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Association between childhood asthma and ADHD symptoms in adolescence – a prospective population-based twin study

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Abbreviations:

ADHD	attention deficit hyperactivity disorder
HI	hyperactivity-impulsivity
IN	inattention
TCHAD	The Twin study of CHild and Adolescent Development
ICS	inhaled corticosteroids
OR	odds ratio
CI	confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
CTCT	cross-trait cross-twin

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Dr Almqvist had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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Abstract

Background

Cross-sectional studies report a relationship between childhood asthma and ADHD symptoms, but the mechanisms are yet unclear. Our objective was to investigate the longitudinal link between childhood asthma and the two dimensions of ADHD (hyperactivity-impulsivity, HI and inattention, IN) in adolescence. We also aimed to explore the genetic and environmental contribution and the impact of asthma medication.

Methods

Data on asthma, HI and IN, birth weight, socioeconomic status, zygosity and medication was collected from the Swedish Medical Birth Register and through parental questionnaires at ages 8-9 and 13-14 years on 1,480 Swedish twin pairs born 1985-86. The association between asthma at age 8-9 and ADHD symptoms at age 13-14 was assessed with generalized estimating equations, and twin analyses to assess the genetic or environmental determinants were performed.

Results

Children with asthma at age 8-9 had an almost twofold increased risk of having one or more symptom of HI (OR 1.88, 95% CI 1.18-3.00) and a more than two-fold increased risk to have three symptoms or more of HI (OR 2.73, 95% CI 1.49-5.00) at age 13-14, independent of asthma medication. For IN, no significant relationship was seen. Results from twin modeling indicate that 68% of the phenotypic correlation between asthma and HI (r=0.23, 0.04-0.37) was due to genetic influences.

Conclusions

Our findings suggest that childhood asthma is associated with subsequent development of HI in early adolescence, which could be partly explained by genetic influences. Early strategies to identify children at risk may reduce burden of the disease in adolescence.

Introduction

Asthma and attention-deficit/hyperactivity disorder (ADHD) are both common chronic disorders affecting children. Asthma is characterized by wheezing, breathlessness and chest tightness affecting about 6-8% in childhood and adolescence (1). ADHD is characterized, according to DSM-IV by hyperactivity-impulsivity (HI) and inattention (IN) with a prevalence of 3-5% in school-aged children (2). Several previous studies, including a meta-analysis (3), have shown an association between asthma and ADHD symptoms (4-6), though studies do exist where a relationship was not found (7, 8). One study of 102,253 children from the National Survey of Children's Health showed a two-fold increased prevalence of ADHD among children with asthma, and even higher rates of ADHD among children with severe asthma (9). Similar dose-response effects have been observed in relation to broad assessments of behavioral problems (10, 11).

The nature of the relationship between asthma and ADHD is not entirely clear. None of the previous studies have distinguished between the two DSM-IV ADHD symptom dimensions, which is a critical issue as HI and IN have partly distinct etiologies (12) and developmental outcomes (13). All of the prior asthma-ADHD association studies have been cross-sectional, which constrains possibilities to study the direction of effect and the developmental link between the two conditions. In addition, possible mechanisms underlying this association remain to be investigated.

Firstly, the association between asthma and ADHD could be due to shared risk factors. Low birth weight, impaired fetal growth and low socioeconomic status are known risk factors for asthma (14, 15) and ADHD (16, 17). None of the previous studies on the asthma-ADHD association have adjusted for birth weight, while most studies have adjusted for gender and different measures of socioeconomic status (5, 9, 10) with remaining stable estimates.

Secondly, the link asthma-ADHD may be due to asthma medication such as inhaled corticosteroids (ICS). There have been case reports of altered behavior and psychosis in small children using ICS (18), but larger studies suggest no evidence of major adverse neuropsychiatric effects (19). One study was able to show higher rates of hyperactivity in children with asthma compared to healthy controls; however the rates were similar to other children under specialist care for non-respiratory complaints, indicating that ICS does not affect behavior (20).

Thirdly, shared genetic factors could account for the observed association between asthma and ADHD. However, although twin studies consistently have shown that asthma and ADHD are heritable disorders (12, 21) examinations of genetic and shared contributions to the overlap between the two conditions is still lacking. Two previous family-based studies have examined the potential impact of familial effects for the association, but failed to find support for such a conclusion (8, 22). Clearly, additional research is needed to clarify this issue.

Our overall aim was to study the longitudinal relationship between childhood asthma and ADHD in adolescence, including genetic and other confounding factors and the impact of asthma medication in a prospective study of 1,480 twin pairs followed from 8-9 to 13-14 years of age. We used a quantitative measure of ADHD to assess DSM-IV symptoms of hyperactivity-impulsivity and inattention, since sophisticated statistical modeling techniques have been used to show that ADHD exists on a severity continuum (23).

Methods

Study design and population

The Twin study of CHild and Adolescent Development (TCHAD) is a longitudinal study from childhood onwards. Study population and data collection has been described elsewhere (24). Data was collected by parental questionnaires when twins born between May 1985 and December 1986 were 8-9 (wave 1, response rate 74.9 %) and 13-14 (wave 2) years old, Figure 1. The waves were separate, so that non-responders from wave 1 were still eligible for participation at age 13-14.

Variables

Asthma was measured as a main outcome by using the standardized question in the International study of Asthma and Allergies in Childhood (ISAAC) study "Has your child ever had asthma" (yes/no). If "yes", follow-up questions regarding age of onset and number of asthma episodes in the previous year were asked. Eczema was measured by the standardized question "Has your child ever had eczema" (yes/no).

Parents provided ratings of ADHD symptoms in their children via a checklist of 14 DSM-IV based items (2) and were asked to check symptoms persisting for at least six months (0/1). A hyperactivity-impulsivity scale was created from the sum of 8 symptoms of hyperactivity-impulsivity listed in DSM-IV and an inattention scale from the sum of 6 items related to inattention. There are strong arguments for considering ADHD as an extreme of a dimensional trait (23) so cutoffs were imposed to create multiple dichotomized variables that identify individuals with; a) one or more HI/IN symptoms (HI-1 and IN-1), b) two or more HI/IN symptoms (HI-2 and IN-2); and so on until f) six or more HI/IN symptoms (HI-6 and IN-6) (12, 25).

Birth weight data was obtained by linking data from TCHAD to the Swedish Medical Birth Register as previously described (16) and categorized into 500 gram intervals.

Socioeconomic status was classified according to the Nordic standard occupational classification and Swedish socio-economic classification (SEI) (26).

Medication was assessed in the questionnaire with the question ”does this child use medication on a regular basis”. All individuals with reported ICS and/or inhaled β2-agonist were considered using asthma medication. The questions on zygosity have been validated with DNA markers in previous studies and proved correct in 95% (24).

Statistical analysis

Odds ratio (OR) with 95% confidence intervals (CI) for the associations between asthma, HI and IN were estimated using the logit link in generalized estimating equations (GEE), which allow us to account for the dependent nature of the twin observations. The longitudinal analyses were exploratory and involved a series of regression models with the multiple dichotomized variables of HI or IN at age 13-14 as outcome variables and asthma at age 8-9 as a predictor. The models were applied with and without controlling for well established covariates, including sex, socioeconomic status, birth weight and eczema. We also added ADHD symptoms at age 8-9 into the model, to estimate the effect of asthma at age 8/9 on increasing HI/IN symptoms between age 8/9 and 13/14. Only data from children with complete answers on asthma, HI and IN were used in the fully adjusted model.

All the statistical analyses were performed in the SAS 9.1.3 using GENMOD procedure (SAS Institute, Inc., Cary, NC.).

Twin methods were used to examine how genetic and environmental factors contribute to the association between asthma and ADHD.

Basically, we fitted a bivariate liability threshold model in MX (27), to estimate the additive genetic (A), shared environmental (C)and non-shared environmental (E) contributions to the overlap in liability between asthma and ADHD. The model also estimates the genetic, shared and non-shared environmental correlations. This statistic varies from -1.0 to +1.0 and indicates the extent to which genetic and environmental influences in one measure overlap with those on a second measure and the genetic, shared and non-shared environmental contribution to the phenotypic correlation between two traits is obtained.

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

Results

The total study population consisted of all 1,812 responders with data on asthma and ADHD symptoms either at age 8-9, age 13-14 or both (Figure 1). In total, 2,134 children had complete answers on asthma and symptoms of ADHD (HI and IN) at age 8-9, 1,883 children had complete answers at age 13-14 and 1,754 children had complete answers at both ages. Table 1 shows rates of asthma HI-3 and IN-3 by background characteristics. Boys showed higher rates of asthma and IN-3. Socioeconomic status was significantly associated with HI and IN at age 8-9 and age 13-14, and birth weight was significantly associated with HI at age 8-9. Almost identical results were observed for all other levels of HI and IN (e.g. HI-4, HI-5, HI-6), data not shown.

In the cross-sectional analyses on the association between asthma and ADHD (HI and IN), the prevalence of twins with asthma increased in the higher categories of HI and IN at both age 8-9 and 13-14. The increase was continuous throughout the categories, although not significant at all levels (Table 2).

In the longitudinal analyses, children with asthma at age 8-9 were more likely to have parent-reported symptoms of HI at age 13-14 (Table 3) and more than two-fold increased risk of HI-3 at age 13-14 (OR 2.50, 95% CI 1.46-4.28) in the unadjusted models. The results were stable after adjusting for sex, birth weight and socioeconomic status. Results also remained at same level after adjustment for previous HI and IN symptoms (OR 2.73, 95% CI 1.49-5.00), suggesting an effect of asthma on change in ADHD symptoms. In stratified analyses of children without early symptoms of ADHD, OR remained stable. The association between asthma and HI did not change with adjustment for eczema (Table 3).

Asthma at age 8-9 was also associated with a significantly increased risk of IN 4-6 (ranging from OR 2.77, 95% CI 1.23-6.26 to OR 8.36, 95% CI 1.52-45.81). However, none of these associations were significant in the adjusted model.

Fifty-eight (44.6%) of the 130 asthmatic children with information regarding asthma medication at age 8-9 were using asthma medication on a regular basis at age 8-9, and fifty (35.5%) out of 141 at age 13-14. There was no significant difference in HI between asthmatic children with or without asthma medication.

Twin analyses were limited to HI-3, because higher cut-off values (i.e., HI-4, HI-5, HI-6) resulted in cells with few of zero participants. Table 4 shows intra-class and cross-trait cross-twin (CTCT; the correlation between twin1's status on asthma and the co-twin's status on HI) correlations for asthma at age 8-9 and HI-3 at age 13-14, by zygosity. MZ intra-class and CTCT correlations were consistently higher than the corresponding DZ correlations, suggesting substantial genetic influences on HI-3, asthma as well as on the overlap between the phenotypes. Bivariate liability threshold modelling suggest that the variance in liability of asthma was explained by genetic (74%; 95% CI: 0.69-0.86) and non-shared environmental influences (26%; 0.14-0.33) influences. The variance in liability of HI-3 was explained by genetic (76%; 0.58-0.88) and non-shared environmental (24%; 0.12-0.42) influences. The genetic and non-shared environmental correlations between asthma and HI-3 were estimated as 0.21 (0.00-0.51) and 0.29 (0.00-0.64), respectively. Calculations of the genetic and non-shared environmental contribution to the phenotypic correlation revealed that 68% of the phenotypic correlation between asthma and HI-3 (r = 0.23, 0.04-0.37) was due to genetic influences.

Discussion

We found that children with asthma at age 8-9 had an almost twofold increased risk of parent-reported HI at age 13-14, compared with children without asthma. The association was consistent also after adjustment for potential confounders. Results from the twin analyses indicate that the association between asthma and HI could be in part due to genetic influences. Thus our results, based on the first twin study on the longitudinal association between asthma and ADHD, support the hypothesis that there is a genetic overlap between asthma and HI phenotypes.

Previous studies have shown a cross-sectional association between asthma and ADHD or HI (5, 6, 9, 20). Important strengths of the current study are that the relationship between asthma and ADHD symptoms was examined prospectively over time, and that the two ADHD dimensions were assessed separately (13). Our study shows that childhood asthma predicts HI in adolescence but not IN, which provide further support for the distinction between the two symptom dimensions of ADHD. In line with the dimensional model of ADHD (23, 28, 29), the prospective asthma-HI link was observed across the range of severity in HI symptoms, and an almost linear increase in risk was seen for each additional HI symptom, which highlight the need for studies that evaluate how asthma is involved in the transition from milder to more severe levels of ADHD symptoms.

The association between parent-reported asthma and HI was stable for sex, birth weight and socioeconomic status. We saw an effect of low birth weight and socioeconomic status on ADHD symptoms at age 8-9 which was expected (16, 17), however birth weight and socioeconomic status had no effect of on asthma, in contrast to previous studies (14, 15). Recent studies have shown a relationship between ADHD, atopic eczema and sleeping problems (30, 31). We did not find any differences in the association between asthma and

symptoms of hyperactivity-impulsivity when adjusting for eczema. Our confounding measures of socioeconomic status, birth weight and eczema may not be strong enough to detect confounding, which could result in an overestimation of the association between asthma and ADHD symptoms. Moreover, our study did not show any significant differences regarding asthma medication and level of HI, which highlights the need of future studies (20).

The results from the twin analysis extends previous research by showing that the association between asthma and HI symptoms is partly influenced by genetic effects. However, despite the large sample, extreme levels of HI/IN and new cases of asthma were rare at age 13-14, which constrains the power of the twin analysis. It should also be noted that our results are inconsistent with two previous family-based studies (8, 22) that failed to identify a familial component underlying the asthma-ADHD association. Both previous studies were based upon a clinically referred sample, used DSM-III-criteria and did not distinguish between HI and IN. Nevertheless, our finding of a genetic overlap between asthma and HI should be considered in future molecular genetic investigations.

This study should be interpreted in the context of its limitations. First, asthma and symptoms of ADHD were assessed using parent-report questionnaires and it is important to underline that this is not equivalent to a diagnosis of ADHD. Also, relying on a single source of informant (i.e, parent-report) to assess ADHD symptoms could be considered to be a limitation of our study. Second, twin studies may not be generalizable, although studies indicate that twins do not differ from singletons concerning risk of asthma (32) while the results regarding ADHD are mixed (33, 34).

Third, although the response rate of this study was relatively high selective attrition is always a concern in longitudinal studies, however previous studies (25, 35) have suggested that bias due to selective attrition is limited.

Fourth, we did not have information on age of onset of ADHD and the possibilities to draw causal conclusions are constrained. For example, we cannot rule out that the observed association between asthma and HI may in part be explained by the presence of unmeasured ADHD symptoms in early childhood. In conclusion, this population-based longitudinal study indicates that early asthma is associated with an increased risk of elevated levels of hyperactivity-impulsivity later in life. These findings highlight the need for increased clinical attention to problems associated with ADHD symptoms in asthmatic children. Exploring the association between asthma and ADHD further may provide better opportunities to target early intervention and support to these children and their families.

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Figure 1. Study population and response rates at ages 8-9 and 13-14 in a cohort of 1,812 Swedish twins born 1985-1986.

TABLE 1. Study population characteristics, asthma and ADHD symptoms in a cohort of 1,812 Swedish twins born 1985-1986.

			Asthma			HI≥3			IN≥3		
	N	%	n	%	p	n	%	P	n	%	P
Age 8-9											
Total	1812		104	5.7		277	15.5		137	7.7	
Missing			-	-		25	-		18	-	
Gender											
Male	892	49.2	66	7.4		155	18.0		86	9.8	
Female	920	50.8	38	4.1	0.0028	122	13.5	0.0159	51	5.6	0.0010
Birthweight, g											
0-1999	211	11.8	15	7.1		37	17.9		22	10.5	
2000-2499	463	26.0	28	6.1		89	19.4		37	8.1	
2500-2999	704	39.5	41	5.8	0.3564	98	14.1	0.0166	50	7.2	0.1918
3000-3499	346	19.4	20	5.8		45	13.2		20	5.8	
≥3500	60	3.4	0	0		4	6.8		4	6.8	
Missing	28		0	0		4	14.3		4	14.3	
SEI											
Sei1	284	16.0	16	5.6		57	20.4		32	11.5	
Sei2	498	28.0	26	5.2		88	17.8		36	7.3	
Sei3	470	26.4	28	6.0	0.9387	49	10.6	<0.0001	28	6.0	0.0003
Sei4	386	21.7	21	5.4		34	8.9		16	4.2	
Other	142	8.0	10	7.0		39	27.7		19	13.5	
Missing	32		3	9.4		10	34.5		6	20.0	
Zygosity											
MZ	747	41.2	44	5.9		108	14.8		47	6.4	
DZ	1027	56.7	57	5.6	0.8083	165	16.2	0.8479	88	8.6	0.4406
Unknown	38	2.1	3	7.9		4	10.5		2	5.3	
Age 13-14											
Total	1812		138	7.7		128	7.1		125	6.9	
Missing	-		30	-		-	-		2	-	
Gender											
Male	892	49.2	90	10.3		71	8.0		71	8.0	
Female	920	50.8	48	5.3	<0.0001	57	6.2	0.1429	54	5.9	0.0814
Birthweight, g											
0-1999	211	11.8	19	9.2		19	9.0		18	8.5	
2000-2499	463	26.0	34	7.4		35	7.6		32	6.9	
2500-2999	704	39.5	61	8.8	0.2394	38	5.4	0.2425	48	6.8	0.7278
3000-3499	346	19.4	22	6.5		27	7.8		24	6.9	
≥3500	60	3.4	1	1.7		6	10.0		2	3.3	
Missing	28		1	3.6		3	10.7		1	3.6	
SEI											
Sei1	284	16.0	22	7.9		27	9.5		28	9.9	
Sei2	498	28.0	38	7.8		41	8.2		29	5.8	
Sei3	470	26.4	34	7.3	0.7215	24	5.1	0.0003	22	4.7	0.0305
Sei4	386	21.7	29	7.4		12	3.1		25	6.5	
Other	142	8.0	15	10.9		17	12.0		14	9.9	
Missing	32		1	3.3		7	21.9		7	21.9	
Zygosity											
MZ	747	41.2	56	7.6		45	6.0		45	6.0	
DZ	1027	56.7	76	7.5	0.1717	80	7.8	0.3510	76	7.4	0.3515
Unknown	38	2.1	6	15.8		3	7.9		4	10.5	

SEI=socioeconomic status. 1) Unskilled and semi-skilled workers 2) Skilled workers/Assistant non-manual employees 3) Intermediate non-manual collar workers 4) Employed and self-employed professionals, higher civil servants, and executives.
MZ=monozygotic.DZ=dizygotic

TABLE 2. Prevalence of Asthma and ADHD-symptoms and odds ratios (OR) for the association cross sectionally in a cohort of 1,812 Swedish twins born 1985-6.

No of symptoms ≥	Responders		Responders with Asthma		Association between ADHD-symptoms and Asthma	
	N	%	n	%	OR*	95% CI
Age 8-9						
HI						
0	2138	100.0	128	6.0		
1	910	42.6	55	6.0	1.03	0.72-1.47
2	592	27.7	42	7.1	1.31	0.89-1.93
3	337	15.8	26	7.7	1.39	0.88-2.19
4	200	9.4	18	9.0	1.63	0.96-2.78
5	118	5.5	13	11.0	1.94	1.03-3.66
6	56	2.6	7	12.5	1.89	0.77-4.65
IN						
0	2145	100.0	129	6.0		
1	839	39.1	61	7.3	1.40	0.97-2.02
2	384	17.9	33	8.6	1.61	1.06-2.45
3	177	8.3	19	10.7	1.81	1.05-3.10
4	62	2.9	10	16.1	2.53	1.23-5.20
5	21	1.0	3	14.3	1.55	0.36-6.63
6	7	0.3	1	14.3	2.08	0.34-12.61
Age 13-14						
HI						
0	1887	100.0	147	7.8		
1	442	23.4	48	10.9	1.65	1.16-2.37
2	231	12.3	24	10.4	1.36	0.86-2.15
3	137	7.3	18	13.1	1.84	1.09-3.12
4	78	4.1	11	14.1	1.78	0.87-3.64
5	36	1.9	8	22.2	3.10	1.26-7.61
6	20	1.1	5	25.0	2.88	0.80-10.33
IN						
0	1886	100.0	145	7.7		
1	655	34.7	56	8.6	1.19	0.84-1.70
2	287	15.2	23	8.0	1.01	0.62-1.65
3	135	7.2	14	10.4	1.37	0.76-2.49
4	54	2.9	8	14.9	1.75	0.72-4.26
5	21	1.1	4	19.1	1.86	0.44-7.81
6	7	0.4	2	28.6	4.29	0.98-18.75

N= total amount of responders on asthma and ADHD-questions who scored this level or higher.

* Reference category is no ADHD symptoms.

TABLE 3. Risk of symptoms of hyperactivity-impulsivity and inattention respectively at age 13-14 by asthma at age 8-9. N= 1,812.

	Unadjusted OR	(95% CI)	OR *	(95% CI)	OR *+	(95% CI)	OR **	(95% CI)	OR **+	(95% CI)
Hyperactivity at age 13-14										
HI-1	1.78	1.09-2.92	1.72	1.12-2.64	1.78	1.11-2.86	1.88	1.18-3.00	1.88	1.14-3.09
HI-2	2.34	1.33-4.14	1.83	1.09-3.07	2.09	1.16-3.77	1.80	1.04-3.11	2.09	1.14-3.85
HI-3	2.50	1.46-4.28	2.52	1.39-4.50	3.01	1.55-5.84	2.73	1.49-5.00	3.60	1.91-6.77
HI-4	2.99	1.62-5.54	3.14	1.60-6.17	3.41	1.62-7.19	2.80	1.30-6.03	3.33	1.44-7.68
HI-5	5.57	2.44-12.71	5.74	2.36-13.96	6.94	2.64-18.25	6.83	2.69-17.37	9.62	3.14-29.51
HI-6	8.92	3.17-25.10	10.00	3.15-31.78	NA	NA	14.32	3.48-58.99	NA	NA
Inattention at age 13-14										
IN-1	1.06	0.73-1.55	1.01	0.70-1.48	0.96	0.63-1.48	0.99	0.63-1.53	0.88	0.54-1.43
IN-2	1.21	0.73-2.00	1.17	0.69-1.98	1.28	0.71-2.28	1.08	0.62-1.88	1.17	0.65-2.09
IN-3	1.61	0.84-3.08	1.59	0.82-3.11	1.81	0.86-3.83	1.62	0.85-3.08	1.94	0.97-3.90
IN-4	2.77	1.23-6.26	2.59	1.13-5.95	2.36	0.85-6.52	2.03	0.86-4.78	2.14	0.81-5.64
IN-5	3.62	1.04-12.57	3.48	0.93-13.07	2.61	0.47-14.33	2.19	0.58-8.29	1.96	0.40-9.66
IN-6	8.36	1.52-45.81	NA	NA	NA	NA	NA	NA	NA	NA

* Adjusted for sex. socioeconomic status and birth weight.
*+Adjusted as above, and for eczema ever at age 8-9.
** Adjusted for sex. socioeconomic status, birth weight and for previous symptoms of inattention and hyperactivity.
**+ Adjusted as above, and for eczema ever at age 8-9.

TABLE 4. Tetrachoric correlation matrices estimated from LT model for MZ and DZ twins.

	N*	Asthma age 8-9	HI-3 age 13-14	CTCT Correlation
MZ	459	0.74	0.76	0.11
		(0.63-0.85)	(0.64-0.87)	(0.00-0.38)
DZ	650	0.41	0.33	0.08
		(0.24-0.58)	(0.17-0.48)	(0.00-0.30)

Note. N, number of twin pairs; MZ, monozygotic; DZ dizygotic.

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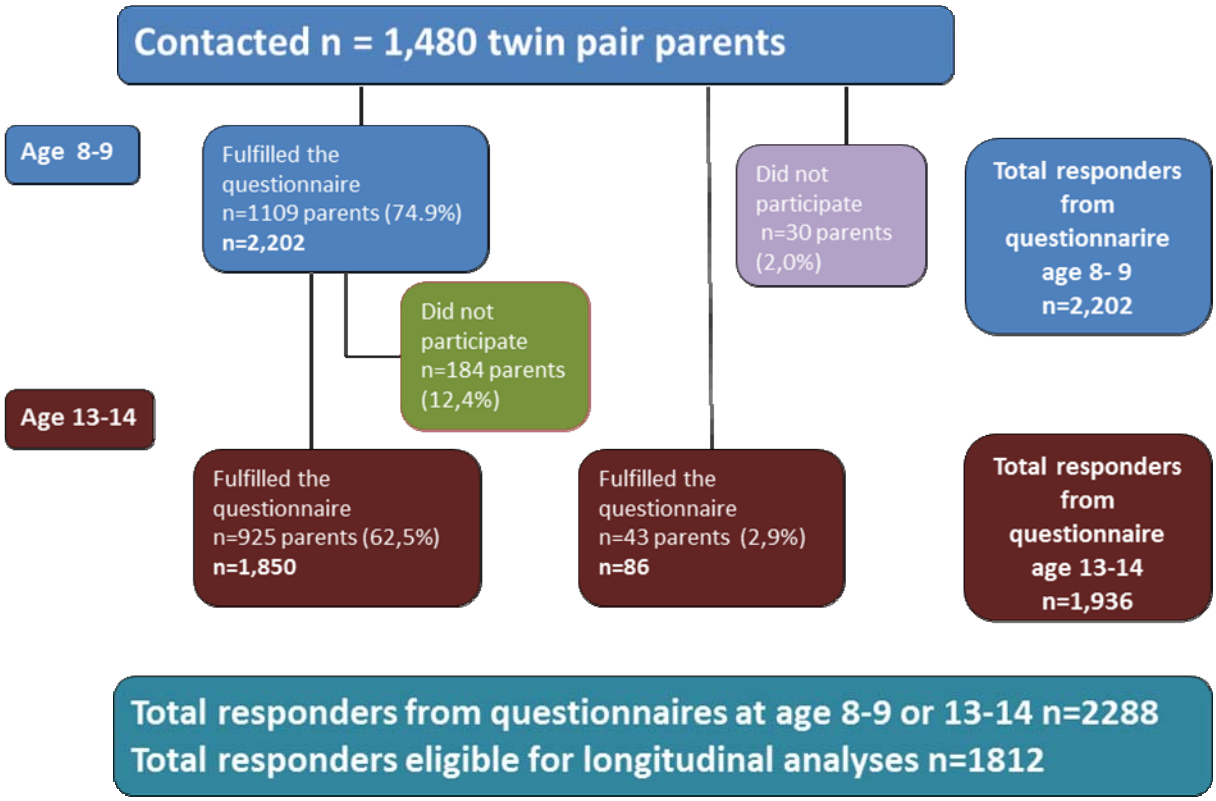
Contacted n = 1,480 twin pair parents
Age 8-9
Fulfilled the questionnaire n=1109 parents (74.9%) n=2,202
Did not participate n=184 parents (12,4%)
Did not participate n=30 parents (2,0%)
Total responders from questionnarire age 8- 9 n=2,202
Age 13-14
Fulfilled the questionnaire n=925 parents (62,5%) n=1,850
Fulfilled the questionnaire n=43 parents (2,9%) n=86
Total responders from questionnaire age 13-14 n=1,936
Total responders from questionnaires at age 8-9 or 13-14 n=2288
Total responders eligible for longitudinal analyses n=1812