Early-Childhood Trajectories of Separation Anxiety: Bearing on Mental Health, Academic Achievement, and Physical Health from Mid-Childhood to Pre-Adolescence

Short title: Separation anxiety and health outcomes

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Background: Separation anxiety disorder is the most prevalent childhood anxiety condition, but no study assessed children for separation anxiety at pre-school age and followed them longitudinally and directly until mid-childhood/early adolescence.

Methods: Multi-informant (children, teachers, family), multi-point (at age 8, 10, 12, 13) assessments of 1290 children of the Quebec Longitudinal Study of Child Development, who had been categorized between age 1.5 and 6 into 4 specific separation anxiety trajectories (1-Low-Persistent, 2-Low-Increasing, 3-High-Decreasing, and the less common: 4-High-Increasing) by growth mixture modeling. Participants in the High-Increasing trajectory were compared to participants in the other 3 trajectories for: a) child's internalizing and externalizing problem behavior; b) physical health; c) academic achievement; d) maternal anxiety.

Results: Multivariate analyses of variance/covariance at separate time points showed the High-Increasing trajectory mostly associated with: a) higher internalizing, but not externalizing, behavior; b) worse academic achievement (most consistently by comparisons to the normative Low-Persistent trajectory; c) higher rates of maternal panic/agoraphobic anxiety; d) worse physical health (most consistently by comparisons to the Low-Persistent trajectory). The High-Increasing trajectory had 2- to 3 fold higher incidences of physical illnesses than the normative Low-Persistent group; this was specific for headaches at age 12 years, chronic asthma at age 10 and 13, and having received asthma-related medication during the past 12 months.

Conclusions: High-increasing separation anxiety in preschool maintains longitudinal relationships to independent health and academic outcomes, at least until pre-adolescence. This knowledge can inform the deployment of clinical resources at the earlier signs of the more impairing manifestations.

Early-Childhood Trajectories of Separation Anxiety: Bearing on Mental Health, Academic Achievement, and Physical Health from Mid-Childhood to Pre-Adolescence

Anxiety disorders are the most prevalent mental conditions in any age group (Sylvester & Pine, 2016), accounting for the largest cost fraction (31.8%) among all mental disorders (DuPont, DuPont & Rice, 2002). General population surveys worldwide show that anxiety disorders' median onset occurs before age 15 (Kessler et al., 2005), and amongst all childhood anxiety disorders, separation anxiety disorder (SEPAD) is the most frequently diagnosed, accounting for up to 50% of referrals (Bell-Dolan, 1995; Cartwright-Hatton, McNicol, & Doubleday, 2006).

Although SEPAD was classified as a 'disorder with onset in infancy/childhood/adolescence', the DSM-5 has extended the range of onset to the full life cycle, so that SEPAD can now pertain to both child and adult psychiatry (Battaglia, 2015; Kossowsky et al., 2013; Milrod et al., 2014; Silove et al., 2015; Bögels, Knappe, & Clark, 2013).

While childhood anxiety disorders can follow self-limiting trajectories (Ginsburg et al., 2014), many children remain clinically anxious, and/or go on to develop other conditions in adolescence/early adulthood (Costello, Copeland, & Angold, 2011). As with most paediatric illnesses (Shonkoff, Boyce, & McEwen, 2009), prompt recognition, knowledge-based criteria to estimate prognosis, and timely treatment are key to reduce the burden and costs of SEPAD.

Little is known on the stability vs. progression of SA/SEPAD into other disorders, the impact on adjustment, and the broader health implications. Only three general population studies addressed these questions with conflicting results: the Great Smoky Mountains study (GSMS; Copeland, Shanahan, Costello, & Angold, 2009; Copeland, Angold, Shanahan, & Costello, 2014) and two adult, cross-sectional studies: the National Comorbidity (NCS; Shear, Jin, Ruscio,

Walters, & Kessler, 2006), and World Health Organization Mental Health Survey (WHOMHS; Silove et al., 2015). Only the GSMS was prospective and based on a developmental cohort.

After the first assessment at ≥ 9 years, the GSMS found that SA/SEPAD declines swiftly (Copeland et al., 2009; Copeland et al., 2014), and levels to nil by age 13-15 years; childhood SEPAD was then longitudinally associated with internalizing (mostly agoraphobia) -but not externalizing (antisocial, drug use)- disorders at 19-21 years (Copeland et al., 2009). By contrast, the adult cross-sectional WHOMHS and NCS that allowed for retrospective lifetime SEPAD diagnoses reported pervasive associations with a host of psychiatric conditions. Retrospectively-estimated childhood-onset SEPAD was associated with an array of internalizing, externalizing, and substance use disorders in the NCS (Shear et al., 2006). Likewise, almost all diagnoses ascertained in the WHOMHS (14 disorders, 6 of which Externalizing) were associated with 'temporally primary' or/and 'subsequent' SEPAD (Silove et al., 2015), suggesting that SEPAD constitutes a risk factor for a wide range of mental disorders.

Concerning longitudinal indices of adjustment, the GSMS did not find childhood/adolescence SEPAD prospectively associated with poorer social outcome, interpersonal, or financial problems in late adolescence/early-adulthood; intriguingly, in the GSMS, childhood SEPAD predicted poorer physical health (Copeland et al., 2014). By contrast, the NCS and WHOMHS portrayed a multilevel impact of SEPAD, and a graded association with: educational attainment/poorer education (Silove et al., 2015; Shear et al., 2006), never having married and having received more medical treatment (Shear et al., 2006).

Thus, the available data on how SEPAD may evolve into/associate with other disorders are quite dissonant between the GSMS, and the NCS and WHOMHS studies. Similarly, when the bulk of adjustment, social/interpersonal and academic functioning data are considered, the

developmental longitudinal GSMS conflicts with the adult cross-sectional and retrospective NCS and WHOMHS studies. Captivatingly, data from both GSMS and the NCS coincide in identifying SEPAD as a gateway to worse physical health, but this remains mechanistically unexplained.

These inconsistencies need clarification to support evidence-based medicine. No study of SA/SEPAD evaluated children at pre-school age, when onset is common (Franz et al., 2013), and followed them longitudinally and directly to assess evolution into mid-childhood/early adolescence. Longitudinal research on SA/SEPAD that starts in the preschool years is necessary, as it targets a time of life when SA can decline and disappear (as typical for most children at this age), or grow into psychopathology (Battaglia et al., 2016). This can inform about specific, age-at-onset-related processes, and help direct resources effectively at the earlier signs of the more impairing manifestations (Sonuga-Barke, 2016).

Here, we evaluated the relationships between 4 distinct SA trajectories that we had previously identified between age 1.5 and 6 years (Supplemental Figure 1), and: internalizing and externalizing symptoms, academic achievement, physical health, and maternal anxiety symptoms, as measured by longitudinal multi-informant assessments between 8 and 13 years of age.

Methods

Design and Setting

This study was part of the QLSCD, which surveys a representative sample of children born in 1997-98 in the province of Quebec, Canada, except for those (altogether 2.1% of Quebec's births) living in Cree/Inuit territories, Indian reserves, and northern Quebec. All QLSCD children were recruited through the Quebec Master Birth Registry via a stratified

procedure based on living area and birth rate. Families were included if pregnancy had lasted between 24 and 42 weeks, and mother could speak French/English.

Participants

A random sample of 2940 singleton infants was initially selected, with parents of 2675 children being reachable by mail/telephone, and 2223 (83.1%) consenting to receive a first home visit when the child was 5 month-old (Jetté & Desgroseillers, 2000). All families had received detailed written information about the aims and procedures of the study and signed a consent form. The protocol was approved by the Quebec Institute of Statistics.

Among the families who participated to the first home visit, 2120 agreed to be re-surveyed regularly during the following years. Here, we focus on all families who had provided 6 serial ratings of children SA symptoms from age 1.5 to 6 years (Battaglia et al., 2016), and who maintained participation into the QLSCD until age 13 years. Sample size varied across waves of assessment and types of data collection, with 2.2% mean annual attrition rate (Supplemental Figure 2).

Through growth mixture modeling of longitudinal data in the QLSCD, we had identified 4 SA trajectories between the age of 1.5 and 6 years (Battaglia et al., 2016; see Supplemental Figure 1). The 4 SA trajectories had shown significant differences for time stability and association with some early-life risk factors since early-childhood. At age 6 years, in the High-Increasing group, SA symptoms had remained pervasive and uniquely associated with higher SA ratings made by teachers (Battaglia et al., 2016). The High-Increasing group was therefore deemed as clinically pertinent and potentially informative longitudinally. We expected this trajectory to reveal longitudinal relationships with one or more of the outcome measures in this study of mid childhood/adolescence.

Measures and Procedure

Serial assessments took place when children were aged 8, 10, 12, and 13 years. Table 1 shows a breakdown by child's age-at-assessment of the data collection procedures, including: subject under study, outcome measures, informant, instruments.

Internalizing and Externalizing Symptoms. Ratings of internalizing symptoms (INT) in the QLSCD 8-12 years interval encompassed: 1) Anxiety symptoms, and 2) Depression symptoms, based on 6 items measured on a 3-point scale selected from the School Behavior Questionnaire (Behar & Stringfield, 1974) common to the 'anxious/depressed' and 'emotionally reactive' CBCL subscales (Achenbach, 1991). These same measures of INT have been used in large population studies, showing satisfactory psychometric properties (Boyle et al., 1993). Ratings of 20 externalizing symptoms' (EXT) items in the QLSCD 8-12 year interval encompassed 4 domains: 1) Hyperactivity, 2) Physical Aggression, 3) Opposition, 4) Behavior Disorder, based on the Social Behavior Questionnaire (Tremblay et al., 1991). The same INT/EXT measures were used for all informants: teachers, person most knowledgeable of the child (PMK, 99.7% of times the mother), and children themselves. See supplemental materials for detailed description of these measures.

Academic Achievement. Teachers rated the overall academic achievement at age 8, 10 and 12 years between the months of March and June, by answering the following question in mailed questionnaires: '*Relative to his/her classmates, how would you rate this child's current overall academic achievement?'* in 5-point ratings (ranging from 1: poor, to 5: excellent).

Physical Health. The PMK rated during a face-to-face interview with a trained research assistant the child's overall physical health at age 8, 10, 12, and 13 years by answering the question '*How would you rate the child's overall physical health?*' in 5-point ratings (ranging

from 1: excellent, to 5: poor). At the same time points, the PMK reported on child's common chronic physical conditions (including: diabetes, cardio-circulatory diseases, headaches, allergy, bronchitis/pneumonia, eczema, renal diseases, and asthma episodes) that had manifested during the past 12-months, had lasted/were expected to last for 6 months or more, and had caused significant impairment (Nikiéma, Spencer, & Séguin, 2010).

Maternal Anxiety. When children were aged 8 and 12 years, mothers reported by self-administered questionnaires their anxiety symptoms on 6 items encompassing 3 domains: 1) panic/agoraphobia; 2) generalized anxiety; 3) obsessive-compulsive. Answers were arranged in 8-point scales ranging from 'never occurs' to 'constantly occurs' (see supplemental materials for detailed description of this measure).

Analyses

Our main goal was to evaluate how participants who had been assigned to the High-Increasing SA trajectory group between 1.5 and 6 years differed from subjects in the remaining 3 SA trajectories across the 4 outcome domains, between the age of 8 and 13 years. For each time point of assessment, we ran univariate/multivariate analyses of variance (MANOVA) or covariance (ANCOVA/MANCOVA) of child's: a) INT or EXT, b) academic achievement, c) overall physical health, and d) types of maternal anxiety. The grouping factor was child's belonging in one of the four trajectories of SA between age 1.5 and 6 years (Battaglia et al., 2016). Significant general ANOVA results were followed by post-hoc Scheffé tests of differences between the High-Increasing and the 3 other trajectory groups.

To control for sex, and the correlation between EXT and INT, the MANCOVAs of participants' symptoms included sex, and EXT/ INT as covariates. Since the PMKs was almost invariably the mother, and anxiety can affect a mother's perception of her child's health, we

controlled for maternal anxiety in the analyses of maternal ratings of child's INT and physical health.

Associations between SA trajectory group memberships, and presence of prospective chronic physical conditions between age 8 and 13 were analysed by χ^2 tests applied to the contingency tables, with p values adjusted after Bonferroni's correction.

Results

Table 2 shows the MANCOVA results of INT symptoms (covariates: 1) child's sex and EXT, and 2) mother's anxiety for PMK's ratings of child's INT), according to SA trajectories. Participants from the High-Increasing SA trajectory showed consistently more internalizing – mostly anxious- symptoms compared to members in the other 3 trajectory groups, across most assessment time points. No significant differences were detectable across the 4 different EXT subscales (hyperactivity/aggression/opposition/behavioral disorder, sex and INT as covariates) at age 8, 10, 12 across the 4 SA trajectories (data available from authors upon request).

Table 3 shows the results of ANOVAs of academic achievement between age 8 and 12 years, and the *p* values by Scheffé's post-hoc testing. Participants in the High-Increasing trajectory achieved generally less than children in the 3 other trajectory groups, with the comparisons to the Low-Persistent normative trajectory yielding the most consistent picture.

Table 4 shows the results of ANCOVA -with maternal anxiety as the covariate- of physical health ratings from age 8 to 13 years. Children in the High-Increasing group were generally rated as more prone to physical illnesses, again with the comparisons to the Low-Persistent trajectory yielding the most consistent picture. Analyses of the frequencies of chronic illnesses across the 4 SA trajectories revealed significant differences only for: asthma at age 10 ($\chi^2 = 9.84$, $df = 3$, $p = 0.020$), headaches at age 12 years ($\chi^2 = 10.99$, $df = 3$, $p = 0.012$), and

asthma at age13 years (χ^2 = 7.86, *df* = 3, *p* = 0.049). At age 13 children in the 4 SA trajectory groups also differed for having developed asthma symptoms under exercise (χ^2 = 9.28, *df* = 3, *p* = 0.026) and having received asthma-related medication (χ^2 = 13.32, *df* = 3, *p* = 0.004) at least once during the past 12 months. All the aforementioned incidences were systematically higher among participants in the High-Increasing compared to the other 3 SA trajectories, and 2- to 3-fold increased incidence compared to the normative, Low-Persistent group (Table S1).

Table 5 shows the results of ANOVA of 3 specific types of anxiety symptoms reported by mothers when children were aged 8 and 12 years, with the relative p values yielded by Scheffé's post-hoc testing. Mothers of children in the High-Increasing trajectory rated themselves as significantly and consistently more anxious than mothers of children in the other trajectories. Maternal panic-agoraphobic symptoms, and to a lesser extent obsessive-compulsive symptoms, most consistently and significantly marked the association with child's belonging in the High-Increasing SA trajectory.

Discussion

Compared to participants whose pre-school SA had remained low, or had followed self-limiting trajectories, participants with prominent and persistent SA between age 1.5 and 6 years went on to show specific, clinically relevant outcomes throughout mid-childhood and pre-adolescence. They had more internalizing -mostly anxious- but not externalizing symptoms, worse overall academic achievement, poorer physical health, and had mothers with higher anxiety scores of prevailing panic-agoraphobic nature. These associations emerged consistently at multiple times of assessment, through different informants, via independent diagnostic instruments, and reflect the breadth of the repercussions of high and persistent SA when it is monitored from early-childhood into mid-childhood and adolescence.

The longitudinal relationship between High-Increasing SA and internalizing, rather than externalizing, symptoms is consistent with the participants' symptoms profile between age 1.5 and 6 years (Battaglia et al., 2016). Similar to our results, the GSMS showed an evolution of childhood SEPAD confined into the internalizing (agoraphobia most prominently), not externalizing, diagnostic domain (Copeland et al., 2009; Copeland et al., 2014). However, in the GSMS the earliest age at assessment was 9 years, and the longitudinal associations with internalization were estimated at 19-21 years (Copeland et al., 2009). By revealing an earlier point of inception, our findings indicate that high and enduring early-childhood SA maps an anxiety condition that tends to persist true throughout mid childhood and preadolescence (our data), possibly extending into early adulthood.

The generally worse academic achievement of High-Increasing SA, a major index of functionality for children and adolescents (Costello, Egger, & Angold, 2005), further supports the notion that participants in this trajectory have a clinical anxiety condition, and is consistent with both the WHOMHS and NCS findings of worse educational attainment associated with adult SEPAD (Silove et al., 2015; Shear et al., 2006).

Participants with pre-school High-Increasing SA had comparatively poorer physical health later in childhood and pre-adolescence. This relation emerged most consistently in the comparisons with the Low-Persistent SA, normative trajectory. The finding was controlled for maternal anxiety, and cannot be attributed to a confounding effect of socio-economic status, for which participants in the High-Increasing and Low-Persistent trajectories were no different (Battaglia et al., 2016). This datum supports findings from both child (Copeland et al., 2014) and adult (Shear et al., 2006) SEPAD. Fine-grained analyses across 8 common chronic physical conditions showed that the High-Increasing SA trajectory was longitudinally associated with two

specific -yet apparently disjointed- health issues; asthma and headache.

Higher-than-expected asthma and respiratory conditions have been described in childhood SEPAD (Fiese, Winter, Wamboldt, Anbar, & Wamboldt, 2010). Altered respiratory physiology and hypersensitivity to mild suffocative stimuli -epitomised by CO_2 hypersensitivity – can mediate the relationship between asthma and SA/SEPAD (Fiese et al., 2010; Grassi et al., 2013; Pine et al., 2000).

An excess of headache was the other physical issue associated with High-Increasing SA. This suggests that beyond the altered respiratory physiology, altered nociception may characterize high SA/SEPAD. Children and adolescents with headaches have an excess of anxiety disorders including SEPAD (Bellini et al., 2013), with migraine and abdominal pain showing strong correlations cross-sectionally and longitudinally (Galli et al., 2007). While independent replication of our finding is needed, it is worth noticing that dyspnea and pain share emotion-related brain networks (Von Leupoldt et al., 2009).

Animal modeling of maternal separation offers further unifying principles for our results. In addition to triggering SA behavior in pups (D'Amato et al., 2011), early interference with maternal cares evokes both respiratory hypersensitivity (excessive hyperventilation) to CO_2, and increased pain sensitivity (D'Amato et al., 2011; Cittaro et al., 2016). These two distinct but interrelated enhancements are underlain by epigenetic enrichment and augmented neural expression of the acid-sensing ion channels ASIC (Cittaro et al., 2016), that are concurrently implicated in detecting transient brain acidification driven by heightened CO_2 (D'Amato et al., 2011), pain (Wemmie, Taugher, & Kreple, 2013) and airway hyper-reactivity (Reznikov et al., 2016), a hallmark feature of asthma.

Some of the environmental components underlying these dynamics are known: early-life adversities interact with genetic factors to enhance reactivity to anxiety-provoking and brain acidifying CO_2 challenges both in man (Spatola et al., 2011) and animals (D'Amato et al., 2011), and disruption of familial ties are risk factors common to heightened SA (Battaglia et al., 2016), SEPAD (Silove et al., 2015), and headache (Lee et al., 2009). Should a diathesis for altered nociception be confirmed by future studies of childhood SA/SEPAD, then manifestations of SEPAD such as headache and abdominal pain might be allowed explanations that are alternative to the routinely assumed roles of: 'eliciting parental attention', 'maintaining an anxious child safely at home', that are common place in clinical discussions.

Our study also provided a unique opportunity for linking early-childhood SA/SEPAD to maternal anxiety longitudinally in a large population-based sample. Compared to mothers of participants in the other 3 SA trajectories, mothers of children in the High-Increasing SA trajectory endorsed higher anxiety scores consistently over time. This was especially true for panic-agoraphobia, and to a lesser degree, obsessive-compulsive and generalized anxiety symptoms. Familial-genetic continuity between childhood SA/SEPAD and adult PD-AGO is thus supported by our longitudinal population-based family study (Roberson-Nay et al., 2010; Roberson-Nay, Eaves, Hettema, Kendler, & Silberg, 2012). Our research design is less exposed to some confounders -including some recollection and selection biases- that are proper of the cross-sectional, high-risk, or patient-control designs (Roberson-Nay et al., 2010).

Some potential limitations apply. First, the QLSCD circumscribed the assessments of SA to the 1.5-6 year interval: we could not address the longitudinal stability of SA *per se* beyond age 6. However, general population follow-up data show swift decrease of SA occurring precisely within the temporal window tracked by this study (Copeland et al., 2009; Copeland et al., 2014).

Second, our data on EXT were exclusively based on teachers' ratings, while INT data were based on multiple informants' ratings. However, comparative analyses of multiple raters' responses showed that teachers' ratings of EXT are sensitive and the most valuable to predict EXT-related clinical repercussions (Stanger & Lewis, 1993), while multiple raters are essential for INT, due to comparatively reduced inter-rater consistency. Third, we analyzed INT/EXT by a reduced number of 3-point items: this may have compressed variance and forced it into narrow categories, as partly reflected by the small eta squares. Fourth, since PD typically manifests after puberty (Copeland et al., 2014; Battaglia et al., 1995; Battaglia, Bertella, Bajo, Binaghi, & Bellodi, 1998), a more extended follow-up of this cohort will be necessary to address the association between SA and PD longitudinally. Fifth, the QLSCD conservative approach to assess chronic physical conditions could result into some loss of sensitivity, and explain the lower than expected 12-month prevalence of some physical illnesses. Coherently, in the QLSCD cohort, across-waves' computations –but not necessarily 12-month prevalence figures- of asthma reports (Nikiéma, et al., 2010) yielded figures comparable with Canadian statistics (http://www.statcan.gc.ca). The prevalence of chronic headache was also lower than expected (http://www.statcan.gc.ca/pub/82-003-x/2014006/article/14033-eng.htm), again possibly indicating relative insensitivity of data collection. The High-Increasing and Low-Increasing groups had similar prevalence of headaches; however, these were clearly in excess compared to the normative Low-Decreasing group. More generally, we based our assessments on questionnaires with a relatively limited number of items for each diagnostic category. This was especially true for physical health and maternal psychopathology, and may have affected the specificity and sensitivity of some findings. Structured interviews, as adopted by cross-sectional studies (e.g.: WHOMS), can gather better-detailed data, but they could prove

burdensome/unfeasible in a longitudinal multi-informant study like ours. Ability to control for a larger set of confounders/co-occurring conditions would also be important, and future research will clarify whether our findings are unique to SEPAD, or if -and to what extent- they apply to other anxiety conditions. Sixth, ratings of maternal anxiety yielded mean scores indicating comparatively low anxiety levels. One could wonder whether child-mother interplays in the High-Increasing group may have contributed to raise maternal anxiety ratings. However, the panic-agoraphobic symptoms that were more distinctive of mothers in the High-Increasing group have their typical onset (Battaglia et al., 1995; Battaglia et al., 1998) before the age at which mothers in the QLSCD gave birth to children (mean: 28.5 years). These elements, together with evidence from metanalyses of SEPAD (Scaini et al., 2012), support a primarily familial-genetic relationship linking child's elevated SA to maternal panic-agoraphobia, and to a lesser degree, a role for shared environmental influences including mother-child interplays.

Conclusions

Very few surveys investigated the evolution of pre-school separation anxiety into mid-childhood/early adolescence. In this study, most comparisons between participants with high-and-persistent separation anxiety in pre-school years and participants who had followed milder/self limiting trajectories, showed significant excesses of: a) internalizing behaviors, b) maternal panic-agoraphobia, c) worse academic achievement, d) worse physical health, in the High-Increasing trajectory. The latter trajectory was associated with specific concentration of asthma-related conditions and headaches between age 10 and 13. Pre-school high-increasing separation anxiety appears as a gateway towards multiple health and academic issues: this can inform the early deployment of clinical resources at the earlier signs of the more impairing manifestations.

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Table 1. Longitudinal outcomes measures by multi-informants and child's age-at-assessment

Subject	Outcome	Informant	Child age (years) at data collection	Method of Assessment
Child	Internalising	Child	10, 12	Face-to-face interview
		Teacher	8, 10, 12	Questionnaire
		PMK	8	Face-to-face interview
Child	Externalising	Teacher	8, 10, 12	Questionnaire
Child	Academic	Teacher	8, 10, 12	Questionnaire
Child	Physical Health	PMK	8, 10, 12, 13	Face-to-face interview + Report of diagnosis by health professionals
Mother	Anxiety	Mother	8, 12	Self-administered questionnaire

PMK = Person most knowledgeable about the child

Table 2. MANCOVAs of child internalizing symptoms at ages 8, 10, and 12 by former trajectories of SA symptoms

Internalizing symptoms by informant	Mean (SD) High-I	Mean (SD) Other trajectories	F	*p*	η^2
8 years					
Anxiety: Teacher			**6.79**	**0.00**	**0.018**
High-I vs. High-D	1.71 (0.56)	1.55 (0.51)		**0.03**	
High-I vs. Low-I		1.49 (0.50)		**0.00**	
High-I vs. Low-P		1.46 (0.50)		**0.00**	
Anxiety: PMK			**10.30**	**0.00**	**0.032**
High-I vs. High-D	1.77 (0.52)	1.57 (0.46)		**0.01**	
High-I vs. Low-I		1.62 (0.43)		0.06	
High-I vs. Low-P		1.46 (0.41)		**0.00**	
Depression: Teacher			**3.19**	**0.02**	**0.009**
High-I vs. High-D	1.39 (0.47)	1.33 (0.41)		0.14	
High-I vs. Low-I		1.32 (0.41)		**0.03**	
High-I vs. Low-P		1.29 (0.38)		**0.00**	
Depression: PMK			**5.71**	**0.00**	**0.018**
High-I vs. High-D	1.47 (0.35)	1.36 (0.38)		0.51	
High-I vs. Low-I		1.46 (0.39)		1.00	
High-I vs. Low-P		1.34 (0.33)		0.06	
10 years					
Anxiety: Teacher			**11.09**	**0.00**	**0.038**
High-I vs. High-D	1.84 (0.63)	1.52 (0.54)		**0.00**	
High-I vs. Low-I		1.49 (0.52)		**0.00**	
High-I vs. Low-P		1.44 (0.51)		**0.00**	
Anxiety: Child			**2.95**	**0.03**	**0.010**
High-I vs. High-D	1.77 (0.56)	1.75 (0.45)		0.94	
High-I vs. Low-I		1.65 (0.44)		0.11	
High-I vs. Low-P		1.63 (0.46)		**0.05**	
Depression: Teacher			**3.65**	**0.01**	**0.013**
High-I vs. High-D	1.47 (0.49)	1.29 (0.42)		**0.00**	
High-I vs. Low-I		1.26 (0.41)		**0.00**	
High-I vs. Low-P		1.26 (0.40)		**0.00**	
Depression: Child			1.03	NS	0.004
High-I vs. High-D	1.56 (0.46)	1.46 (0.42)			
High-I vs. Low-I		1.43 (0.38)			
High-I vs. Low-P		1.46 (0.41)			
12 years					
Anxiety: Teacher			**4.20**	**0.01**	**0.014**
High-I vs. High-D	1.44 (0.50)	1.49 (0.48)		0.37	
High-I vs. Low-I		1.58 (0.54)		**0.01**	
High-I vs. Low-P		1.46 (0.52)		0.47	
Anxiety: Child			**3.90**	**0.01**	**0.013**
High-I vs. High-D	1.66 (0.54)	1.46 (0.48)		**0.02**	
High-I vs. Low-I		1.59 (0.51)		0.49	
High-I vs. Low-P		1.50 (0.48)		**0.03**	
Depression: Teacher			1.84	NS	0.006
High-I vs. High-D	1.37 (0.45)	1.33 (0.46)			
High-I vs. Low-I		1.33 (0.45)			
High-I vs. Low-P		1.26 (0.39)			
Depression: Child			1.46	NS	0.005
High-I vs. High-D	1.47 (0.48)	1.33 (0.33)			
High-I vs. Low-I		1.38 (0.40)			
High-I vs. Low-P		1.36 (0.39)			

Significant results after controlling for sex, concurrent externalizing symptoms, and maternal anxiety (when INT was rated by PMK, meaning: Person most knowledgeable about the child) are indicated in bold; NS = Non-significant results; High-I = High-Increasing trajectory of separation anxiety (6.9%); High-D = High-Decreasing trajectory of separation anxiety (10.8%); Low-I = Low-Increasing trajectory of separation anxiety (22.1%); Low-P = Low-Persistent trajectory of separation anxiety (60.2%). η^2 indicates effect size.

Table 3. ANOVAs of child academic achievement at ages 8, 10, and 12 by former trajectories of SA symptoms

Children academic variables	Mean (SD) High-I	Mean (SD) Other trajectories	F	*p*	η^2
8 years					
Overall achievement			**5.47**	**0.00**	**0.019**
High-I vs. High-D	3.61 (0.95)	3.80 (0.90)		0.15	
High-I vs. Low-I		3.91 (0.89)		**0.01**	
High-I vs. Low-P		4.01 (0.87)		**0.00**	
10 years					
Overall achievement			**6.78**	**0.00**	**0.025**
High-I vs. High-D	2.90 (1.12)	3.26 (1.13)		**0.05**	
High-I vs. Low-I		3.33 (1.19)		**0.01**	
High-I vs. Low-P		3.52 (1.13)		**0.00**	
12 years					
Overall achievement			**5.82**	**0.00**	**0.019**
High-I vs. High-D	2.97 (1.07)	3.25 (1.10)		0.12	
High-I vs. Low-I		3.25 (1.18)		0.09	
High-I vs. Low-P		3.49 (1.14)		**0.00**	

Significant results are indicated in bold; tests of differences between the High-Increasing and the 3 other trajectory groups were conducted by post-hoc Scheffé test. High-I refers to the High-Increasing trajectory of separation anxiety (6.9%); High-D refers to the High-Decreasing trajectory of separation anxiety (10.8%); Low-I refers to the Low-Increasing trajectory of separation anxiety (22.1%); Low-P refers to the Low-Persistent trajectory of separation anxiety (60.2%). η^2 indicates effect size.

Table 4. ANCOVAs of child physical health at ages 8, 10, 12 and 13 years by former trajectories of SA symptoms

Child health	Mean (SD) High-I	Mean (SD) Other trajectories	F	*p*	η^2
8 years					
Overall physical health			**4.01**	**0.01**	**0.013**
High-I vs. High-D	1.65 (0.76)	1.44 (0.64)		**0.01**	
High-I vs. Low-I		1.50 (0.65)		0.24	
High-I vs. Low-P		1.40 (0.62)		**0.01**	
10 years					
Overall physical health			**3.82**	**0.01**	**0.012**
High-I vs. High-D	1.62 (0.79)	1.50 (0.68)		0.25	
High-I vs. Low-I		1.51 (0.67)		0.59	
High-I vs. Low-P		1.37 (0.60)		**0.02**	
12 years					
Overall physical health			**3.73**	**0.01**	**0.010**
High-I vs. High-D	1.64 (0.79)	1.44 (0.68)		**0.02**	
High-I vs. Low-I		1.50 (0.63)		**0.04**	
High-I vs. Low-P		1.38 (0.60)		**0.01**	
13 years					
Overall physical health			**3.14**	**0.02**	**0.009**
High-I vs. High-D	1.62 (0.74)	1.46 (0.66)		0.10	
High-I vs. Low-I		1.52 (0.64)		0.23	
High-I vs. Low-P		1.36 (0.58)		**0.01**	

Significant results after controlling for maternal anxiety symptoms are indicated in bold; High-I refers to the High-Increasing trajectory of separation anxiety (6.9%); High-D refers to the High-Decreasing trajectory of separation anxiety (10.8%); Low-I refers to the Low-Increasing trajectory of separation anxiety (22.1%); Low-P refers to the Low-Persistent trajectory of separation anxiety (60.2%). η^2 indicates effect size.

Table 5. ANOVAs of mothers' self-assessed anxiety symptoms by child's trajectories of SA symptoms

Mother's anxiety	Mean (SD) High-I	Mean (SD) Other trajectories	F	*p*	η^2
8 years					
Panic/agoraphobia			**26.03**	**0.00**	**0.059**
High-I vs. High-D	1.87 (1.38)	1.48 (1.38)		**0.02**	
High-I vs. Low-I		1.29 (1.12)		**0.00**	
High-I vs. Low-P		0.94 (1.03)		**0.00**	
Generalized Anxiety			**13.58**	**0.00**	**0.032**
High-I vs. High-D	2.60 (1.58)	2.23 (1.60)		0.07	
High-I vs. Low-I		2.05 (1.53)		**0.00**	
High-I vs. Low-P		1.71 (1.44)		**0.00**	
Obsessive-compulsive			**22.37**	**0.00**	**0.051**
High-I vs. High-D	1.56 (1.70)	1.11 (1.29)		**0.01**	
High-I vs. Low-I		1.02 (1.41)		**0.00**	
High-I vs. Low-P		0.62 (1.10)		**0.00**	
12 years					
Panic/agoraphobia			**16.51**	**0.00**	**0.040**
High-I vs. High-D	1.70 (1.43)	1.27 (1.33)		**0.01**	
High-I vs. Low-I		1.21 (1.11)		**0.00**	
High-I vs. Low-P		0.90 (1.08)		**0.00**	
Generalized Anxiety			**10.47**	**0.00**	**0.025**
High-I vs. High-D	2.70 (1.51)	2.17 (1.54)		**0.02**	
High-I vs. Low-I		2.23 (1.61)		**0.02**	
High-I vs. Low-P		1.84 (1.55)		**0.00**	
Obsessive-compulsive			**16.32**	**0.00**	**0.039**
High-I vs. High-D	1.38 (1.45)	0.98 (1.43)		**0.02**	
High-I vs. Low-I		0.98 (1.38)		**0.01**	
High-I vs. Low-P		0.59 (1.06)		**0.00**	

Significant results are indicated in bold; tests of differences between the High-Increasing and the 3 other trajectory groups by post-hoc Scheffé test. High-I refers to the High-Increasing trajectory of separation anxiety (6.9%); High-D refers to the High-Decreasing trajectory of separation anxiety (10.8%); Low-I refers to the Low-Increasing trajectory of separation anxiety (22.1%); Low-P refers to the Low-Persistent trajectory of separation anxiety (60.2%). η^2 indicates effect size.