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Abstract

This study investigated if crying, sleeping or feeding problems that co-occur (multiple regulatory problems) or are persistent predict attention problems and diagnoses of ADHD in childhood and adulthood. Participants were 342 individuals who were assessed at 5, 20 and 56 months for crying, sleeping and feeding (regulatory problems) and at 6, 8 and 28 years for ADHD diagnoses, attention problems and attention span. Infants/toddlers with multiple/persistent regulatory problems had an increased risk of receiving an ADHD diagnosis both in childhood and adulthood compared to those who never had regulatory problems. Multiple/persistent regulatory problems were further associated with a high-decreasing attention problems trajectory from childhood to adulthood. Interventions to alleviate early regulatory problems may prevent the development of attention problems.

Early Crying, Sleeping, and Feeding Problems and Trajectories of Attention Problems from Childhood to Adulthood

ADHD type problems, characterized by hyperactivity-impulsivity and inattention, are common during childhood affecting up to 7% of school-aged children (Boyle et al., 2011). Increasing evidence suggests that ADHD emerges early in the preschool years and is associated with academic underachievement, behavioral problems and poorer social outcomes (Klein et al., 2012). ADHD symptoms in preschool years have been shown to remain moderately stable throughout childhood (Karam et al., 2015; Lavigne, Lebailly, Hopkins, Gouze, & Binns, 2009), start decreasing in the late teenage years (Monuteaux, Mick, Faraone, & Biederman, 2010) but persist into adulthood for a subgroup of those with ADHD in childhood (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2016). Although a meta-analysis study revealed that the persistence rate of ADHD symptoms into adulthood is approximately 15%, the reported prevalence rates in individual studies vary widely between 4% and 70% (Faraone, Biederman, & Mick, 2006). This variability in the prevalence rate may be explained by the assessment of different subtypes of ADHD since the presentation of ADHD symptoms changes from childhood to adulthood (Faraone et al., 2006). In particular, hyperactivity symptoms are highly prevalent during preschool years but gradually become less evident throughout adolescence and adulthood (Biederman, Mick, & Faraone, 2000; Faraone et al., 2006), whereas attention problems may remain more stable (Biederman et al., 2000; Larsson, Lichtenstein, & Larsson, 2006). Thus, a focus on attention problems may help to identify children who show similar trajectories in attention until adulthood.

Several longitudinal studies have prospectively investigated the development of childhood attention problems and assessed mean symptom levels or proportions of ADHD diagnoses at various time points (Biederman et al., 2000; Hart, Lahey, Loeber, Applegate, & Frick, 1995; Larsson et al., 2006; O'Neill, Rajendran, Mahbubani, & Halperin, 2017;

Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004). The problem with this approach is that not all individuals may follow the same pattern of development over time. Instead, there may be different subgroups in the target population that follow distinctive trajectories (Pollak, 2015), however there are few studies that have analyzed whether there are trajectories of attention development that subgroups follow. The few studies which determined the trajectories of subgroups over time generally focused on overall ADHD symptoms (Larsson, Dilshad, Lichtenstein, & Barker, 2011; van Lier, van der Ende, Koot, & Verhulst, 2007) or used high-risk or clinical samples (Jester et al., 2005; Malone, Van Eck, Flory, & Lamis, 2010; Nagin & Tremblay, 1999) but usually had short durations of follow-up. Likewise, studies which focused on the trajectories of attention problems in particular had short follow up intervals in which the longest follow up was until adolescence (Arnold et al., 2014; Galera et al., 2011; Larsson et al., 2011; Robbers et al., 2011; Sasser, Calvin, & Bierman, 2016). To illustrate, one study reported on two subgroups who followed a different pattern of attention problems over time from 8 to 17 years (Larsson et al., 2011), while other studies identified three subgroups of attention problems trajectories from 1.5 to 8 years of age (Galera et al., 2011), 6 to 12 years of age (Robbers et al., 2011), from 6-12 to 9-15 years of age (Arnold et al., 2014) and from 8 to 18 years of age (Sasser et al., 2016). None of the studies measured the trajectories of attention problems from childhood to adulthood so far, although it has been suggested that attention problems may follow stable trajectories into adulthood (Breeman et al., 2016).

Even though above mentioned studies clearly indicate that attention problems persist to a moderate degree, existing research generally focused on early predictors of later attention problems at one time point in an individual's life (Biederman et al., 1996; Johnson & Marlow, 2011; Rodriguez et al., 2009) and provided little information regarding the predictors of persistence of attention problems (Caye et al., 2016). Identifying the early

symptoms in infancy/toddlerhood which may differentiate children who are more likely to follow a trajectory of high attention problems from childhood to adulthood would be crucial to identify infants/toddlers at increased risk and to advise practitioners regarding developmentally sensitive early assessments (McGoey, Eckert, & Dupaul, 2002). Two existing studies suggested several factors as predictors of high attention problems trajectory. One study identified parental stress, inconsistent parenting, emotion dysregulation and aggression as predictors of high ADHD trajectory from 8 to 18 years of age (Sasser et al., 2016). A second study (Galera et al., 2011) identified preterm birth, low birthweight, prenatal tobacco exposure, young maternal age, maternal depression, paternal history of antisocial behaviour and non-intact family as predictors of high attention problems trajectory from 17 months to 8 years of age. These studies suggested several predictors relating to individual differences in children and parental behaviour and experiences, all making a small contribution to explain trajectories.

The present study was conceived to investigate specifically whether early individual differences in crying, sleeping and feeding, considered as self-regulation of behavioural state, a prerequisite for prolonged attention, predicts adverse development of attention regulation in childhood and into adulthood.

Human infants are born immature compared to most other mammals. Fussing and crying of the infant secures that parents stay close for safety and it triggers the let-down reflex with milk being released from the mother's breast (Winberg, 2005) to facilitate breastfeeding. Fussing and crying follows a characteristic crying curve in the first three months of life in which crying peaks at 6 weeks (i.e. 2 hours and 15 minutes) and then reduces to approximately 70 minutes by 3 months of age in industrial societies (Wolke, Bilgin, & Samara, 2017). Large individual differences are found right from birth (Barr, 1990) and across societies. The large reduction in fuss/cry behaviour at 3 months coincides with the

first biobehavioural shift (Wolff, 1987) and the development of primary intersubjectivity (Trevathen, 1987), indicating changes in both behavioural control and cognitive abilities in distinguishing oneself and others in interaction. Infants who do not master this transition in acquiring self-soothing and continue to fuss or cry at significantly higher levels after 3 months (i.e. >2 hours per 24 hours) have been considered to have a regulatory problem (von Kries, Kalies, & Papousek, 2006). Similarly, sleep-wake regulation evolves during infancy aided by light alterations, parent interventions and routines and neurophysiological maturation and infants start to sleep less during the day and sleep more during the night (Bamford et al., 1990; Wolke, 1994). All infants wake up 5-7 times per night but there are individual differences in how well infants are able to regulate waking by self-soothing themselves back into sleep (Galland, Taylor, Elder, & Herbison, 2012). By three months of age, many infants are able to use self-soothing skills, which is predictive of long night time sleep (St James-Roberts, Roberts, Hovish, & Owen, 2015). Similar to crying and sleeping, feeding is essential to secure survival of infants (Wolke, 1994). In general, human infants double their weight in the first 3 to 6 months which is entirely driven by food intake (Wolke, 1994). At around 3-4 months infants start to show a preference for salt in food which is low in breast milk and become interested in trying new textures of food (Harris & Booth, 1987; Reilly, 2006). These and other anatomical and physical changes such as oral-motor skills prepare the introduction of new textures of food and have been shown to indicate a sensitive period (Harris & Mason, 2017). The acceptance of textured food requires infants to overcome a natural tendency of neophobia (Bryant-Waugh, Markham, Kreipe, & Walsh, 2010). Again, there are large individual differences and strong indications that infants differ in sensory sensitivity and ability to self-regulate acceptance of new texture and tastes (Farrow & Coulthard, 2018). The abilities to self-regulate crying, sleeping and food intake have been found to occur at 3-6 months after the first bio-behavioural shift (Wolff, 1987).

Originally, it has been noticed that crying, sleeping and feeding regulatory problems (RPs) usually occur together in clinically referred infants, i.e. parents present their infant rarely with one of these RPs alone (Hofacker & Papoušek, 1998; Papoušek, Schieche, & Wurmser, 2007; Wolke, Gray, & Meyer, 1994). Epidemiological studies have further confirmed that these RPs occur together in up to one third of infants with any other RPs (i.e. multiple RPs) and parents of infants with multiple or persistent RPs are more likely to seek professional help since they consider these to be most challenging (von Kries et al., 2006; Wolke, Meyer, Ohrt, & Riegel, 1995). Approximately 2-8% of infants experience multiple RPs beyond three months of age (Schmid, Schreier, Meyer, & Wolke, 2010; St James-Roberts, 2012; von Kries et al., 2006). These infant RPs have been previously associated with the development of attention problems in childhood (Hemmi, Wolke, & Schneider, 2011). Another meta-analysis revealed that children with ADHD had significantly higher bedtime resistance, more sleep onset difficulties, and night awakenings compared to controls when measured using questionnaires (Cortese, Faraone, Konofal, & Lecendreux, 2009). This association remained significant for sleep onset latency and sleep apnea when measured objectively (e.g. actigraphy) (Cortese et al., 2009). Similarly, a recent systematic review suggested that there is strong empirical support for the association between eating disorders and ADHD (Levin & Rawana, 2016). It was suggested that individuals who have an eating disorder are likely to display the main symptoms of ADHD which are inattention, hyperactivity and impulsivity (Farber, 2010; Sala et al., 2017). Individuals with ADHD maybe less attentive to internal signs of hunger (Davis, Levitan, Smith, Tweed, & Curtis, 2006) or feeding problems during infancy may result in neurodevelopmental vulnerabilities with inattention symptoms being an important feature (Galler et al., 2012).

In particular, multiple RPs (Becker, Holtmann, Laucht, & Schmidt, 2004; Bilgin & Wolke, 2016; Hemmi et al., 2011) or persistent RPs have been repeatedly reported to be

associated with ADHD type problems up to adolescence (Becker et al., 2004; Hyde, O'Callaghan, Bor, Williams, & Najman, 2012; Schmid & Wolke, 2014). However, previous studies either had short follow-up periods, small sample sizes, or used retrospective designs (Becker et al., 2004; Desantis, Coster, Bigsby, & Lester, 2004; O'Callaghan et al., 2010; Thunström, 2002). Thus, it remains unknown if multiple/persistent RPs in infancy/toddlerhood have far reaching consequences and are still associated with attention problems in adulthood.

The association between RPs and attention problems may be explained by shared features, risk factors and neurobiological mechanism. To start with, infants/toddlers with multiple or persistent RPs have difficulties to inhibit a current state such as crying and night waking (Hemmi et al., 2011), which leads them to be distressed for long periods of time (St James-Roberts, 2012). The ability to return to a settled awake state is a prerequisite to attend to external stimuli for prolonged periods. Likewise, children with attention problems have difficulties inhibiting stimuli and regulating their attention to focus on a task at hand. Second, both RPs and attention problems are predicted by the same prenatal risk factors ranging from premature birth to increased maternal stress and alterations in HPA function (Banerjee, Middleton, & Faraone, 2007; Bolten et al., 2013; Petzoldt et al., 2014) as well as environmental risk factors such as psychosocial problems and family adversity (Biederman, Faraone, & Monuteaux, 2002; Schmid et al., 2010; Thunström, 2002; Wurmser et al., 2006). Lastly, RPs are suggested to share common underlying neurobiological mechanism with attention problems. For instance, alterations were found in the same brain regions in both patients with eating disorders (Frank, 2013) and ADHD (Bush, Valera, & Seidman, 2005). Furthermore, dopaminergic system and prefrontal cortex functions have been found to play an important role in both sleeping difficulties and ADHD (Cassoff, Wiebe, & Gruber, 2012).

Converging evidence suggests that both multiple or persistent RPs and attention problems might be phenotypes of underlying developmental neural dysregulation, i.e., problems to regulate or inhibit on-going behaviour and corresponding brain activity (Bush, 2010; Schmid & Wolke, 2014). Untested is whether early infant multiple/persistent RPs might indeed be associated with different trajectories of varying levels of attention problems through childhood and adulthood.

Overall, the aim of this prospective study over nearly three decades was first, to examine whether infants/toddlers with multiple/persistent RPs have more attention problems, lower attention span, and higher odds for ADHD diagnoses in adulthood than those without any infant regulatory problems. Second, to examine whether multiple/persistent RPs during infancy/toddlerhood predict stable attention problem and attention span trajectories from childhood to adulthood.

METHODS

Study Design and Participants

The Bavarian Longitudinal Study (BLS) is a prospective geographically defined whole population sample of neonatal at-risk children born between January 1985 and March 1986 in Southern Bavaria (Germany) (Wolke, Ratschinski, Ohrt, & Riegel, 1994).

The present study utilizes data collected from birth to adulthood (Appendix 1 in the Supplement). From the 1495 children invited for the 6-year assessment, for the prospective case-control follow-up study in adulthood we excluded childhood participants who had at any time a single or non-persistent RP or where there were any missing data on crying, sleeping or feeding problems at any time at assessment from 5 to 56 months (Figure 1). Of the eligible 708 participants for this prospective case-control study, we were able to follow up 342 individuals at a mean age of 27.6 ($SD = 1.8$, $range = 25-31$) years. 311 participants who

never had RPs and 55 participants who had multiple/persistent RPs were lost to follow up (eTable 1). Participants who did not complete the study in the never RP group differed from participants who remained in the study in that they had parents with lower socioeconomic status ($p < .01$). Participants who did not complete the study in the multiple/persistent RPs group differed from participants who remained in the study in that they had significantly lower gestational age ($p < .001$) and birth weight ($p < .001$) and had parents of lower socioeconomic status ($p < .05$).

Ethical approval for the study was granted by the ethics committees of the University of Munich Children's Hospital, the Bavarian Health Council (Landesärtekammer Bayern), and the University Hospital Bonn. Informed consent was obtained from parents (childhood) and participants (adulthood).

Measures

Multiple/Persistent Regulatory Problems

As part of a neurodevelopmental assessment, research paediatricians asked parents via a standard interview about their children's crying, sleeping, and feeding problems at age 5 months. At 20 and 56 months, sleeping and eating problems were assessed via standardized parental interviews and neurological examinations of oral motor function conducted by paediatricians. Paediatricians had been trained to achieve an inter-rater reliability $>90\%$ and received three-monthly booster workshops in order to maintain high reliability throughout the data collection period. The assessments at 5 and 20 months were carried out corrected for prematurity, and the assessment at 56 months was carried out according to chronological age (Schmid et al., 2010). The definitions for crying, feeding and sleeping problems at 5 months and sleeping and eating problems at 20 and 56 months are given in eTable 2 in the Supplement.

Children with multiple RPs were those who had at least two problems at 5 months and they were dichotomized into two groups: 0= never, 1=multiple RPs. Persistent RPs were defined as having at least one problem at 5, 20 and 56 months and they were dichotomized into two groups: 0= never, 1= persistent RPs. Subsequently, multiple and/or persistent RPs were combined and coded into a binary variable: 0= never RPs, 1= multiple or persistent RPs (eTable 2 in the Supplement).

Parent/Self rated attention problems

Parents, mostly mothers (88%), rated their children's attention problems at 6 and 8 years using the validated attention problems subscale of the German version of the Child Behavior Checklist (CBCL) (Achenbach, 1991; Arbeitsgruppe Deutsche Child Behavior Checklist, 1998a). In adulthood (25-31 years), participants rated their attention problems using the German version of the Young Adult Self-Report (YASR) (Achenbach, 1997; Arbeitsgruppe Deutsche Child Behavior Checklist, 1998b). At each assessment, items were rated on a scale from 0 (*not true*) to 2 (*very or often true*) and then summed into a total score with higher scores indicating more attention problems.

The informant differed in childhood (parent report) compared to adulthood (self-report). Nevertheless, it is a common practice to use parent reports for children and self-reports for adults who are mostly not living with their parents anymore (Faraone et al., 2006). In addition, age-appropriate versions of the same scale were used in childhood and adulthood.

Observer-rated attention span

Psychologists rated the child's attention span using the Tester's Rating of Child Behavior (TRCB) (Wolke, 1996) at 6 years and 8 years and the Tester's Rating of Adult Behavior (TRAB) (Wolke, 2012) in adulthood (Jaekel, Wolke, & Bartmann, 2013). Both in childhood and adulthood attention span was judged during a cognitive assessment lasting one hour.

Additionally, it was judged across all tasks during the assessment day in adulthood (Breeman

et al., 2016; Jaekel et al., 2013). Psychologists scored the individual's attention on a scale from 1 (very short attention span) to 9 (very long attention span). Attention span scores showed moderate reliability at all assessment points ($ICC_{6y} = .67$; $ICC_{8y} = .72$; $ICC_{28y} = .66$).

ADHD diagnoses. ADHD diagnoses at 6 and 8 years were made according to the structured and validated Mannheim Parent Interview (Esser, Blanz, Geisel, & Laucht, 1989) that allowed for a clinical DSM-IV diagnosis. All raters were trained to greater 90% inter-rater agreement (Jaekel, Baumann, Bartmann, & Wolke, 2018). The presence of ADHD diagnosis in adulthood was made with the DSM-IV based adult ADHD rating scale completed by participants (Kooij et al., 2005). This adult ADHD rating scale is considered a valid measure of ADHD and associated psychosocial impairment in adulthood (Kooij et al., 2005).

According to guidelines by the authors (Kooij et al., 2005), adults exhibiting four out of nine inattentive symptoms or four out of nine hyperactivity/impulsivity symptoms 'often' or 'very often' are considered significantly impaired. Thus, they received a diagnosis of predominantly inattentive (ADHD-IA), predominantly hyperactive-impulsive (ADHD-HI), or ADHD combined type (ADHD-C).

Descriptives and Covariates

Gestational age, sex (male) and socioeconomic status (SES) were included as covariates since they have previously been shown associations with attention problems. Gestational age at birth was determined from maternal reports of the last menstrual period and serial ultrasounds during pregnancy. Information on family SES at birth was collected via structured parental interviews and computed as a weighted composite score derived from the occupation of the head of each family (usually the father) together with the highest educational qualification held by either parent into three categories of low, medium and high SES (Bauer, 1988). Moreover, age at assessment in adulthood was included as a covariate to adjust for the age range in adulthood assessment.

Statistical Analysis

To examine the differences between infants/toddlers with multiple/persistent RPs and infants/toddlers who never had RPs, we performed independent sample t-tests for continuous variables and X^2 test for categorical variables using SPSS 24.

Longitudinal attention problems and attention span trajectories were analyzed with latent class growth analysis (LCGA) using Mplus (version 8) to identify distinct groups of individuals based on their attention trajectories. LCGA is a special case of growth mixture modelling that assumes homogeneity of growth parameters within each latent subgroup (Muthen & Muthen, 2000). This approach discerns homogenous classes defined by different developmental trajectories of attention (Jung & Wickrama, 2008), which is useful in identifying how different groups of people who share common characteristic develop over time. The Full Information Maximum Likelihood (FIML) approach was used to handle missing data.

In order to determine the optimal number of latent classes, we examined several model fit indices: Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), Lo-Mendell-Rubin (LMR), Vuong-Lo-Mendell-Rubin (VLMR) and the entropy value (Jung & Wickrama, 2008). Briefly, we started with one class and compared these fit indices to the fit indices of a successively greater number of trajectory classes until a greater number of classes did not result in improved fit values. In addition to statistical model fit indices, several other criteria were considered to determine the optimal number of latent classes, i.e. the probability of belonging to a latent class should be 0.80 or higher; the smallest class should include at least 5% to 10% of the sample; parsimony of models, their interpretability and theoretical justification, and the substantive relevance of class should be considered. Gestational age, sex (male), SES and age at assessment in adulthood were treated as potential covariates. We used automatic R3STEP approach to model auxiliary variables, which adjusts for the impact of

covariates while estimating the number of latent classes and shown to produce less-biased estimates than traditional methods (Vermunt, 2010). The statistical significance was set at $p < .05$.

RESULTS

Final Sample Characteristics

Eighty-three participants had multiple/persistent RPs (24.3%) and 259 (75.7%) never had RPs. The group of participants with multiple/persistent RPs ($N = 83$) consisted of 38 (45.8%) who had persistent RPs, 34 (41%) who had multiple RPs and 11 (13.2%) who had both multiple and persistent RPs. Eleven (13.6%) had RPs at one measurement point, 21 (25.9%) participants had RPs at two measurement points and 49 (60.5%) had RPs at three measurement points (eTable 3 in the Supplement). There were no significant differences between infants/toddlers with multiple/persistent RPs and those who never had RPs on the majority of demographics variables (Table 1). However, infants/toddlers with multiple/persistent RPs were older at the adulthood assessment than those who never had RPs (Table 1).

Do infants/toddlers with multiple/persistent regulatory problems have more attention problems in childhood and adulthood?

Infants/toddlers with multiple/persistent RPs had higher attention problem scores both in childhood (CBCL) and adulthood (YASR) in comparison to those who never experienced RPs (Table 2). Although there were no significant differences between the two groups during childhood in attention span (TRCB), infants/toddlers with multiple/persistent RPs had significantly lower attention span scores in adulthood (TRAB) compared to those who never

experienced RPs (Table 2). Moreover, Figure 2 shows that significantly more infants/toddlers with multiple/persistent RPs had ADHD diagnoses in childhood and adulthood than those who never had RPs. In addition, infants/toddlers with multiple/persistent RPs more often had specific ADHD diagnoses both in childhood and adulthood. At 6 years of age (OR= 2.92, 95% CI= 1.20-7.05) and in adulthood (OR= 4.00, 95% CI= 1.18-13.67), they were more likely to have predominantly inattentive subtype, whereas at 8 years of age (OR= 3.26, 95% CI= 1.03-10.32) they were more likely to have predominantly hyperactivity/impulsivity diagnoses.

Do multiple/persistent regulatory problems during infancy/toddlerhood predict stable attention problems and attention span trajectories across adulthood?

Attention Problems Trajectory Classes

Likelihood ratio tests (LMR and VLMR) and fit indices (BIC and AIC) suggested that a three-class model was a significantly better fit than the two-class alternative (Table 3). However, classification precision (entropy) results suggested that the two-class model was better able to represent attention problems rather than the three-class alternative. Because the three-class model provided the better statistical model, we decided to explore the three-class model using a sensitivity analysis, in order to examine whether there were actually three distinct classes (Appendix 2 in the Supplement). Due to lower posterior probabilities and unclear class distinctiveness, we decided to select the two-class model. Therefore, the initial series of latent class growth analyses (LCGA) suggested two distinct underlying patterns of attention problems within participants from childhood to adulthood, which we labelled as “high-decreasing attention problems” and “low attention problems” (Figure 3). 87.2% of the children were found to display consistently low levels of attention problems, whereas 12.8%

exhibited a pattern of attention problems that were consistently high but decreasing towards adulthood.

Attention Span Trajectory Classes

Likelihood ratio tests (LMR and VLMR) and suggested that a two-class model was significantly better fit than the one-class and alternative (Table 3). Furthermore, a two-class model showed lower fit indices (BIC and AIC) compared to three-class model (Table 3). Moreover, there was no significant improvement in the model fit for the three-class model.

The two distinctive patterns of attention span from childhood to adulthood that were identified from the initial series of LCGA are shown in Figure 3. 74% of the participants were found to have consistently medium levels of attention span, whereas 26% exhibited a pattern of attention span, which starts at medium level at 6 years but continues to increase until adulthood.

Predicting Attention Problems and Attention Span Trajectory Class Membership by Multiple/Persistent RPs

Multiple/persistent RPs were significantly associated with the high-decreasing attention problems trajectory from childhood to adulthood (OR= 1.18, 95% CI= 1.02-2.37). On the other hand, there was no significant association between early multiple/persistent RPs and the levels of attention span trajectories from childhood to adulthood. Rather than multiple/persistent RPs, low gestation (OR= 0.32, 95% CI= 0.22-0.41) was associated with the medium attention span trajectory.

Discussion

The current study found that multiple/persistent RPs are associated with increased odds of ADHD diagnoses and attention problems from childhood to adulthood, along with decreased

attention span in adulthood. We identified two trajectories of attention problems from childhood to adulthood: low and high-decreasing. Moreover, we identified two trajectories of attention span from childhood to adulthood: medium and medium-increasing.

Multiple/persistent RPs were associated with high-decreasing attention problems trajectory from childhood to adulthood.

Findings of this study add further support for the association between early RPs and increased childhood attention problems (Schmid & Wolke, 2014) and extend the literature by showing that the impact of early RPs on attention problems is still apparent in adulthood. Attention problems decreased from childhood to adulthood as previously reported (Faraone et al., 2006), and ADHD diagnoses were more frequent at 8 years (school age) compared to 6 years (preschool) and adulthood. Attention problem scores were higher and ADHD diagnoses were more frequent in adults who had multiple/persistent RPs in early childhood compared to those who never had RPs at any assessment points. Although these findings are strong for parent rated attention problems in childhood, they are weaker for observed attention span in a testing situation. This could be due to the fact that parents were the shared informant for both RPs and attention problems. Difference in observer-blind attention span between infants/toddlers with multiple/persistent RPs and those who never had RPs was only apparent in adulthood. Nevertheless, this difference was reduced when covariates were introduced. Lower gestational age was associated with decreased attention span and age of assessment in adulthood was associated with increased attention span in accordance with previous literature (Breeman et al., 2016).

Even though the majority of the studies on inattention trajectories revealed three subgroups who shared a similar development of attention problems over time (Arnold et al., 2014; Galera et al., 2011; Robbers et al., 2011; Sasser et al., 2016), our study identified two classes. A similar number of trajectories were identified in a large population based twin study

(Larsson et al., 2011), with a high-increasing trajectory and a low trajectory when assessed at 8-9, 13-14 and 16-17 years of age. This finding of a high-increasing trajectory was different from the high-decreasing trajectory identified in the current study, however a decreasing trajectory might be more in line with normative developmental expectations during adulthood in comparison to adolescence (Faraone et al., 2006).

The finding that multiple and/or persistent RPs during infancy/toddlerhood distinguished trajectories of high-decreasing attention problems from childhood to adulthood suggests that problems in behavioural regulation during infancy is related to regulation problems in adulthood. The stability in trait is supported by the studies showing an association between crying, sleeping and feeding problems during infancy and ADHD in adulthood (Galler et al., 2012; Thunström, 2002). This also might suggest that initial multiple and/or persistent deficits in regulatory competences might be an early phenotype for attention problems (Schmid & Wolke, 2014). This supports a developmental cascade in which persistent differences in behavior maximally affect the next most proximate phase of development, which in turn affects the following phase (Bornstein, Hahn, & Wolke, 2013; Hyde et al., 2012). Initial persistent deficits in regulatory competences might be early markers for similar processes of attention in childhood (Barkley, 1997). Thus, rather than assuming that a given risk factor such as early RP (i.e., at one time point) directly predicts later attention problems, a cascade model of development suggests that infant behaviour provides the starting point of a trajectory of dysregulation through time of domain-related age-appropriate constructs towards a mature phenotype (Bornstein et al., 2013; Holtmann et al., 2011). However, it also means that, on average, multiple/persistent regulatory problems are set on a developmental journey of higher attention problems. However, this direction may be altered by appropriate intervention at each point on this journey. It also may suggest that the early the trajectory is interrupted and altered, the easier this trajectory can be changed.

There are alternative explanations. Firstly, the presence of a particular gene polymorphism of the dopaminergic system has been reported in both attention problems in childhood (El-Faddagh, Laucht, Maras, Vohringer, & Schmidt, 2004) and regulatory problems in infancy (Becker, El-Faddagh, Schmidt, & Laucht, 2007). However, the evidence is based on small sample sizes and needs replication studying both attention problems and regulatory problems. Secondly, maladaptive parenting such as low maternal sensitivity may increase infant RPs (Degangi, Porges, Sickel, & Greenspan, 1993). However, the limited evidence so far indicates that RPs occur despite sensitive parenting or may even adversely affect sensitive parenting (Bilgin & Wolke, 2017; Philbrook & Teti, 2016). Thirdly, neurodevelopmental factors that are both associated with RPs and attention problems, such as lower gestational age may be responsible for the association between RPs and attention problems. Indeed, those of lower gestational age have been reported to have slightly raised rates of RPs (Bilgin & Wolke, 2016) and attention problems (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). However, in the analysis we controlled for gestational age and the findings were only slightly altered. In particular, multiple and/or persistent RPs appear to be a stable individual difference that affect regulation of attention across childhood into adulthood.

Strengths and Limitations

There are several strengths of this study. The design of this study is prospective from infancy to adulthood. Moreover, this study included multiple measures and data sources in a large sample of individuals who had multiple/persistent RPs and controls. There are also limitations. First, RPs were not assessed via structured diaries. However, this might not be possible in general population samples due to high drop-out rates in diary studies (Barr, Kramer, Boisjoly, McVey-White, & Pless, 1988). Second, the sample of the current study included preterm and full-term infants. However we controlled for gestational age and the

differences in rates on RPs have been found to be small between even very preterm infants and full term (Bilgin & Wolke, 2016). Third, different versions of the same scales were used in childhood and adulthood assessments for both attention problems and attention span. The difficulty in the measurement of the same behaviour from childhood to adulthood using the exact same measure has been acknowledged by other researchers (Caye et al., 2016).

However, the same constructs were used with comparable scales and scoring was adapted according to age, just like IQ-tests assess similar constructs (e.g. performance IQ) but have to use items of higher difficulty with advancing age from childhood into adulthood. Since the current study measured attention across different developmental periods, the difference in the manifestation of attention problems were needed to be taken into consideration in the assessments. This is essential to construct a developmentally appropriate assessment.

Conclusion

To conclude, the impact of multiple/persistent RPs in infancy and toddlers on attention problems persist into adulthood. Assessments of crying, sleeping and feeding problems should be conducted by paediatricians at regular intervals during infancy and toddlerhood to identify those who might be at risk of developing attention problems. This is important due to the fact that untreated attention problems can have high social and societal costs such as academic and occupational underachievement, delinquency, and difficulties with personal relationships (Barkley, 2006). Early interventions for infant or toddler RPs may help prevent an adverse developmental cascade culminating in a chronic attention problems pathways.

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Table 1. Demographics of the Sample

	Multiple/Persistent RPs (N= 83)	Never (N= 259)	p
GA (weeks): M (SD)	36.71 (4.39)	36.73 (4.17)	.97
BW (gr): M (SD)	2611.27 (950.80)	2704.88 (959.59)	.44
SGA: N (%)	24 (28.9%)	53 (20.5%)	.11
Male: N (%)	40 (48.2%)	131 (50.6%)	.71
Maternal Age (years): M (SD)	29.3 (5.03)	28.9 (5/03)	.55
SES: N (%)			
SES-high	26 (31.3%)	81 (31.3%)	.99
SES- middle	33 (39.8%)	111 (42.9%)	.62
SES- low	24 (28.9%)	67 (25.9%)	.59
Age at assessment in adulthood (years): M (SD)	28.14 (1.9)	27.43 (1.8)	.002

GA, gestational age; BW, birth weight; SGA, small for gestational age. SES, socioeconomic status; reported values are either means and standard deviations or frequencies and percentages.

Table 2. Comparison of the Attention Problems, Attention Span and ADHD Diagnosis between Children with and without Multiple/Persistent Regulatory Problems

	6 years			8 years			25-31 years		
	Multiple/Persistent (N= 83)	No MRP/Persistent (N=259)	p	Multiple/Persistent (N= 83)	No MRP/Persistent (N=259)	p	Multiple/Persistent (N= 83)	No MRP/Persistent (N=259)	p
Attention Problems ^a : M (SD)	4.1 (3.1)	2.7 (2.5)	<.001	2.5 (2.6)	1.8 (2.1)	.02	2.9 (2.3)	2.1 (1.9)	.002
Attention Span ^b : M (SD)	6.00 (1.91)	6.04 (1.7)	.694	6.4 (1.5)	6.6 (1.4)	.29	7.0 (1.5)	7.5 (1.3)	.004
ADHD Diagnosis (N/%)	16 (19.3%)	24 (9.3%)	.014	20 (24.1%)	34 (13.1%)	.02	15 (9.4%)	24 (19.0%)	.021

^aParent report at 6 and 8 Years and self-report at 25-31 years; ^bObserver rated

Table 3. Model fit indices of Latent Class Growth Analysis (LCGA) estimated within attention problems and attention span from childhood to adulthood

	Number of Classes	Bayesian Information Criteria (BIC)	Akaike Information Criteria (AIC)	Lo-Mendell-Rubin (LMR) p value	Vuong-Lo-Mendell-Rubin (VLMR) p value	Parametric Bootstrapped Likelihood Ratio Test	Entropy	Number of subjects per class
Attention problems	1	4444.33	4413.70	-	-	-	-	340
	2	4405.36	4363.24	.09	.08	<.001	.86	38/302
	3	4387.52	4333.92	.01	.01	<.001	.82	30/188/122
	4	4389.32	4324.23	.54	.52	<.001	.79	239/46/38/17
Attention Span	1	3487.94	3457.33	-	-	-	-	339
	2	3472.25	3430.16	.002	.002	<.001	.68	83/256
	3	3480.77	3427.21	.17	.15	.19	.68	96/209/34
	4	3492.89	3427.86	.76	.75	.66	.66	114/116/22/57

Figure 1. Flow diagram of participants

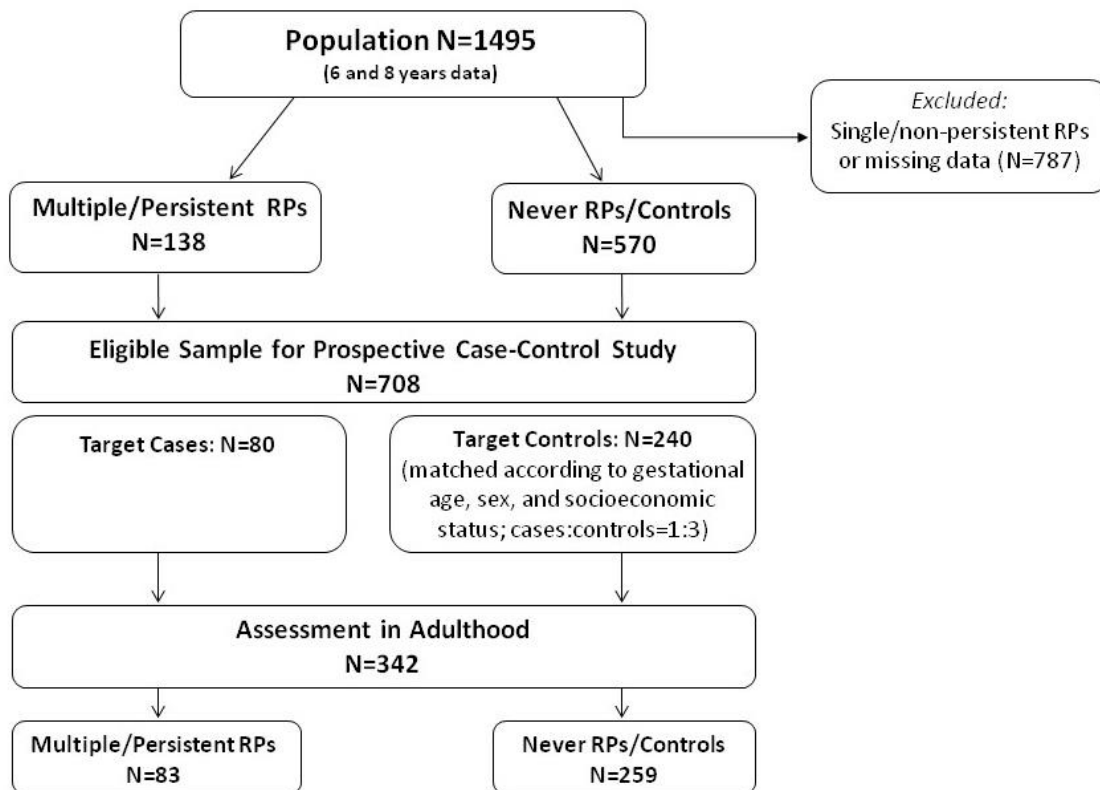


Figure 2. Percentage of ADHD diagnoses at 6, 8, and 25-31 years in infants who had multiple/persistent RP and who did not

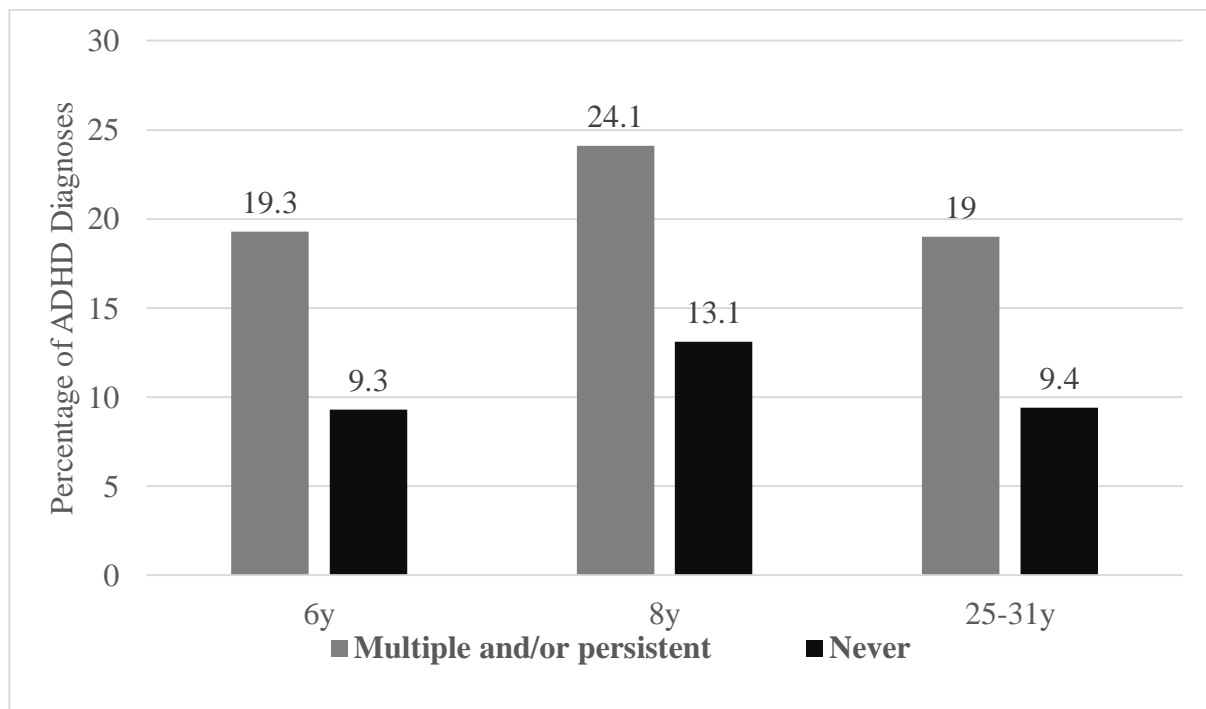
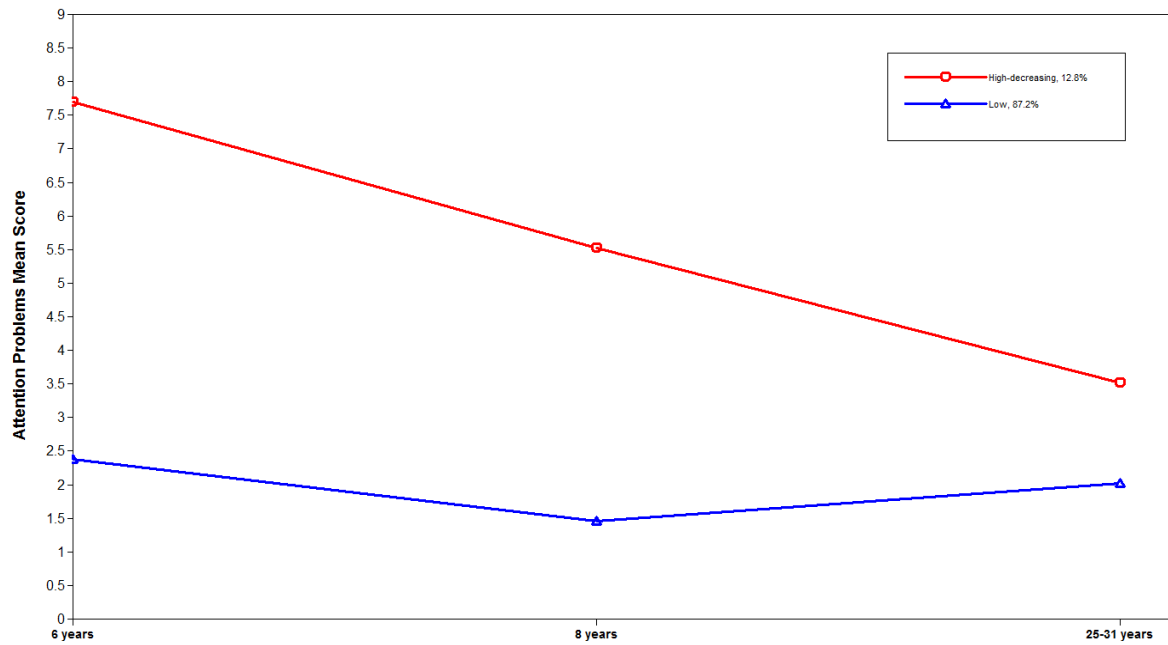


Figure 3. Distinctive trajectories of attention problems (A) and attention span (B) from childhood to adulthood

A



B

