with low SES (social and environmental deprivation) could strongly exacerbate symptoms of, if not cause, ADHD through instability at home and inconsistent parenting. That low SES plays a role in the level or severity of symptoms a child experiences has been supported by findings in my studies analysing existing data exploring timing, duration and changing SES (studies 4 and 5). My systematic review (study 1) and mediation analysis (study 3) demonstrate that there is also evidence that low SES increases the risk of a diagnosis of ADHD. It seems likely that the contribution of SES to the cause of ADHD is additive and interactive with genetic risk and likely other environmental risk factors. My study found that financial difficulty is associated with an odds ratio of around two for ADHD: figures similar to those cited for other risks (Thapar et al., 2013).

Educational practitioners raised a salient point about the nosology of ADHD when some individuals queried whether, if entirely caused by environmental factors, ADHD is in fact a misdiagnosis: practitioners believed ADHD as clinically defined to be due to genetic factors (they called this “pure” or “true” ADHD). I can interpret this as a misunderstanding of the fundamental definitions of psychiatric disorder as discussed in the Introduction, although this interpretation by the practitioners in my study is not in line with the belief that that there is a fundamental difference between the causes of mental and physical illnesses (Kendell, 2001). It appears that practitioners believe there to be two extreme types of ADHD, one that would fit into the “mental” illness category, caused by low SES and other social factors, and one that fits into the “physical” illness category, caused by genetics. It may be that practitioners infer that because ADHD is known to have genetic causes, this must represent it being a “true” disorder and therefore reasonable to label and diagnose. Practitioners are however untrusting that if ADHD symptoms are perceived to be caused by the environment they should be labelled or diagnosed as ADHD.

In the scientific literature this notion of environmentally-caused disorder is not new, but much of the focus has been around symptoms of ASD. In his seminal studies on the Romanian orphans who experienced severe early deprivation, Rutter (1977) noted that 12% of the children developed symptoms typically seen in ASD: something he termed “quasi-autism”. Longer durations in

the orphanages were associated with increased risk of autistic features. Recently, Webb (2013) has introduced a similar argument for ADHD, positing that “phenocopy ADHD” results from early experiences of violence and abuse that are factors more likely to be present in low SES households. There are two pertinent questions that stem from this: how might low SES lead to symptoms in children that mirror those found in children of high SES who have ADHD (presumed to be more heavily genetically-influenced)? And if ADHD can indeed be entirely caused by low SES, should it not be diagnosed (as ADHD)? I will discuss these in turn.

Mechanistic links from socioeconomic disadvantage to ADHD

An increasing body of evidence is finding support for the theory that symptoms of ADHD are due to a neurodevelopmental delay. Children with ADHD follow different neurodevelopmental trajectories compared with typically developing children, and there are some consistent differences in the physiology of the brains of children with and without ADHD. ADHD is associated with atypical neural connectivity (particularly in the Default Mode Network), a smaller total brain volume, less cerebral tissue and thinner cerebral cortex than in children without ADHD (Johnson et al., 2015, Lindström, Lindblad and Hjern, 2011, Shaw et al., 2007, Sripada, Kessler and Angstadt, 2014).

Recently, studies have been published that evidence the impact of early adversity and deprivation on neural development. Only one study has made an explicit link between lower cortical thickness, institutional deprivation and symptoms of ADHD, providing evidence that increased levels of ADHD symptoms in these children are attributable to thinner areas of the cortex that in turn are a consequence of institutional deprivation (McLaughlin et al., 2014). These findings are consistent with neurodevelopmental delay theory. Studies following the Romanian orphans cohort described above found smaller global volumes of both grey and white matter, and some differences in amygdala volumes in previously-institutionalised children compared with never-institutionalised children (Mehta et al., 2009). Studies of other children adopted from European orphanages find high levels of symptoms of impulsivity as well as potential structural differences in the uncinate fasciculus: the last white matter tract to mature in the human brain (Eluvathingal et al., 2006).

Follow-up study of the original Romanian orphans sample has demonstrated that symptoms of inattention and over-activity persist into adolescence. The authors describe this as evidence that there may be a critical period of neurodevelopmental programming early in life whereby the detrimental neurodevelopmental effects of deprivation become fixed (Stevens et al., 2008), as suggested by educational practitioners in study 2 (environment becoming biology). This is in line with the findings from my study that explore the role of timing in exposure to low SES: I found that experience of financial difficulties prior to the age of seven was associated with higher levels of ADHD symptoms both during that period and later in childhood, however later exposure to financial difficulties was not associated with symptoms of ADHD. My research supports this theory of a sensitive period of development where children are most vulnerable to the impacts of low SES early in life. Evidence on neurobiological effects of neglect and abuse in childhood was recently synthesised by Teicher and Samson (2016): they also conclude that there is emerging evidence for sensitive periods in neurological development, however focus their review on experiences of abuse and maltreatment, factors more common among those living in socioeconomically disadvantaged circumstances but not synonymous with low SES. The association between SES and ADHD is highly likely to operate through processes closely associated with low SES: my research suggests family and home environmental factors may confer some of this risk. Understanding of neurodevelopment in children in relation to parenting involvement and exposure to stressful family environments in early childhood may reveal the mechanisms through which the SES-neurodevelopment association operates.

Whether this different neurological development in children exposed to low SES is mediated by epigenetic pathways remains unclear. Teicher and Samson (2016) suggest that these differences can be interpreted as an adaptive survival response due to the known functions of the brain regions which were found to differ in maltreated children. This mechanism of adaptive response to the environment a child grows up in is congruent with Bronfenbrenner's ecological systems theory. A likely candidate for a biological pathway that disrupts normal brain development is epigenetically-mediated through oxidative stress, inflammatory or immune response biological pathways (Nigg, 2016). However, in my epigenetics study I did not find strong evidence

that facets of low SES are reflected in differential DNA methylation other than for 15 individual CpG sites and eight differentially methylated regions, on pathways not related to those mentioned above. This may be because of the relative lack of severe socioeconomic deprivation in the ARIES subsample, and also because of the lack of statistical power to detect small, consistent differences in CpG sites across the epigenome. Further studies to explore the hypothesised biochemical pathways, such as inflammatory pathways impacted via altered neurotransmitter synthesis (Nigg, 2016), could evaluate epigenetic markers at specific candidate sites and would have more power to detect differences.

Conceptualisation of ADHD, if it is caused by environmental factors

As put forward by some practitioners in my qualitative study, and supported by existing evidence, it is likely that low SES can be considered a close proxy for a risk factor, likely related to the psychosocial stresses experienced by parents, that contributes to the aetiology of ADHD in varying strength depending on other risk factors and genetic predisposition of the child. This theory of factors related to low SES exacerbating ADHD symptoms is supported by the results of my analyses of existing data exploring timing, duration and change in SES (studies 4 and 5): I found evidence for a sensitive period of exposure in early childhood (before age seven), and that experiencing low SES consistently across this period was associated with the highest mean ADHD symptom levels. I also found that there is some suggestion that changing SES circumstances result in higher mean levels of ADHD symptoms than for those who are high SES and do not experience changing SES. Those who consistently experienced low SES had the highest mean symptom levels. Whilst these findings are in line with the stance that low SES exacerbates symptoms of ADHD, I was not able to disentangle whether symptoms of ADHD are ameliorated by increasing SES.

The above evidence demonstrates that there are likely to be common neurological pathways and deficits that can be caused by low SES, and are found in children with ADHD from all socioeconomic backgrounds. It can be argued that children who are thought to have ADHD caused by their socioeconomic and environmental background should be diagnosed and treated in the same manner as children from high SES backgrounds presenting

symptoms. As the neurobiology behind ADHD is heterogeneous to some extent and as yet no form of neuroimaging is able to contribute towards a gold standard diagnosis for ADHD, opponents of my view could argue that this is currently unsubstantiated and further research is needed to establish common neurological pathways caused by experiencing low SES and leading to the expression of symptoms of ADHD (McLaughlin et al., 2014). As discussed in the Introduction, there is less quandary around diagnosis when genetic and environmental factors contribute differentially to physical illness: if someone experiences a myocardial infarction due to poor diet, smoking and other environmental factors, this is still considered to be a heart attack in the same manner as if caused by genetic predisposition.

Contribution to the contextual understanding of ADHD

The popular view of the aetiology of ADHD in the scientific literature was reflected by the practitioners in my qualitative study: participants frequently discussed how they had heard ADHD was “genetic” or “in the brain”. As described in Chapter 1, these beliefs reflect the focus of research on the aetiology of ADHD from the 1960’s: described as a move from social psychiatric approaches of understanding ADHD, which were largely unsuccessful, to a biological psychiatric focus from the 1970’s (Smith, 2008).

This historically reductionist approach to understanding ADHD has only relatively recently been contested, and within the last few years a variety of articles have been published expressly calling for a holistic, biopsychosocial approach to understanding ADHD (Richards, 2012). In addition to this, in the 1970’s concerns about “medicalisation” arose due to the increasing role of medicine in society, and the risk of pathologising normal human experience and fears of social control through the medical professions. This was followed by the era of genetic determinism, sometimes termed as “geneticism” (Hedgecoe, 1998); opponents to this approach have written prolifically about the need for multi-causal models of disease rather than endorsing simplistic beliefs that genes and disorders are genetically determined. This is becoming more widely applied in research on ADHD. Current evidence reflects that extremely complex gene-environment interactions can be elucidated: each of these interactions are likely to only contribute to a small part of the risk for a disorder such as ADHD, much like the influence of SES (Enoch et al., 2010, Ficks and Waldman, 2009).

The views held by the practitioners in my study were less complex than the current research understanding of the aetiology of ADHD, although did reflect some awareness of contributions of both genes and environment.

In spite of the increasing scientific knowledge and acceptance of the complexity of the aetiology of ADHD, a small critical psychiatry movement publishes books and papers arguing that ADHD is socially constructed (Timimi, 2005a, Timimi, 2005b). The publicity surrounding critical psychiatry theories and availability of colourful, appealing, practitioner and parent-targeted books may reinforce the perceptions described by the practitioners in my study: that although they hear or learn that ADHD is mainly genetically determined, they do not believe this to apply to the majority of the children they see. This leads to practitioners endorsing claims like Timimi's (2005a), who asserts that societal norms and lack of structured parenting has created a cultural problem where boys' (to some extent) normal behaviour is considered to be a medical diagnosis (see Chapter 1). Some have even argued that misreporting of studies by the media as well as misrepresentation (by omitting known facts or drawing inappropriate generalisations and implications) in research papers has fuelled the current lay-(mis)understanding of ADHD (Cortese, Faraone and Sergeant, 2011).

The implications of this are that up to date, evidence based knowledge on ADHD should be communicated to teachers and other educators that work with these children. It is plausible that different beliefs about the cause of a child's problem behaviour may lead to lack of referral to specialist services for children who could benefit from treatment, either psychological or pharmacological. If educators view children with symptoms of ADHD as having environmentally-caused hyperactivity they may not support referral of the child for assessment and diagnosis. One study has examined the effectiveness of a brief educational intervention with teachers, which they found improved teacher recognition of ADHD. However, the cause of ADHD was not one of the topics covered in the session (Sayal et al., 2006). The authors also did not present information on SES of the children involved so no conclusions can be drawn about whether there is a bias against identification of children of low SES or children whose problems are believed to be caused by the environment.

Another study conducted in the USA found that when asked, teachers who described problem behaviour not as ADHD stated in some cases that this

was because they were “attributing the child’s problem behaviour to environmental factors”. Twelve of the 21 teachers responded to a question about why the child had behaved the way they had described this as being due to environmentally-based factors, and several endorsed this environmental-cause view in addition to knowing the child had been diagnosed with ADHD (Arcia et al., 2000).

Discussion of the role of gene-environment interactions in the aetiology of ADHD

One recent US study has found evidence for gene-environment interactions between SES, measured by parental education, and inattentive symptoms of ADHD. The authors find evidence to support a diathesis-stress model of ADHD whereby genes that confer risk have much stronger effects in environments that confer psychosocial risk, potentially through epigenetic modification of gene expression (Rosenberg et al., 2012). This could explain why children in low SES circumstances have an increased symptom level relative to those not in low SES families: if the distribution of risk alleles is equal across the population then only those exposed to increased psychosocial risks will be detrimentally affected by this. Interestingly, the authors controlled for parental ADHD symptoms and found that education had an effect over and above this (Rosenberg et al., 2012). However, a more recent study finds conflicting evidence when exploring the role of the family environment and its interaction with the 5HTTLPR genotype: that there is evidence for differential susceptibility (if you have the risk genotype you are more susceptible to both positive and negative environmental experiences in exacerbating or ameliorating associations), in relation to family conflict and cohesion on inattentive symptoms of ADHD (Elmore et al., 2015). These findings illustrate that gene-environment interactions may vary widely between candidate genes and environments, risk and resilience may be differentially promoted by different gene-environment interactions and the construction of a complete picture of the interaction between SES and early environments and ADHD has only just begun.

It is likely that SES also has differential influences on ADHD through interaction with susceptible genotypes as well as through rare genetic variations

that contribute to the risk of ADHD (Thapar et al., 2015). One study has directly investigated SES as a moderator of the relationship between the BDNF gene and ADHD (Lasky-Su et al., 2007). Other environmental exposures such as parenting involvement levels may mediate the SES-ADHD association (Nigg, Nikolas and Burt, 2010): I found evidence for this in my mediation analysis. In a review of gene-environment interaction studies on ADHD, Nigg, Nikolas and Burt (2010) conclude that there is evidence for a genotype-environment interaction on ADHD when psychosocial factors are the environmental exposures. Environmental exposures which they found to be associated with genotype (mainly DAT-1 and 5-HTT) interactions were psychosocial adversity (often containing factors reflecting SES such as income), marital instability and parenting or home environment, reflecting putative pathways between SES and ADHD. In contrast, the authors found little evidence for replicable gene-environment interactions in prenatal exposures such as to maternal smoking and alcohol consumption during pregnancy (Nigg, Nikolas and Burt, 2010). Subsequent studies have found conflicting evidence, one reports evidence for a gene-environment interaction between low birth weight, genetic risk of three dopamine genes and ADHD (Jackson and Beaver, 2015). Since the publication of Nigg, Nikolas and Burt's review, one study has found evidence for an interaction between the MAO-A genotype, and found that negative parenting predicted inattentive symptoms only for those who had the high activity MAO-A allele. Positive parenting was not moderated by MAO-A genotype (Li and Lee, 2012). This provides evidence for differential susceptibility to risk factors in individuals with particular alleles that could lead to increased risk of (inattentive type) ADHD.

There are two points from these findings that are of interest. Firstly, there is little current evidence for pre- or perinatal gene-environment interactions on ADHD. This is in line with my findings that SES exerts an effect on ADHD symptoms across early childhood rather than the effect being fixed at birth. Secondly, most of the substantive findings outlined above find associations with the inattentive symptom domain of ADHD. It is possible that there is a different pattern or strength of association for hyperactive-impulsive symptoms, or that inattention is heavily genetically influenced whereas hyperactivity may be more responsive to the environment. It is also of interest that the most common forms of ADHD are the combined subtype (both hyperactive/impulsive and inattentive

symptoms) and the inattentive subtype, very few children are diagnosed with ADHD presenting only hyperactive/impulsive symptoms (Ford, Goodman and Meltzer, 2003). Whether this represents a baseline genetic risk for inattention and environmental exacerbation of hyperactivity is unclear and would need further research to determine. If this is the case, as hyperactivity does not often occur without inattention, studying the early lives of children with the hyperactive/impulsive subtype may elicit evidence as to whether this profile of ADHD may be more heavily environmentally and socially influenced and thus whether there may be different treatment indications for clinicians depending on a child's symptom profile.

10.5 Implications in the context of Bronfenbrenner's bioecological systems theory

As outlined in the Introduction, Bronfenbrenner's bioecological systems theory continues to be a useful framework for understanding the findings of my studies (Bronfenbrenner, 1994, Bronfenbrenner and Bronfenbrenner, 2009, Bronfenbrenner and Morris, 2006). I find evidence that the environment around the child does impact on their likelihood of a diagnosis of ADHD and symptom levels. As I have found different associations by pattern of changing SES in families, this suggests to some extent that modification of the environment may lead to decreases in symptoms of ADHD. I argue that the findings from my studies support the emerging notion of SES as a proximal risk factor for ADHD, not a distal one as it has long been described (Kelly, Kelly and Russo, 2014).

Environmental changes, because they are linked to SES, could be made at a variety of levels within Bronfenbrenner's model. Alleviating financial pressures for families with young children is likely to improve a host of environmental factors around the child, not least those proximal interactions between the child and parents that are key in shaping behaviour and development. Parents that have less financial pressure are more likely to provide a stable, stimulating home environment for their child. This may have impacts on ADHD symptoms at an individual level, but also leads to the question of whether targeting more distal layers of Bronfenbrenner's model that relate to SES (society, culture and policy) may have a wider and more substantial impact on ADHD in the UK.

Implications for clinical practice

As I found that financial difficulty at birth is associated with double the risk of ADHD at age seven compared with the risk for children whose families are not in financial difficulty, clinicians should be aware of the impacts of psychosocial and environmental factors on health. SES should be considered a risk factor for ADHD, however if a family has experienced pervasive poor socioeconomic circumstances then, based on my findings, it seems unlikely that these impacts on ADHD would be easily reversible, especially if the child is over seven years old. If children do have altered neurodevelopmental trajectories due to chronic low SES, then the understanding of their presentation of ADHD should be considered by clinicians to be as pervasive as for other children from more affluent backgrounds.

If, however, a child displays increased symptoms of ADHD following a change in family socioeconomic circumstances and is still within the sensitive window prior to age seven, interventions to reduce psychosocial stressors in the family may well ameliorate symptoms. Interestingly, there is limited evidence for effective psychosocial interventions for children with ADHD, with only four well-established treatments (Evans, Owens and Bunford, 2013). Parenting interventions are found to be associated with a reduction in ADHD symptoms and this adds weight to the theory that the mediating processes between SES and ADHD operate via parents (Coates, Taylor and Sayal, 2014). Targeting psychosocial treatments for those with higher levels of socioeconomic deprivation at family level may be more effective than recommending interventions for individual children with ADHD. The effectiveness of these treatments for such children would however still need to be established before becoming a clinical recommendation, and there are likely to be barriers to delivering effective psychosocial treatments to families that do not have many socioeconomic resources, as well as challenges around parenting interventions for child ADHD when parents also have ADHD (Ellis and Nigg, 2009).

Implications for social policy

Low socioeconomic status is associated with a broad range of negative health outcomes across the life course. This has been acknowledged widely since the Black report in the UK, and emphasised more recently with the Marmot report (Black, 1982, Marmot, 2005). Marmot (2005) cites factors

relevant to my findings as key social determinants of health: stress, early life and unemployment. Sweden has introduced policy changes committing to reducing social inequalities in health, and the UK has identified reducing health inequalities as a key policy, and one that will likely impact on the SES-ADHD association. However, a subsequent analysis of these two countries emphasises that the health of lone mothers is still poor in both, and in the UK half of this disadvantage is related to poverty (Whitehead, Burström and Diderichsen, 2000). The economic recession in 2007 led to the UK adopting a policy of austerity: the detrimental impact this has had on mental health of the nation has been highlighted in comparison to countries that responded to the recession with economically-stimulating policies. It may be that conclusions drawn from my studies are applicable to families currently with young children, as there was also a recession in the UK in 1990-1991. Importantly, it was found that although the health of well-educated women improved during the most recent recession, women with low educational levels experienced declining health during the same period (Copeland et al., 2015).

The UK committed to a plan of reducing health inequalities in 1999, and some policy interventions such as Sure Start programmes that focus on the importance of young families and supporting those in low-income families are directly applicable to the SES-ADHD association. In 2003, the English strategy put billions of pounds into improving maternal and child health, reducing underlying poverty and improving life chances for children. These policies were however largely ineffective at reducing inequalities, and income inequality remained unchanged (Mackenbach, 2011). In 2010, a further Marmot report outlined six policy objectives to target health inequalities, all involving maximising socioeconomic opportunities for everyone, and emphasising the need for action at all levels of society and policy (Marmot et al., 2010). Interestingly, in recent advice for schools issued by the Department for Education, socioeconomic disadvantage is listed as a community risk factor for poor mental health, rather than a family-level risk. The Department of Education report emphasises the limited resources of child and adolescent mental health services and suggests that schools may even wish to commission their own specialist services (Department of Education, 2015).

Budget cuts to public health are planned to continue annually with 3.9% of the budget due to be cut each year until 2020. This is resulting in cuts to

crucial services such as those around child mental health. If this continues then it is likely that the association between socioeconomic disadvantage and ADHD will perpetuate and even increase as those who rely most on social welfare, low SES families, will be hit the hardest by cut backs to services that are essential for their wellbeing. These reforms are particularly relevant to the findings of my thesis that contribute to growing evidence for causal associations between socioeconomic disadvantage and mental health problems such as ADHD.

Reports of increasing prevalence of child mental health problems in the UK reinforce the need for policies targeting reduction of socioeconomic and other adversities for families with young children (The Guardian, 2016). Policies that support single parent families and alleviate financial stress for those living under conditions of housing instability and poor economic circumstances are likely to lead to a decrease in severity and potentially prevalence of childhood ADHD. There is currently a lack of knowledge of the most effective ways to address these issues, and further research is needed in this area, perhaps by exploring differences in child mental health across countries with different forms of social welfare policy.

These population-level approaches are needed, especially in light of the demographics of the UK population. The national focus on the impending burden of an ageing population is crucial, however there is a risk that the generation of young adults that will be required to support the older generation will have a high prevalence of impairing mental health problems. This will be exacerbated if there continues to be insufficient funding for mental health, austerity measures that freeze or remove child and other benefits, and increasing economic inequality in the UK. Whilst there are many avenues to explore that could address these concerns, a global approach to mental and physical health and a detailed understanding of the layers of biological, social and environmental factors that contribute to this will be critical for success.

Whilst research into epigenetic and genetic mechanisms that may underpin the translation from environmental risk to biologically-based psychiatric disorder is valuable and of interest, it removes the focus from holistic environments that can be improved to individual “personalised” treatment for disorder. The rationale for studying and understanding the aetiology of ADHD is ultimately to understand how we can prevent, effectively treat, or minimise the risks of children developing impairing levels of symptoms: something that can

only be done by addressing both the proximal and distal environments involved in child development.

10.6 Strengths and Limitations of Methodologies

The studies in my thesis use four methodologies to explore the association between family SES and childhood ADHD. Each has strengths: consolidation of existing research on the association allowed for an understanding of the complexity of the association and began to provide evidence that an association between SES and ADHD has been found across countries and cohorts. Analyses of existing data using the ALSPAC allowed for the association to be investigated in more depth in the UK context, and conclusions that are drawn result from data from thousands of individual families and are likely to generalise across the UK. Conducting a qualitative study added depth and understanding of implications for the findings of the other studies. By incorporating the beliefs and understanding of those who work with children with ADHD, quantitative findings could be extrapolated into the impact they have on debates around the nosology of ADHD.

I chose the ALSPAC for the majority of my analyses as not only did they measure SES in a wide variety of ways, they did so longitudinally across childhood with repeated measures of some SES measures and of ADHD symptoms. This meant I could construct longitudinal models investigating mediating effects, as well as test sensitivity to SES across time relative to ADHD symptoms across childhood. The main limitation of the ALSPAC data is that I could not control for parental ADHD or genetic ADHD risk, thus my findings do not infer causation. However, the longitudinal design of my empirical studies does to some extent account for this, although only if genetic effects are fixed in their impact on ADHD, something that seems unlikely given the emerging evidence for gene-environment interactions in susceptibility to ADHD. It may be that it will not be possible to ever untangle these influences, nor should we if a reductionist approach does not reflect the natural complexity of their interactions (Thapar et al., 2013), but understanding of small, separate pathways that can contribute to the development of ADHD raises possibilities for effective prevention and intervention targets. An additional limitation is that attrition in ALSPAC is more frequent for those who are of low SES and who have children with high levels of mental health symptoms (Wolke et al., 2009).

Longitudinal methodologies are stronger than cross-sectional designs, and although cross-sectional studies may capture the relevant measures, they do not have the power to investigate the direction of associations. Longitudinal designs are a step closer to being able to infer cause and effect, although I could not account for genetic confounding. Cohorts with similar repeated measures following children that are adopted as well as living with their birth parents may be useful designs for subsequent work, and some studies have recruited families that have used surrogate mothers in order to tease apart the links between genetic influence and the pre and peri-natal environments: sample sizes of these populations are however very small (Thapar et al., 2009). Another avenue for further investigation is the use of population registers such as those analysed in the quasi-experimental studies conducted in Scandinavia: these have routinely collected data on most of the population and can be linked across families, however often do not include the precise data that the researcher may be interested in (e.g. having diagnostic codes for ADHD but no information on symptom levels) (Larsson et al., 2013).

Using a sub-sample of the ALSPAC population to investigate putative causal pathways in which SES might impact on biological systems and neurological development allowed me to infer whether epigenetic mechanisms involving DNA methylation was a likely pathway. I did not find strong evidence for this, and there are limitations to the approaches currently used in epigenome-wide association studies, as well as the ARIES sample having relatively small numbers of severely socioeconomically deprived individuals. Further research into areas of the epigenome that are thought to be biologically linked to the expression of ADHD and sensitive to environmental interactions may yield more promising findings, such as the MAO-A gene. If low SES and ADHD are characterised by overlapping neurodevelopmental abnormalities, it may be that exploring epigenetic pathways involved in neurodevelopment are a good target for future research.

I also focussed most of my quantitative analysis on one SES predictor of ADHD: financial difficulties. As literature in the field argues that choice of measure of SES should be based upon individual research goals, my choice was appropriate as I found financial difficulties to be the strongest SES predictor of ADHD. However, this limits the generalisability of my findings to other facets of SES, and contributes to the heterogeneity of SES measures commonly used

by researchers, making it difficult to synthesise parallel findings across populations meaningfully. In three studies I do investigate a range of SES facets: my systematic review (study 1), mediation analysis (study 3) and epigenetics study (study 6) explore a range of SES measures. These findings therefore make a broader contribution to understanding SES and ADHD, or the pathways through which SES might exert effects on health and development.

Consideration of intergenerational transmission of SES and parental ADHD

One limitation of the ALSPAC dataset is that there is no measure of parental ADHD. This section will provide a brief overview of the limitations of this in relation to the findings of my analyses of existing data and considerations for future studies exploring the impact of parental ADHD.

ADHD is currently known to be both highly influenced by heritable factors and is now considered to persist into adulthood in a high proportion of those with childhood ADHD (Faraone et al., 2015). It is increasingly understood in a biopsychosocial aetiological framework that recognises the multiple influences that contribute to its aetiology. It is however difficult to disentangle whether the SES-ADHD association observed in my studies is due to social selection because the parents of the children with ADHD are also likely to have ADHD and thus are less likely to have completed higher educational qualifications or hold stable employment (Russell et al., 2013), or whether the impact of the family environment during childhood causally impacts on child risk of ADHD independent of parental ADHD. Using longitudinal data is a strength as it allowed me to explore the association between SES and ADHD across childhood, and my findings show that there is evidence to support a dynamic SES-ADHD association. This could theoretically be reduced by improving the SES of families with young children, but further research would be needed to determine whether this is an effective intervention. If symptom levels are shown to be lower across childhood in families that have a reduced socioeconomic burden in spite of the complex interactions through which SES exerts its effects on ADHD, then there could be a societal-level method for reducing prevalence of impairing levels of symptoms.

A recent meta-analysis estimated that 21% of children with ADHD have a parent with ADHD. Other psychological disorders are also more common in

parents of children with ADHD than parents of children that do not have ADHD (Cheung, 2015). Whether adult ADHD is a persistence of child ADHD has also recently been contested: Moffitt et al. published a surprising study last year analysing adults from the Dunedin cohort born in 1972-3. The authors use the longitudinal data to follow children with symptoms of ADHD forward, and adults with symptoms of ADHD backward. Their results challenge the assumption that ADHD in adults is a result of persistence of childhood ADHD: in their sample 90% of those with adult ADHD did not have a childhood history of ADHD (Moffitt et al., 2015). This not only has implications for the conceptualisation of ADHD as a childhood-onset disorder, but it also has implications as to the use of accounting for parental ADHD symptoms when studying child ADHD, if it cannot be determined whether parental ADHD symptoms have had onset in childhood. Of interest is that those with adult-onset ADHD did not show the same neurocognitive impairments as individuals with childhood-onset ADHD. This expands my discussion of the classification and nosology of ADHD in children exponentially, and more research needs to be done prior to drawing conclusions about whether the adult-onset constellation of ADHD symptoms is sufficiently different from child-onset profiles to be defined as a different disorder (Castellanos, 2015).

The findings of Moffitt et al.'s (2015) study have challenged the commonly-accepted view of childhood ADHD persisting into adulthood and accounting for all cases of adult ADHD. A discussion of the DSM-5 criteria for diagnosing adult ADHD is beyond the scope of my thesis, however there are also implications from Moffitt et al.'s findings for the diagnostic criteria currently used for adult ADHD.

A meta-analysis exploring persistence factors in ADHD identified four studies that stratified their samples by SES. Three found no difference in persistence rates for children of differing SES. This suggests that it is not likely that ADHD persistence is strongly related to SES. Therefore children with ADHD who are low SES are not more likely than other children with ADHD for their disorder to persist into adulthood, and thus may not be more likely to have children also with ADHD born into low SES circumstances (Caye et al., 2016). Social selection may not operate through this route however: it is commonly thought that the impact of ADHD leads to young adults with the disorder who are at risk, not completing their education, having poor occupational outcomes

and therefore are more likely to slide into lower socioeconomic strata (Russell et al., 2013). They are then more likely to have a child with ADHD themselves. There are subtle differences between these two mechanisms of social selection: in the first mechanism, low SES contributes to severity and persistence of ADHD, which with a combination of genetic susceptibility leads to an intergenerational cycle of persistent ADHD and low SES. However in the second mechanism, all those with childhood ADHD are at risk of becoming low SES and then having children with ADHD born into these socioeconomic circumstances.

This could be disentangled by following children with ADHD and their families across generations: in light of Moffitt et al.'s (2015) findings, recruiting or assessing ADHD from adulthood may not be sufficient and so prospective longitudinal studies, starting with children, and following through to the outcomes of their offspring in the next generation are needed to fully understand this relationship. ALSPAC has begun to recruit the children of the original cohort (known as CoCo), however as ADHD is not a highly prevalent condition and only 175 children were originally diagnosed with ADHD this cohort may lack the power needed to tease out the intergenerational SES-ADHD mechanisms. Interestingly, the systematic review of the persistence of childhood ADHD finds varied rates of persistence, from 11-79%. There was some evidence to suggest that these effects were stronger for the inattentive subtype of ADHD, adding weight to the theory that this constellation of symptoms may be more genetically determined than hyperactive-impulsive symptoms. Many of the included studies however prospectively followed clinical samples, and all included population-based studies had a retrospective design (Caye et al., 2016). In light of this and Moffitt et al.'s (2015) findings it is clear that prospective, community based studies are needed to untangle this relationship.

With regard to the sample used for my studies, it can be argued that accounting for parental ADHD would not necessarily control for genetic predisposition to ADHD but more for parenting factors that could be impaired for adults with ADHD (Harvey et al., 2003). Whilst it would have been of interest and a useful confounder to control for, the conceptual nature of my studies focussing on timing, duration and change in SES purposely did not control for a variety of confounders known to be related to SES: parental ADHD could be

argued to be one of these. The purpose of my studies on timing, duration and changing SES was to begin to shed light on the relationship between the complex heterogeneous concept of SES and its relation with ADHD. This has implications for health inequalities in the UK and the severity of ADHD symptoms, and policy-level approaches to alleviating socioeconomic pressures on families with young children may address some of these mechanisms without the need for specific elucidation of precise risk pathways. I also investigated a range of putative mediators of the association, and cumulative presence of adversity was the mediator most strongly associated with the SES-ADHD pathway. This fits in with the diathesis-stress model of ADHD whereby increasing adversities are related to increasing detrimental effects of environmental influences on symptoms of ADHD (that may interact with risk alleles).

10.7 Future research

I have alluded to areas for future research in previous chapters and above, this section summarises designs and research questions that follow from the work in my thesis.

Limitations of the studies included in my systematic review highlight the need for clear and consistent reporting of results around SES, even if they are not the main focus of the study, and the use of comparable measures across studies. With the advent of open-access and data sharing policies, it may be that future reviews can access individual data from studies that allow for a coherent evaluation of existing evidence on SES associations with health. Initiatives such as the CLOSER data harmonisation programme should be expanded and publicised to researchers in the field, however future research should also use theoretically informed choices of SES measure depending on the outcome of interest.

Educational practitioners in my qualitative study believed ADHD that is diagnosed but perceived to be caused by the environment to be a misdiagnosis. This has striking implications as to whether these beliefs impact on the recognition and referral of children from low SES families exhibiting impairing levels of ADHD symptoms, and this should be further researched. Further work should also be done to determine whether severely disadvantaged children do meet full criteria for ADHD or whether their symptoms should be considered to

be reflective of a “quasi” or “phenocopy” ADHD that might be best and most effectively treated with different approaches to those currently endorsed.

Following my series of analyses with the ALSPAC, it is clear that there is a need for further research into how and why SES is associated with ADHD. There are a wide variety of avenues for further research: studies exploring the development of children that have grown up in the most socioeconomically deprived circumstances will allow researchers to determine whether the SES-ADHD relationship is strong and robust (especially as the ALSPAC sample is relatively socioeconomically advantaged in comparison to some populations). It could be that the association I found between SES and ADHD is driven by a small number of individuals that experience severe deprivation.

Thorough and frequent collection of repeated measures of SES and ADHD symptoms are needed in order to identify whether changing SES really does lead to exacerbation or amelioration of ADHD symptoms, and if so, the timings and trajectory of symptom change may inform the mechanisms by which this association operates. As data in ALSPAC were collected somewhat ad-hoc for the first years of the children’s lives, I was not able to establish this.

Studies that have prospectively followed children into adulthood and then enrol the next generation (their children) into the cohort are likely to be powerful in untangling the impact of parental ADHD on SES and child development. This will be complex for studying ADHD as diagnostic definitions and recognition of impairing levels of symptoms change over time, leading to varied prevalence estimates. Additionally, epidemiological cohorts have a prevalence of childhood ADHD of around 1.5% in the UK (Russell et al., 2013). Therefore, selective sampling of children at risk for ADHD or other developmental disorders will allow for a larger sample of second-generation children.

My epigenome-wide association study did not replicate the results of other published epigenetics papers investigating SES. The heterogeneity between studies and findings likely reflects the infancy of the field, and further understanding of the epigenome as well as methodological improvements should yield more informative results in the future. In the meantime, focussing epigenetic research on target genes, particularly those implicated in studies finding gene-environment interactions relevant to SES and developmental disorders, may provide additional insight into the SES-ADHD relationship. In addition, investigating epigenetic profiles of children growing up in conditions of

severe socioeconomic deprivation may highlight likely epigenetic differences more than in the relatively un-deprived ARIES sample.

The studies in my thesis did not manage to elucidate precise mechanisms by which SES may exert its effects on ADHD: the most sensitive measure appears to reflect financial and potentially psychosocial stressors, and the association was mediated by cumulative adversities and parental involvement in child activities. Two of these factors appear to be closely related to stress, which may exert effects through either stress-mediated biochemical pathways, or through environmental impact on neural development. Further research into both of these avenues is needed, although I anticipate that research focussing on neurodevelopmental delay in socioeconomically deprived children and children with ADHD will be most fruitful. If it can be determined that experiencing socioeconomic disadvantage promotes abnormal brain development that parallels those found in children with ADHD (even from high SES backgrounds), SES can be considered to causally contribute to the neurological manifestation of ADHD. This would have massive implications for the importance of early intervention and policy for families in disadvantaged circumstances with young children, especially if future research confirms these effects are fixed by the age of seven.

10.8 Conclusion

My thesis presents a body of research that adds to the scientific knowledge of the association between socioeconomic disadvantage and childhood ADHD. It has added to the emerging evidence that SES exacerbates predisposition to ADHD symptoms. I did not find evidence that SES is likely to have had a large impact on epigenetic profiles of children, and believe that the association is largely mediated by family psychosocial stressors impacting on neurodevelopment through pathways related to the home learning environment and suboptimal conditions for healthy child development. SES should be considered a small but significant contributor to the risk of ADHD, similar to identified risk genes and gene-environment interactions, all with small but cumulative impact on the risk of developing ADHD. As educational practitioners believe ADHD that is diagnosed, but perceived to be caused by the environment, as a misdiagnosis, further work to determine whether this impacts on referral or treatment of disadvantaged children needs to be done to ensure those who would benefit from treatment for symptoms of ADHD do not miss out.

Appendices

Contents

Appendix 1

Systematic review protocol

Systematic Review	
PROJECT TITLE: Is there an association between Attention Deficit/Hyperactivity Disorder or hyperactivity in children and family socio-economic status? A Systematic Review	
Project team:	Abby Russell (née Higgins) Ginny Russell Tamsin Ford Rebecca Williams
Project Advisors:	Evidence Synthesis Team
Version/date:	Version 1.1 5th November 2013
Correspondence	Abby Russell (née Higgins) a.e.higgins@exeter.ac.uk

Project Title

Is there an association between Attention Deficit/Hyperactivity Disorder or hyperactivity in children and family socio-economic status?

Questions

- Is there evidence for an independent association between ADHD (or hyperactivity/ inattentive profiles) and low SES?
- Does this association exist independently of between-study variables, e.g. culture, diagnostic assessment used?
- Does this association appear to vary across different developmental stages?

1.1 Decision Problem

There have been several studies that have found an association between ADHD and low socio-economic status (Ford et al., 2007a, Döpfner et al., 2008, Froehlich et al., 2007). This review will systematically investigate whether this association does indeed exist, and the factors that influence it.

1.1.1 Purpose

Various studies investigating both risk factors for and prevalence of ADHD have commented on the increased prevalence in children from disadvantaged backgrounds (Thapar et al., 2013, Pastor and Reuben, 2008, Sauver et al., 2004, Paananen et al., 2013). As yet, no study has systematically evaluated these claims so it is currently unclear whether this is indeed a true effect, due to selective reporting or indeed a common misconception. The topic is difficult to evaluate due to the heterogeneity of measures used in this field- ADHD is often diagnosed in a variety of ways, and socio-economic status (SES) is often reported as an index calculated from several measured variables, or as one or many of these variables.

The systematic review will examine the variety of measures and quality of evidence linking ADHD and measures of SES, and if sufficient data is available a meta-regression will be carried out to generate an overall effect size.

1.1.2 Exposure

Studies which provide a clearly stated measure of SES of the family of origin (i.e. the family with which the child is/has grown up) will be included. Those which use

an index of a combination of variables will be included if the authors explain how the index was derived. Measures of SES include, but are not limited to, family income, unemployment, poverty index, index of multiple deprivation and parental education.

1.1.3 Population

The review will examine ADHD-diagnosed or clinically impaired hyperactive children, adolescents and adults. The age range of study participants will be discussed in the review due to theoretical considerations of the validity of a diagnosis at a young age (as hyperactive behaviours are known to be present in typically developing toddlers and young children); however as it is not yet clear at what age relevant studies include participants, such papers will not be excluded based on young age until thorough examination.

Similarly, there are few studies in the field that examine ADHD symptoms in adults, however these must be identified in order to examine whether any association with low SES continues throughout the life course.

1.1.4 Comparator N/A

1.1.5 Outcomes to be examined

- Is there evidence for an independent association between ADHD (or hyperactivity/ inattentive profiles) and low SES?
- Does this association exist independently of between-study variables, e.g. culture, diagnostic assessment used?
- Does the strength of this association appear to vary across different developmental stages?

Summary of eligibility criteria

Criteria	Specification	Notes
Population	Children, adolescents (and adults)	No age or gender restriction
ADHD Diagnostic measures	ADHD diagnosed using validated measure. Including, but not limited to; • DISC • Conners' Ratings scales • Parent report of clinical diagnosis • SDQ • CBCL	Likely to be heterogeneity in whether clinical impairment is measured Number of informants should be noted (i.e. teacher, parent, child)
SES measures	Including, but not limited to: • Family income • Parental education • Poverty index • IMD	Include studies that measure at least one aspect of SES. If studies calculate an index using several variables, how this was calculated must be transparent in the publication. SES must be measured during childhood (reflecting the family SES not that of the ADHD proband) Distinguish between SES measured by collated ecological data (IMD) and individual-level data
Setting	Any	Distinguish between clinically referred samples and community settings Note country/countries sample is from
Study design	Population surveys, cross sectional studies, longitudinal studies and cohort studies.	
Date	1994 onwards	Publication of DSM-IV

1.2 Methods of synthesis of evidence of clinical effectiveness

This review will be undertaken following the general principles published by the NHS centre for reviews and dissemination, and reported according to CONSORT guidelines.

1.2.1 Search strategy

The search strategy will be empirically derived, the methodology of which is described in detail by Hausner et al (Hausner et al., 2012). In summary, this method involves identifying a key set of known relevant papers, which are used to derive frequent terms that can then be applied as search filters. It has the advantage of improving both accuracy and sensitivity of electronic searches. The search strategy used for Medline and adjusted for other databases can be seen below.

The following electronic databases will be screened to identify relevant articles (databases selected based on multi-disciplinary research in the field e.g. education, social policy, psychology):

- ERIC
- Assia
- Cinahl
- Medline
- PsycInfo
- Embase
- Social Policy and Practice
- HMIC
- PubMed

Searches of forward and backward citations of included studies and contacting known experts in the field will also be utilised to identify papers of relevance.

1.2.2 Study selection criteria and procedures

1.2.2.1 Types of study to be included

Outcomes

ADHD

Studies that employ a validated measure of ADHD (either dimensional or diagnostic) to identify the target population will be included (e.g. DISC, Conner's rating scale, parent report of clinical diagnosis, SDQ). Due to anticipated

heterogeneity in studies identified, studies will not be excluded based on ADHD diagnostic measures unless there are severe limitations in the method used.

Studies which diagnose ADHD regardless of the condition of clinically significant impairment will be included, as will those which measure ADHD by reports from any number of sources (e.g. teacher, parent, healthcare professional, researcher or a combination of the above).

Design

Population surveys, cross-sectional studies, longitudinal studies and cohort studies will be included.

Types of publication

Publications from peer-reviewed journals will be included as well as statistical or government reports. There will be no restriction on language of publication. Included publications will have been published from 1994 onwards, to reflect the implementation of the latest DSM guidelines regarding a diagnosis of ADHD (DSM-IV).

1.2.2.2 Types of study to be excluded

Case studies, editorials or opinions will not be included. Dissertations and conference abstracts will be excluded.

1.2.2.3 Study selection

This will be undertaken in a two-stage process. Firstly, all identified articles will be screened by title and abstract by two raters, and independently rated as to whether they are to be included, excluded or unsure. If the unsure papers cannot clearly be excluded following discussion between the two raters, the full text will be obtained for a more detailed examination. Papers on which agreement cannot be reached will be evaluated by a third rater.

The second stage will involve obtaining full text articles of all those included and unsure papers, and screening will again take place by two reviewers. Articles that continue to pose a conflict of opinion will be discussed with a third reviewer if necessary.

1.3 Quality assessment strategy

The quality of studies will be assessed and discussed as part of the systematic review. It is anticipated that there will be wide variation in study quality. Cochrane

guidelines will be used in order to determine the quality of studies from which meta-analyses will be undertaken if appropriate (see below).

1.4 Data extraction strategy

Data will be extracted independently by both the first author and a second reviewer.

1.5 Data synthesis

It is as yet unclear as to whether there will be sufficient data to carry out a meta-analysis, however if data is of sufficient quality, a pooled effect size of the association between ADHD and SES will be calculated.

Systematic Review Search Strategy

Systematic reviews aim to remove subjectivity in reporting of the scientific literature regarding the topic of review. The most common search strategy involves experts putting together search criteria based on knowledge of the field, and utilising existing strategies from other similar reviews. Whilst this leads to identification of many relevant articles, there are two key limitations. Firstly, the time needed to develop the search criteria and filter through identified articles that are identified by the search but not suitable for inclusion in the review can be extensive. Secondly, there is an element of subjectivity surrounding words chosen for the search itself, which may exclude relevant literature unbeknownst to the researcher.

In the case of the current review, a different approach with the aim of further reducing bias in search strategy will be adopted: an empirically derived search strategy. Developed by Michael Simon and Elke Hausner (2010) this strategy utilises analysis of the frequency and specificity of terms that occur in known or key literature on the topic of choice, and using these terms to develop a strategy which minimises identification of non-relevant articles, whilst retaining all relevant papers within the search.

When developing the strategy for this review, initial key references were identified from the publication on which this PhD is based (Russell et al, under revision). These were then screened to ensure they included a measure of both ADHD and SES, and their references scanned until a set of 38 papers which would be definitely included in the systematic review were identified (38 papers as used in the example by Hausner et al, 2012). In other cases, existing systematic reviews

can be used to provide these key references, however none have been published in this area as yet, leading to the need to identify key references ourselves.

Of these 38 papers, known as the Development Set, 25 were randomly assigned to the Test Set, and 13 to the Validation Set (fig 1). Using PubReMiner, a program developed to analyse PubMed search results, and a unique ID (PMID) for each citation, tables were generated showing the most frequent text terms and Medical subject heading (MeSH) terms for the development set (full tables in appendix).

Text Terms

As per Hausner et al (2012) terms which appeared in more than 25% of the development set were examined further (134 terms- see appendix for full tables). Of these, those which appeared on average three or more times per article were then selected (Table 1). These candidate terms were further divided into terms related to ADHD, those related to SES and other terms.

MeSH Terms

Of the MeSH terms appearing in more than 25% of the development set, potential key terms were selected based on whether they were of relevance to the review aims and not too overarching (for example, ‘child’ was a MeSH term in 22 of the 25 articles in the development set, but would not be of use in identifying only those articles relating to ADHD and SES). Of these, six terms were identified (one of them had five synonyms) and explored further (Table 2).

At this point a trial-and-error approach was adopted, as per the authors’ suggestion (in Hausner et al, 2012). The goal of this stage is to be able to identify as many of the 25 citations in the development set as possible with the most efficient or ‘streamlined’ search strategy. For example, adding the term “mental disorders” to a search which identified 21 of the development set raised the number identified to 25, however this also identified many more irrelevant citations in the Medline database.

Terms such as poverty, risk and income were added and removed. Additional references identified by i.e. adding “risk” to the search were scanned to evaluate if they would fit the systematic review requirements. It was found that by removing “risk” as a term, but keeping “poverty” and “income” the highest specificity could

be found- with all relevant articles remaining in the search results as well as those of the test set.

The optimal strategy was then tested by using the validation set. The best fitting strategy identified 24/25 of the development set, and 13/13 of the validation set, or 37/38 of the test set overall (table 3).

Attention Deficit Disorder with Hyperactivity/diagnosis [MeSH Terms]

AND Socioeconomic Factors [MeSH Terms]

AND ADHD OR Hyperactiv* [Title/Abstract]

AND socioeconom* OR adverse* or economic* or poverty or income [Title/Abstract]

AND epidemiolog* OR Prevalen* [Title/Abstract]

It also identified 103 citations in total, which will then be scanned for inclusion or exclusion in the systematic review.

This search will be adapted for the other databases listed in the protocol.

Figure 1: flow chart showing development of search strategy

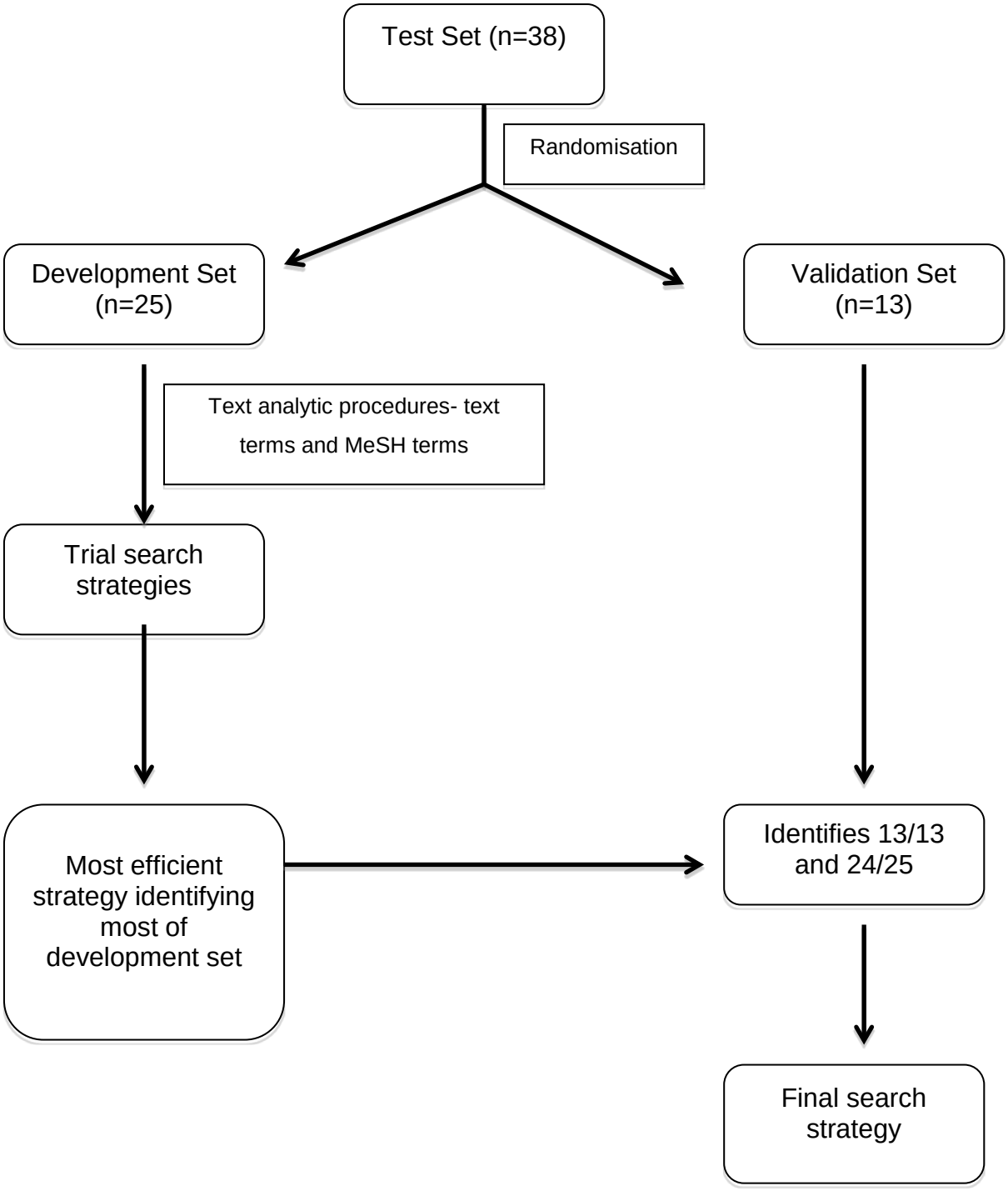


Table 1: Text term frequency in development set for terms in more than 25% of set

Italic- terms relating to ADHD further explored

Bold- terms relating to SES further explored

Article Count	Word Count	% articles in	N per article	Word
25	89	100	3.6	DISORDER *
24	74	96	3.1	CHILD *
21	*154*	*84*	*7.3*	*ADHD*
21	85	84	4.0	CHILDREN *
21	*57*	*84*	*2.7*	*HYPERACTIVE* *
20	68	80	3.4	FACTOR *
18	*47*	*72*	*2.6*	*DIAGNOSE* *
18	**48**	**72**	**2.7**	**EPIDEMIOLOGY**
18	57	72	3.2	PARENT *
16	41	64	2.6	AGE *
16	37	64	2.3	ASSOCIATE *
16	69	64	4.3	FAMILY *
15	**54**	**60**	**3.6**	**RISK ***
13	34	52	2.6	STATISTIC *
12	53	48	4.4	HEALTH
12	**33**	**48**	**2.8**	**SOCIOECONOMIC ***
11	30	44	2.7	DATA
11	22	44	2.0	LOW
11	32	44	2.9	MENTAL
10	27	40	2.7	EFFECT *
10	**47**	**40**	**4.7**	**PREVALENT ***
9	23	36	2.6	ASSOCIE *
9	25	36	2.8	NUMERIC *
9	23	36	2.6	PSYCHOLOGY
9	25	36	2.8	SOCIAL
9	33	36	1.3	SYMPTOM *
8	20	32	2.5	GENDER *
8	**29**	**32**	**3.6**	**RATE ***
7	27	28	3.9	CI
7	**19**	**28**	**2.7**	**INCOME**
7	28	28	4.0	PROBLEM *
6	**20**	**24**	**3.3**	**ADVERSE ***
5	15	20	3.0	DSM
5	9	20	1.8	ECONOMIC *
5	13	20	2.6	EDUCATE *
5	14	20	2.8	MOTHER *
5	**11**	**20**	**2.2**	**POVERTY**
5	19	20	3.8	PREGNANCY
5	13	20	2.6	TYPE *

Table 2: MeSH term frequency in development set for terms in more than 25% of set

Italic- Terms explored further

Bold- synonyms of ADHD

Frequency	MeSH
15	**Attention Deficit Disorder with Hyperactivity**
10	*Risk Factors*
9	*Attention Deficit Disorder with Hyperactivity/diagnosis*
6	**Attention Deficit Disorder with Hyperactivity/ diagnosis/ epidemiology**
2	**Attention Deficit Disorder with Hyperactivity/ diagnosis/ psychology**
1	**Attention Deficit Disorder with Hyperactivity/diagnosis/genetics**
8	*Prevalence*
7	Child, Preschool
7	Health Surveys
7	*Socioeconomic Factors*
6	**Attention Deficit Disorder with Hyperactivity/ diagnosis/ epidemiology**
5	*Mental Disorders*
5	Sex Distribution
4	Adult
4	Child Behavior Disorders
4	Cohort Studies
4	Odds Ratio
4	Parents
4	Pregnancy
4	Questionnaires
4	Social Class

Table 3: Final search strategy

MEDLINE SEARCH

	Attention Deficit Disorder with Hyperactivity/diagnosis	MeSH
AND	Socioeconomic Factors	MeSH
AND	ADHD or hyperactiv*	title/abs
AND	Socioeconomic* or adverse or disadvantag* or poverty or income	title/abs
AND	Epidemiolog* or prevalen*	title/abs

http://www.crd.york.ac.uk/PROSPEROFILES/6160_PROTOCOL_20130931.pdf

Appendix 2

Certificate of ethical approval for qualitative study

UNIVERSITY OF EXETER | MEDICAL SCHOOL

University of Exeter Medical School
Research Ethics Committee

Certificate of Ethical Approval

Research Institute/Centre: Institute of Health Research

Title of Project: A qualitative study of school practitioners' experiences and beliefs about young people with ADHD

Name(s) of Project Research Team member(s): Ms Abigail Russell, Dr Darren Moore, Dr Ginny Russell and Prof Tamsin Ford

Project Contact Point: Ms Abigail Russell

This project has been approved for the period

From: **August 2014**

To: **October 2015**

University of Exeter Medical School
Research Ethics Committee approval reference: Aug14/B/049

Signature: Peta Foxall

Date: 15 August 2014

Name of Chair
Peta Foxall, PhD

Your attention is drawn of the attached paper "Guidance for Researchers when Ethics Committee approval is given", which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Application Reference Number 14/06/049

EXPLORING TEACHERS' EXPERIENCES OF ADHD

UEMS REC REFERENCE NUMBER: Aug14-B-049

INFORMATION SHEET FOR PARTICIPANTS- VERSION NUMBER 2: July 2014

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you of any kind and we thank you for considering our request.

What is the aim of the project?

This PhD research project aims to explore the beliefs and experiences of school staff regarding personal experience of pupils with Attention Deficit/Hyperactivity Disorder (ADHD). ADHD is defined as when a child demonstrates inattentive, hyperactive and impulsive behaviours in multiple settings. These behaviours must have emerged prior to the age of twelve years and cause functional impairment to the child or young person.

Description of participants required

We would like those staff who work with young people in a school setting who have had experience working with young people with ADHD to take part.

We wish to recruit all types of educational staff, for example teachers, head teachers, special education teachers, teaching assistants, student teachers and advisory teachers.

What will participants be asked to do?

Should you agree to take part in this project, you will be asked to participate in either a one-to-one interview **or** a focus group with up to eleven other members of staff and a researcher. Whether you are asked to participate in the interview or focus group will depend on how many staff within your school participate in the study - if there are more than three staff involved we will hold a focus group to encourage discussion between yourself and your colleagues, otherwise we will hold interviews. You will be asked about your experiences of working with young

people with ADHD. As we are looking to explore your personal experience, we do not have many set questions to ask; instead we have several overall themes around the topic that we will explore with you. You should experience no discomfort during the task.

Time commitment

The interview or focus group should last no more than one hour, and we will do our best to arrange to do this at a time and place convenient for you.

Can participants change their mind and withdraw from the Project?

Please be aware that you may decide not to take part in the project. You may withdraw from participation in the project at any time and your data will be removed, without any disadvantage to yourself of any kind.

What data or information will be collected and what use will be made of it?

The data we collect will be a recording of the group discussion or your interview, and any notes taken by the interviewer at the time. The recording will be transcribed (written down word for word) and made anonymous. It will then be analysed along with other interviews and focus groups we are conducting. The data collected will be securely stored in such a way that only the researchers working on the project will be able to gain access to it.

This project involves an open-questioning technique where the precise nature of the questions asked have not been determined in advance, but will depend on the way in which the interview develops. Consequently, although the School Research Ethics Committee is aware of the general areas to be explored in the interview, the Committee has not been able to review the precise questions to be used.

In the event that the line of questioning does develop in such a way that you feel hesitant or uncomfortable, you are reminded of your right to decline to answer any particular question(s).

We are collecting experiences from around 25 educational staff, and the interviews and focus groups will be analysed in order to draw out themes and perceptions which are relevant to school staff's experience of young people with

ADHD. The results of this project may be published, but any data included will not be individually identifiable.

A summary of the study findings will be sent to your school. You will be provided with a copy of your transcript and also the findings of the study if you wish.

Why me?

We are aiming to collect data on a diverse range of experiences from those who educate children and young people with ADHD in order to better understand perspectives and potentially inform policies about school-based treatment or interventions for those young people. You have been identified by Abigail Russell as potentially having had experience which may be of interest to us.

What if participants have any questions?

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Abigail Russell
The Institute of Health Research,

Child Health Group
01392 722985

or

Dr Darren Moore
The Institute of Health Research

Child Health Group
01392 727405

Complaints

If you have any complaints about the way in which this study has been carried out please contact the Chair of the University of Exeter Medical School Research Ethics Committee:-

Peta Foxall, PhD
Chair, UEMS Research Ethics Committee
Email : P.J.D.Foxall@exeter.ac.uk

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee

EXPLORING TEACHERS' EXPERIENCES OF ADHD

UEMS REC REFERENCE NUMBER: Aug14-B-049

CONSENT FORM FOR PARTICIPANTS - VERSION NUMBER 2: JULY 2014

I have read the Information Sheet Version Number 2 Dated July 2014 concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

I know that:

1.	my participation in the project is entirely voluntary;	Y / N
2.	I am free to withdraw from the project at any time without any disadvantage;	Y / N
3.	the data will be retained in secure storage;	Y / N
4.	this project involves an open-questioning technique where the precise nature of the questions asked have not been determined in advance, but will depend on the way in which the interview/focus group develops.	Y / N
5.	we do not anticipate any discomfort or harm to arise through taking part in the project	Y / N
6.	the results of the project may be published but my anonymity will be preserved.	Y / N

I agree to take part in this project.

.....	.....	.....
(Printed name of participant)	(Signature of participant)	(Date)
.....	.....	.....
(Printed name of researcher)	(Signature of researcher)	(Date)

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee

Focus group topic guide/schedule (same topics covered in interviews)

Can we first go around the room and can I ask everyone to say their name, and also tell us if you are currently working with any pupils diagnosed with ADHD? (this is so that on the tape we can tell whose voice is whose!)

To start off, thinking about your personal experiences working with children with ADHD; is there a child in particular at the school or group of children of the same age whom everyone knows and can discuss? Could you tell me about them?

What sort of behaviours do you notice in pupils with ADHD that you don't see in your other pupils? Does it depend on the time of day? Why? (e.g. may be worse after lunch because eaten sugary stuff, medication given in the morning may wear off by afternoon etc)

What sort of ADHD behaviours cause disruption? How do you manage these in the classroom/area you work in? What is that like for you?

Discuss/expand on:

- classroom management
- discipline/reward systems
- teacher vs school regulations on how to manage pupils- how the teacher feels about/experiences this- at what point do you flag up to senior management that you are struggling with the pupil's behaviour?
- how is it for the pupil with ADHD?
- ADHD pupil as one in class of many vs in 1:1 situations or small group?
- Personal experiences/emotions: "How did that make you feel?"
- **Strengths and challenges** faced by the teacher and pupil**- "have you found ways to channel these behaviours in a positive way?** What do you do?" or "we have talked about the negative impacts it can have, on the flip side, are there any advantages?"
- peers "how do you think that impacted on the other children in the class? How was their relationship with the pupil with ADHD?"

Going back to your personal experiences, **can you tell me about any challenges you have faced connecting with a pupil with ADHD? Are there any strategies you have used to build relationships with pupils with ADHD?** (note-likely some won't have anything to say here)

Could you tell me about the ways in which others behave towards a child with a diagnosis of ADHD?

- Peers- do they perceive the extra attention given as being rewarded for 'bad' behaviour?
- other staff
- parents
- how they see themselves
- stigma

Has anyone/have you had a child under your care whom you suspected had ADHD? What was that like? What did you do? What was the result? How do you think that impacted on the child? And you?

Discuss/expand on:

- Labelling- pros and cons
- Referral process
- Responsibility

At home/parents

We have talked about your experiences in the classroom/we just talked about parents, what are your impressions of the home lives of children with ADHD? Could you give me an example?

- Home vs school environments
- Parent evenings, sending letters/forms home
- How much is 'genuine' ADHD and how much is learned bad behaviour?

Possible: Clinical diagnosis

ADHD as I have described it today is considered to be a clinical disorder. What are your thoughts/opinions on this (whether these children ought to be diagnosed/is it a thing)? Real/biological vs environmentally caused ADHD?

Discuss/expand on:

- **What actually 'causes' it? 'real' vs 'environmental'?**
- Some people consider it to be badly behaved children, what do you think?

- Labelling
- Treatment, medication

Possible: Are there things that you think increase the likelihood of a child being diagnosed with ADHD or referred for diagnosis?

Discuss/expand on:

- Home
- School
- level of disruption/problem behaviour

That's the end of the topics I wanted to cover, is there anything I haven't asked about that you would like to talk about today?

Other

Can I ask you to tell me about how you would feel if you had a new pupil joining your class, or in your new class there is a pupil who is diagnosed with ADHD? Has anyone had this experience? How was it? Did your preconceptions match up to how it turned out?

And if there was a child in the school whom you suspected of having ADHD, how confident would you be to refer them for diagnosis? (e.g. on a scale of 1-10) could you tell us how you came to that conclusion?

What is the pathway for referral for assessment here? Who would you go to in the school to discuss the pupil you are worried about? And who contacts the parents? (has anyone here had experience of this they could share with us?)

Notes: Bold: key questions, italics: supplementary questions

Appendix 3

Certificates of ethical approval for all analyses of existing data in the ALSPAC

UNIVERSITY OF EXETER | MEDICAL SCHOOL

University of Exeter Medical School
Research Ethics Committee

Certificate of Ethical Approval

Research Institute/Centre: Institute of Health Research

Title of Project: Exploring the association between Attention Deficit/Hyperactivity Disorder (ADHD) and socioeconomic disadvantage

Name(s) of Project Research Team member(s): Abigail Russell (previously Higgins), Dr Ginny Russell and Prof Tamsin Ford

Project Contact Point: Abigail Russell (previously Higgins)

This project has been approved for the period

From: **April 2014**

To: **April 2015**

University of Exeter Medical School
Research Ethics Committee approval reference: Apr14/A/046

Signature: Peta Foxall

Date: 24 April 2014

Name of Chair
Peta Foxall, PhD

Your attention is drawn of the attached paper "Guidance for Researchers when Ethics Committee approval is given", which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Application Reference Number 14/04/046

UNIVERSITY OF EXETER | MEDICAL SCHOOL

University of Exeter Medical School Research Ethics Committee

Certificate of Ethical Approval

Research Institute/Centre: Institute of Health Research

Title of Project: Exploring the association between Attention Deficit/Hyperactivity Disorder (ADHD) and socioeconomic disadvantage
- *Extension of project timeframe to match ALSPAC approval*

Name(s) of Project Research Team member(s): Abigail Russell (previously Higgins), Dr Ginny Russell and Prof Tamsin Ford

Project Contact Point: Abigail Russell (previously Higgins)

This project has been approved for the period

From: **April 2015**

To: **September 2016**

University of Exeter Medical School
Research Ethics Committee approval reference: Aug15/D/046Δ1

Signature: Peta Foxall

Date: 4 August 2015

Name of Chair
Peta Foxall, PhD

Your attention is drawn of the attached paper "Guidance for Researchers when Ethics Committee approval is given", which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Application Reference Number 14/04/046Δ1

UNIVERSITY OF EXETER | MEDICAL SCHOOL

University of Exeter Medical School
Research Ethics Committee

Certificate of Ethical Approval

Research Institute/Centre: Institute of Health Research

Title of Project: Exploring the association between Attention Deficit/Hyperactivity Disorder (ADHD) and socioeconomic disadvantage
- *Additional study in collaboration with Dr Matthew Suderman, University of Bristol*

Name(s) of Project Research Team member(s): Abigail Russell (previously Higgins), Dr Ginny Russell, Prof Jonathan Mill and Prof Tamsin Ford

Project Contact Point: Abigail Russell (previously Higgins)

This project has been approved for the period

From: **January 2016**

To: **September 2016**

University of Exeter Medical School
Research Ethics Committee approval reference: Jan16/D/046Δ2

Signature: R Garside

Date: 7 January 2016

Name of Co-chair
Ruth Garside, PhD

Your attention is drawn of the attached paper "Guidance for Researchers when Ethics Committee approval is given", which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Application Reference Number 14/04/046Δ2

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