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Persistence of parental-reported asthma at early ages: A longitudinal twin study

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Abstract

Background: Currently, we cannot predict whether a pre-school child with asthma-like symptoms will have asthma at school age. Whether genetic information can help in this prediction depends on the role of genetic factors in persistence of pre-school to school-age asthma. We examined to what extent genetic and environmental factors contribute to persistence of asthma-like symptoms at ages 3 to asthma at age 7 using a bivariate genetic model for longitudinal twin data.

Methods: We performed a cohort study in monozygotic and dizygotic twins from the Netherlands Twin Register (NTR, $n = 21{,}541$ twin pairs). Bivariate genetic models were fitted to longitudinal data on asthma-like symptoms reported by parents at age 3 and 7 years to estimate the contribution of genetic and environmental factors.

Results: Bivariate genetic modeling showed a correlation on the liability scale between asthma-like symptoms at age 3 and asthma at age 7 of 0.746 and the contribution of genetics was estimated to be 0.917. The genetic analyses indicated a substantial influence of genetic factors on asthma-like symptoms at ages 3 and 7 (heritability 80% and 90%, respectively); hence, contribution of environmental factors was low. Persistence was explained by a high (rg = 0.807) genetic correlation.

Abbreviations: A, additive genetic effects; ALSPAC, Avon longitudinal study of parents and children; APRS, asthma polygenic risk score; C, shared or common environment effects; DZ, dizygotic; E, non-shared environmental effects; GWAS, genome-wide association studies; NTR, Netherlands twin register; MZ, monozygotic; SNPs, single nucleotide polymorphisms; PIAMA, prevention and incidence of asthma and mite allergy.

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Conclusion: Parental-reported asthma-like symptoms at age 3 and asthma at age 7 are highly heritably. The phenotype of asthma-like symptoms at age 3 and 7 was highly correlated and mainly due to heritable factors, indicating high persistence of asthma development over ages 3 and 7.

KEYWORDS
asthma, asthma-like symptoms, children, discordant twin design

1 | INTRODUCTION

Asthma often originates early in life,[1,2] and its clinical presentation may be characterized by a remitting or relapsing course.[3–5] Currently, it is difficult to accurately identify asthma onset, because conclusive diagnostic tests suitable for young children are lacking.[2] Asthma-like symptoms, that is, wheezing, coughing, and shortness of breath, are common in early childhood, but insufficiently specific to diagnose asthma reliably.[2] At present, we are unable to predict which infant with asthma-like symptoms ultimately develops a transient phenotype, for example, remission of asthma-like symptoms, or persistent asthma, with continuation of asthma-like complaints up to school age.[6–9] Understanding to which extent childhood asthma onset is influenced by genetic and environmental factors and to which extent these contribute to remission and persistence may improve risk-stratification and facilitate targeted management of children at risk of persistent asthma.

The classical twin study is a common tool to estimate genetic and environmental contributions to complex human traits, including disease, based on the fact that monozygotic (MZ) twins are genetically (nearly) identical and dizygotic (DZ) twins share on average 50% of their segregating genes. Both types of twins share their prenatal environment and grow up in the same family environment. A larger resemblance in MZ compared to DZ twins for a trait or disease is consistent with a genetic contribution to that trait.[10] A study in Dutch 5-year-old twins with asthma-like symptoms and Swedish 9-to-12-year-old twins with mid-childhood asthma[11–13] suggested that genetics accounted for 60%–90% of variance in susceptibility to asthma. However, cross-sectional twin studies cannot address the childhood-asthma course and do not reveal contributions of genetics and environment to persistence or remission. High heritability at various ages does not necessarily imply that the same genes are active.[14]

Only a few genetic studies analyzed asthma-like symptoms in children.[15,16] In Avon Longitudinal Study of Parents and Children (ALSPAC, n = 7,045 children), 244 independent single nucleotide polymorphisms (SNPs) and 13 SNPs from 17q21 were associated with asthma and investigated whether these were associated with six wheezing phenotypes.[15] SNPs encoding *ORMDL3*, *IKZF3*, and *GSDML* were associated with intermediate-onset and persistent, but not early-onset wheezing.[15] The SNPs from 17q21 accounted for most associations with doctor-diagnosed asthma.[15] A meta-analysis in 2,007 children in Prevention and Incidence of Asthma and Mite Allergy (PIAMA) and 7,247 in ALSPAC found that SNPs encoding *IL33* and *IL1RL1* were associated with asthma, intermediate and late-onset wheeze phenotypes.[16]

In this large, longitudinal twin study, we aimed to estimate the extent to which genes and environment contribute to asthma-like symptoms at 3 and 7 years and in persistence of the asthma phenotype from age 3 to 7. Our main interest lies in genetic persistence as expressed in the genetic correlation across these ages and contribution of genetic effects to these phenotypic correlations.

Key Message

A large part of the variance in liability to parental-reported asthma-like symptoms at age 3, and asthma at age 7 was explained by genetic factors. The high phenotypic correlation between asthma-like symptoms at age 3 and asthma at age 7, was almost entirely explained by persistence of genetic effects.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We conducted a cohort study of twins aged 3 and 7 years included in the Netherlands Twin Register (NTR), a birth cohort initiated in 1987.[17] Twins are registered by their parents after birth and recruited with help of a Dutch commercial organization and the Dutch Association for Parents of Multiples. Data are collected by surveys at 0, 2, 3, 5, 7, 9/10, and 12 years. The response rates were 40%–75%. Here, we analyzed data collected between 1989 and 2016. Informed consent was obtained from parents or the guardians. The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam, an Institutional Review Board certified by the U.S. Office of Human Research Protections (IRB number IRB00002991 under Federal-wide Assurance- FWA00017598; IRB/institute codes, NTR 03-180). All data were anonymized. Survey data were available for 7,329 MZ and 14,212 DZ pairs (including twins with data only for age 3 or 7; there were 2,646 MZ and 4,857 DZ pairs with longitudinal asthma data). We determined twin zygosity from survey questions[18] or from

DNA or blood polymorphisms (29% of same-sex twin pairs). The survey included questions on eye, hair, and facial color and shape resemblance, and whether twins were mistaken for each other. NTR validation studies showed that 97.2% of the twins were correctly classified.[17]

2.2 | Outcomes

A child was considered to have asthma-like symptoms at age 3 and asthma at age 7 based on the survey question: "Can you indicate for each of the following conditions whether it applies?" followed by a checked box for asthma, chronic bronchitis, or chronic non-specific respiratory disorders. Since pre-schoolers cannot reliably perform lung function testing and, thus, cannot have an asthma diagnosis confirmed, we refer asthma-like symptoms instead of asthma at age 3. Clinicians refer to asthma persistence, whereas in genetic models, the statistical term is stability. Here, we use persistence of asthma-like symptoms at ages 3 and 7.

2.3 | Asthma polygenic risk score

In addressing genetic continuity, we included an asthma polygenic risk score (APRS), defined based on SNPs identified in previous genetic association studies. To calculate the APRS, we included 26 top hits associated with asthma-like symptoms or childhood asthma phenotypes from six genome-wide association studies (GWAS) investigating SNPs associated with childhood-onset asthma and two candidate-gene replication studies investigating whether previously reported SNPs were associated with childhood asthma phenotypes (Table S1). The APRS was calculated by counting risk alleles (0/1/2) per SNP. In our study population, 6,694 children (of whom 3,628 MZ, 1,874 same-sex DZ and 1,192 opposite-sex DZ) were genotyped on Affimetrix 6.0, Affimetrix Axiom, or Illumina GSA platforms.[17]

2.4 | Statistical analysis

We analyzed longitudinal twin data at ages 3 and 7 by genetic covariance structure analysis[19] based on a liability threshold model,[20] where we assume that a continuous liability (or susceptibility) to develop asthma underlies the phenotypic dichotomy (0/1). The liability dimension is assumed to be a normal distribution, which is reasonable as asthma is highly polygenic (i.e., subject to effects of many genes[13]). The threshold value is estimated from the data and depends on phenotype prevalence. Specifically, the estimated threshold equals the standard normal quantile associated with probability of a phenotype value of 1 in the sample. Twin resemblance was summarized by tetrachoric correlations: the correlation between asthma liabilities of twins (Figure 1). MZ and DZ tetrachoric correlations are informative concerning genetic and environmental contributions to individual differences in liability,[13] as we expect MZ correlations to be higher than DZ correlations when genes contribute to variation in liability.

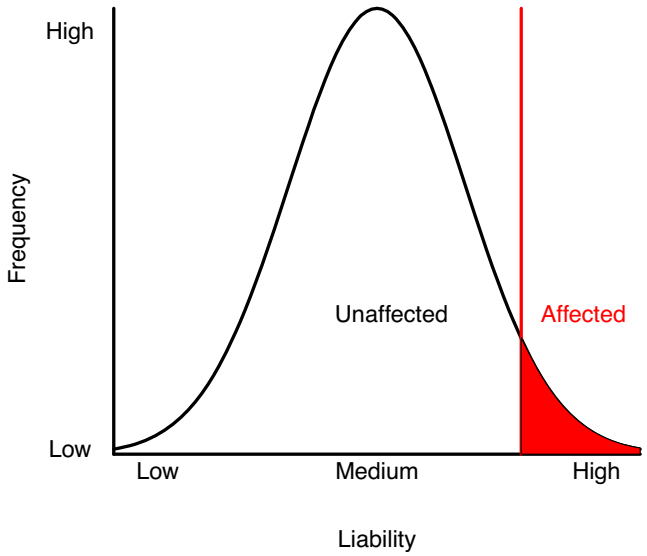

FIGURE 1 Liability threshold model. A threshold in the liability to disease (x-axis) determines for an individual their affected/unaffected status of a disease or disorder. A tetrachoric correlation summarizes the resemblance in liability of two individuals such as mono- or dizygotic twins

The contribution of additive genetic effects (A), shared or common environment (C), and non-shared environment (E) to asthma liability variance at age 3 and 7 was estimated by fitting a genetic covariance structure model to the twin data. We obtained estimates of the contributions of A, C, and E to the variance and the covariance of the liabilities at ages 3 and 7. A path diagram is shown in Figure 2, in which A, C, and E contributions are parameterized by means of Cholesky decomposition (a common parameterization of the multivariate ACE twin model). The parameters of the model as included in Figure 2 are associated with the A part: that is, a_{11}, a_{21}, and a_{22} and likewise for the A and E part. In terms of these parameters, estimates of the total A variance at ages 3 and 7 are a_{11}^2 and $a_{21}^2+a_{22}^2$, respectively, with similar application to the C and E part, The total liability variance is the sum of these components, that is, $a_{11}^2 + c_{11}^2 + e_{11}^2$ at age 3, and $a_{21}^2+a_{22}^2 + c_{21}^2+c_{22}^2 + e_{21}^2+e_{22}^2$, at age 7. Note that the liability is standardized to that the components add up to 1 at age 3 and age 7. This implies that a_{11}^2, $a_{21}^2+a_{22}^2$ etc. can be interpreted as proportions of liability variance. The contribution of A, C, and E to the phenotypic stability is determined by the products $a_{21}{*}a_{22}$, $c_{21}{*}c_{11}$, and $e_{21}{*}e_{11}$. In Figure 2, common environment at age 7 was not included in the model because the C variance at age 7 was close to 0. Based on the model, we can obtain the correlation of A at age 3 and A at age 7 as follows: $rA = (a_{21}{*}a_{11})/ (a_{11}^{2*} a_{21}^2+a_{22}^2)^{½}$. Similarly for E correlation, we have $rE = (e_{21}{*}e_{11})/ (e_{11}^{2*} e_{21}^2+e_{22}^2)^{½}$.

In addition, Figure 2 included the APRS, which does not vary over time as it depends on a person's genotype, but its contribution at two ages can differ, as indicated by the distinct parameters b_3 and

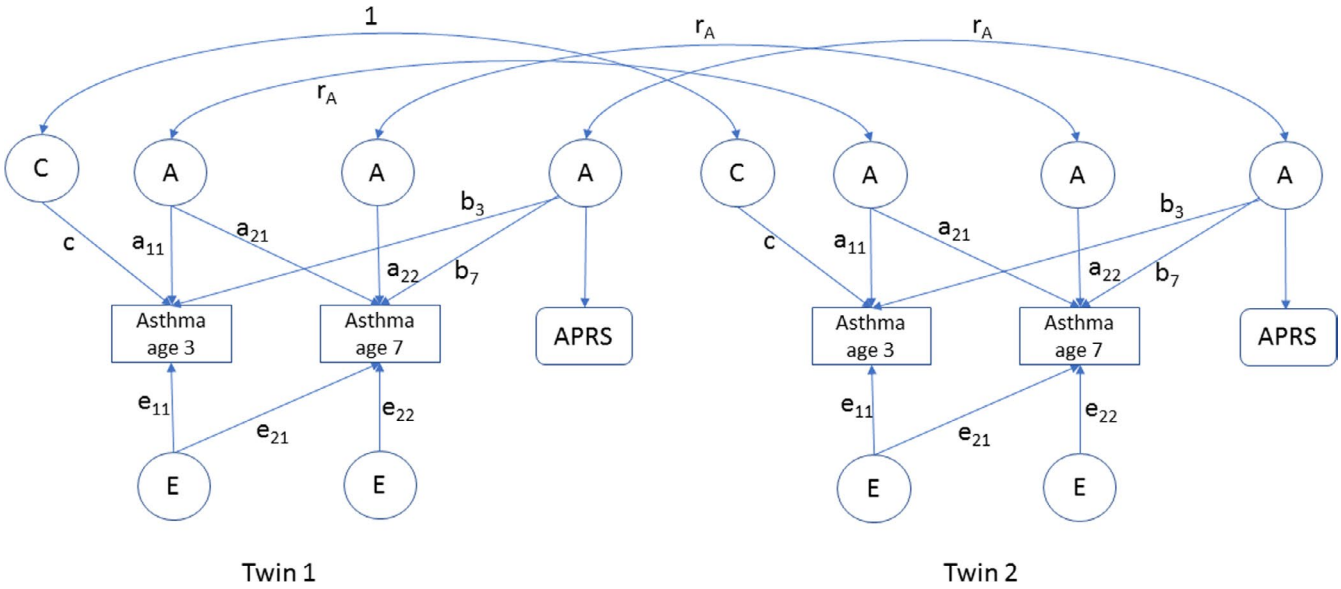

FIGURE 2 Longitudinal latent factor model including measured asthma outcome data at age 3 and 7 years, and a asthma polygenetic risk score (APRS). A: Additive genetic factor score, C: Shared or common environmental factor score (included at age 3), E: Non-shared environmental factor score. APRS, asthma polygenetic risk score based on genotype information. r_A =the genetic correlation between the factor scores of the two twins and equals 1 for MZ) and 0.5 for DZ pairs

b_7. By regressing the asthma liability on the APRS, we estimated contributions of APRS to liability variance at ages 3 and 7, and liability covariance between ages 3 and 7. Parameters b_3 and b_7 represent age-dependent influences of the APRS at ages 3 and 7, respectively. To obtain parameter estimates, we fitted this model using OpenMx in R version 3.5.3 (R Core Team, 2020) by raw-data maximum likelihood, including all available data. We included gender as a covariate (omitted from Figure 2), to accommodate the main effect of gender on asthma (i.e., gender differences in prevalence of asthma at ages 3 and 7).

3 | RESULTS

3.1 | Study population characteristics

For descriptive purposes, we show the different asthma phenotypes in our study population (Table 1). Of the 15,213 individuals with parental report of asthma-like symptoms at ages 3 and 7, 8 (0.05%) individuals were excluded due to missing zygosity information, 2,154 children were included in one of the three asthma-phenotype groups: 1) transient asthma (5.6%, i.e., asthma-like symptoms at age 3, but not at age 7), 2) school-age onset asthma (3.8%, i.e., no asthma-like symptoms at age 3, but asthma at age 7), and 3) persistent asthma (4.8%, i.e., asthma-like symptoms at age 3, asthma at age 7). 13,059 children never experienced asthma (85.8%, i.e., no asthma-like symptoms at age 3, no asthma at age 7). Within the asthma-phenotypes there were more males (58.3% (transient asthma), 61.6% (persistent asthma), 56.0% (school-age onset asthma), compared to never asthma (48.0%)). Children with an asthma phenotype were more likely to have atopy (25.6% (transient asthma), 35.7% (persistent asthma), 30.4% (school-age onset asthma), versus 13.2% that never had asthma), and were generally less often breastfed compared to never asthma (39.4% (transient asthma), 43.3% (persistent asthma), 44.7% (school-age onset asthma) versus 36.2% never asthma). In the school-age asthma onset group more children were without older siblings (89.4%) compared to persistent asthma (47.3%) and transient asthma (41.3%). Characteristics and numbers individuals with asthma-like symptoms at ages 3 and 7 are provided in Table S2. There were 3,087 children with asthma-like symptoms at age 3 (1,053 MZ, 1,027 DZ same-sex and 1,006 DZ opposite-sex) and 2,273 children with asthma at age 7 (774 MZ, 758 DZ same-sex and 741 DZ opposite-sex). The phenotypic correlation in liability between asthma-like symptoms at ages 3 and 7 was 0.746.

3.2 | Longitudinal genetic analysis

Table 2 includes MZ and DZ tetrachoric correlations for asthma at ages 3 and 7. Based on these correlations, a model including additive genetic and non-shared environmental effects was selected to estimate heritability and genetic and non-genetic correlations for asthma at ages 3 and 7, with a contribution of shared environment (C) tested at age 3. The results demonstrate strong genetic contributions to asthma susceptibility: heritability at age 3 was 0.796 and heritability for asthma at age 7 0.904. Shared environment (C) explained 15.7% of the liability variance at age 3. Genetic and environmental correlations for asthma-like symptoms at age 3 and 7 years in this model were estimated at 0.917 and 0.083, respectively. The results further showed that the APRS did not contribute to the liability variance, in a model with equal regression coefficients at ages 3 and 7, the p-value was 0.40 (Table S3).

TABLE 1 Demographics of individual children in the different asthma phenotypes and ages

	Dynamic phenotypes between age 3 and 7		Stable phenotypes between age 3 and 7	
	Transient asthma (*n* = 847)	School-age onset asthma (*n* = 573)	Persistent asthma (*n* = 734)	Never asthma (*n* = 13,059)
Zygosity				
MZ	292 (34.5%)	187 (32.6%)	255 (34.7%)	4,630 (35.5%)
DZ same-sex	277 (32.7%)	305 (53.2%)	252 (34.3%)	4,209 (32.2%)
DZ opposite-sex	278 (32.8%)	278 (48.5%)	227 (30.9%)	4,214 (32.3%)
Gender				
Male	494 (58.3%)	321 (56.0%)	452 (61.6%)	6,271 (48.0%)
Breastfeeding				
None	334 (39.4%)	256 (44.7%)	318 (43.3%)	4,722 (36.2%)
<2 weeks	96 (11.3%)	44 (7.7%)	80 (10.9%)	1,194 (9.1%)
2–6 weeks	118 (13.9%)	72 (12.6%)	71 (9.7%)	1,925 (14.7%)
6 weeks – 3 months	86 (10.2%)	73 (12.7%)	90 (12.3%)	1,661 (12.7%)
3–6 months	71 (8.4%)	37 (6.5%)	59 (8.0%)	1,243 (9.5%)
>6 months	68 (8.0%)	48 (8.4%)	57 (7.8%)	1,190 (9.1%)
Missing	74 (8.7%)	43 (7.5%)	59 (8.0%)	1,124 (8.6%)
Outside home child care				
None	58 (6.8%)	40 (7.0%)	58 (7.9%)	963 (7.4%)
1–4 h week^{-1}	93 (10.9%)	67 (11.7%)	100 (13.6%)	1,947 (14.9%)
5–8 h week^{-1}	232 (27.4%)	151 (26.4%)	187 (25.4%)	4,185 (32.0%)
9–16 h week^{-1}	172 (20.3%)	110 (19.2%)	142 (19.3%)	3,379 (25.9%)
17–24 h week^{-1}	144 (17.0%)	106 (18.5%)	122 (16.6%)	2,808 (21.5%)
>24 h week^{-1}	42 (5.0%)	38 (6.6%)	55 (7.4%)	1,094 (8.4%)
Missing	106 (12.5%)	61 (10.6%)	70 (9.5%)	1,890 (14.5%)
Educational attainment mother				
≤9 years	50 (5.9%)	24 (4.2%)	55 (7.5%)	424 (3.2%)
10–12 years	236 (27.9%)	177 (30.9%)	194 (26.4%)	3,215 (24.6%)
<2 years tertiary	368 (43.4%)	233 (40.7%)	324 (44.1%)	5,576 (42.7%)
≥2 years tertiary	193 (22.8%)	139 (24.3%)	160 (21.8%)	3,835 (29.4%)
Missing	0 (0%)	0 (0%)	1 (0.1%)	9 (0.1%)
Educational attainment father				
≤9 years	57 (6.7%)	37 (6.5%)	58 (7.9%)	663 (5.1%)
10–12 years	234 (27.6%)	177 (30.9%)	244 (33.2%)	3,304 (25.3%)
<2 years tertiary	314 (37.1%)	170 (29.7%)	235 (32.0%)	4,573 (35.0%)
≥2 years tertiary	230 (27.2%)	184 (32.1%)	189 (25.7%)	4,445 (34.0%)
Missing	12 (1.4%)	5 (0.9%)	8 (1.1%)	74 (0.6%)
Atopy	217 (25.6%)	174 (30.4%)	262 (35.7%)	1,720 (13.2%)
Missing	184 (21.7%)	118 (20.6%)	157 (21.4%)	2,296 (17.6%)
Older siblings				
None	355 (41.9%)	512 (89.4%)	347 (47.3%)	5,982 (45.8%)
Missing	113 (13.3%)	61 (10.6%)	97 (13.2%)	1,867 (14.3%)

Note: Atopy was based on parental-reported hay fever or eczema before the age of 5 years old.

During childhood, asthma prevalence in boys is higher than in girls. Therefore, we investigated whether the heritability for asthma liabilities is sex-dependent by testing whether the twin correlations differed as a function of sex. Specifically, we carried out a test of rMZFF =rMZMM and rDZMM =rDZM = rDZMF). The last test also includes a test for qualitative sex differences.[21] Results showed the correlations within MZ and DZ groups did not differ as a function of sex, so we infer that there is no sex moderation at age 3 and age

TABLE 2 Tetrachoric correlations and estimates for asthma at ages 3 and 7, estimates for the model without asthma polygenic risk score

	MZ (*n*)	MZ cor	DZ same-sex (*n*)	DZ opposite-sex (*n*)	DZ cor	Proportion due to A heritability	Proportion due to C	Proportion due to E
						Standardized liability variance components		
Age 3	7,329	0.954	7,177	7,035	0.555	0.796	0.157	0.046
Age 7	7,329	0.904	7,177	7,035	0.452	0.904	0*	0.096
						Liability covariance		
Age 3 and 7	$r_{liability}$: 0.746					R(A) = 0.807	NA	R(E) = 0.934
Contribution to $r_{liability}$						0.685	NA	0.062
Proportions						0.917	NA	0.083

Note: * Fixed to zero. Adjusted for gender.

Abbreviations: AAPRS, asthma risk score; C, shared environment component; cor, correlation; DZ, dizygotic; E, non-shared environment component; MZ, monozygotic; *n*, number of twin pairs including twins with missing data; NA, not applicable; R(A), genetic correlation; R(E), environmental correlation.

7 (Supplementary information 2) and also that the same genes are expressed in boys and girls.

4 | DISCUSSION

Heritability accounted for a large part of the variance in liability to parental-reported asthma-like symptoms at ages 3 and 7. The high phenotypic correlation between asthma-like symptoms at ages 3 and 7 was almost entirely explained by persistence of genetic effects.

The heritability of asthma at 3 and 7 years corresponds with previous twin studies.[11–13] Our finding that environmental factors are not substantially contributing to susceptibility of asthma-like symptoms at age 3 and 7 aligns with other studies reporting high heritability. A Swedish study in over 25,000 9-to-12-year-old twins asking whether the child ever had asthma demonstrated that non-shared environmental contribution was 13% and heritability was 87%. These results were validated with asthma diagnosis data from the National Patient Register.[11] Thus, our study implies that persistence of asthma symptoms in childhood is more likely due to genetically driven mechanisms. The absence of sex moderation at age 3 and age 7 also corresponds with earlier research showing that there were no sex differences in asthma heritability.[13]

To our knowledge, none of the previous twin studies have incorporated an APRS to their model to estimate contribution of currently known genetic loci to asthma phenotypes and our APRS has not been incorporated in a non-twin study. We did not find an effect of the APRS which was defined by a count of asthma risk alleles (0/1/2) per earlier identified SNP. This may indicate that childhood asthma is highly polygenic and heterogeneous.[22,23] We hypothesize that some SNPs may be relevant for one childhood asthma subtype but may not be accounting for another subtype and that a more powerful APRS depends on a next generation of genetic association studies.

A strength of our study is the large cohort including over 20,000 Dutch twin pairs of which over 7,500 twin pairs had longitudinal data describing whether they had asthma-like symptoms at ages 3 and 7. Our design can estimate the contribution of all genetic and environmental factors (shared and non-shared). There is uncertainty whether asthma-like symptoms at young age help predicting childhood asthma onset at school age. Therefore, our main focus was on contribution of genes and environment to asthma persistence over age 3–7 which has yet to be investigated in a bivariate twin model. It was thought that twins are not representative to estimate risk of asthma, but this concern has been addressed previously.[24] A study in Swedish twins (n = 756,363) and singletons (n = 456,239) indicated that the observed higher risk of childhood asthma in twins compared to singletons appears to be mediated by differences in gestational age and birthweight between these populations.[24]

This study also had some limitations. Firstly, outcome misclassification may have occurred since clinical data of asthma-like symptoms and asthma were not available. The asthma-like symptom phenotype at age 3 is less precise due to difficulty in the diagnosis. Nevertheless, data were retrieved from surveys sent to parents at age 3 and 7, minimizing recall bias. Second, gene-environment interactions were not investigated in our model. However, in 5-year-old Dutch twins overlapping to a large extent with our study population, a dedicated set of analyses tested for interactions with gestational age, time in incubator, breastfeeding, maternal educational attainment, maternal smoking during pregnancy, current parental smoking, presence of older siblings, and of childcare outside home, gene-environment interactions were barely identified. Several investigated environmental factors did increase risk of asthma, but did not modify genetic influences on asthma, with only one exception, namely prematurity.[25] These results make it unlikely that gene-environment interactions lead to overestimation of heritability of asthma development in our model. Third, we assume equal environments for MZ and DZ twins, that is, MZ twins share their early environment in the uterus to the same extent as DZ twins. Violation of this assumption seems unlikely given the fact that this bias has not been observed in other diseases.[26] Fourth, there may be an overestimation of never asthma, because children with asthma-like symptoms only at 1–2 years but not at 3 years were assigned as never

asthma. Moreover, we could not investigate children under 3 years and environmental factors may play a larger role in this group.

Genes play a substantial role to persistence of asthma over ages 3 and 7, and we could use this knowledge to define high versus low-risk groups. Prediction of asthma risk and persistence is likely improving with larger GWAS and potentially when results such as (epi) genetic and gene-gene interaction scores are added to prediction models.

To conclude, our results show that parental-reported asthma-like symptoms at age 3 and asthma at age 7 are highly correlated and heritable, indicating high persistence of asthma development over ages 3 and 7. Future studies should elucidate genetics of well-diagnosed, persistent childhood asthma further and identify mechanisms that could be targets of future interventions.

CONFLICT OF INTEREST

AHM has received research grants outside the submitted work from Lung Foundation of the Netherlands, GSK, Boehringer Ingelheim and VERTEX, she is the PI of a P4O2 (Precision Medicine for more Oxygen) public private partnership sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (Boehringer Ingelheim, Roche Breathomix, Fluidda, Ortec Logiqcare, Philips, Quantib-U, Smartfish, SODAQ, Thirona, TopMD and Novartis), and she has served in advisory boards for AstraZeneca, GSK and Boehringer Ingelheim with money paid to her institution. G.H. Koppelman reports grants from Lung Foundation of the Netherlands, TEVA the Netherlands, UBBO EMMIUS Foundation, TETRI Foundation, GSK, and VERTEX, outside the submitted work; and G.H. Koppelman participated in a global advisory board on pediatric asthma for GSK and an advisory board meeting to PURE-IMS. C. Longo, C.E.M. van Beijsterveldt, S.J.H. Vijverberg, D.I. Boomsma, C. Dolan, M. Bartels, J.J. Hottenga, M.W. Pijnenburg and E.M.A. Slob report no conflict of interest for this study.

AUTHOR CONTRIBUTIONS

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PEER REVIEW

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SUPPORTING INFORMATION

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Persistence of parental-reported asthma at early ages: a longitudinal twin study

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Supplementary information

Supplementary information 1. Brief description of the quality control and studies used to calculate the asthma polygenic risk score

Quality control

Prior to imputation, quality control was performed on each separate platform (Hardy Weinberg Equilibrium p-value $<1\times10^{-6}$, Minor Allele Frequency cutt-off $<1\times10^{-6}$, call rate per SNP <0.95 and call rate per individual ≥ 0.90). DNA samples not matching gender, familial Identity By Descent, CEU ancestry or whom had an excess of homo- and heterozygosity (-0.10 < PlinkF > 0.10) were removed. For each platform, data were then converted to build38, aligned to TOPMED imputation panel, phased (Eagle) and imputed (Minimac4) on the Michigan imputation server using internal imputation and data QC protocols[9]. No significant differences were found between APRS scores across the genotyping platforms (p=0.142).

The expected twin correlations of the APRSs are 1 in MZ twins (as they are genetically identical) and 0.5 in DZ twins. APRS correlation equaled one in MZ twins, as expected, and 0.524 in DZ twins, which is close to its expected value of 0.5.

Selected studies

Data of the platforms were merged to single best guess Plink genotypes, and the 26 SNPs were selected. MZ missing APRS were imputed if one MZ twin did have the score and the other did not. A brief description about the included studies from which the 26 SNPs were derived is given below:

Ferreira 2019 Am J Hum[1]
A GWAS in UK Biobank (n=447,628) to identify subtype specific genetic associations of childhood-onset and adult-onset asthma.

Pividori 2019 Lancet Res Med[2]
A GWAS in 376,358 individuals of UK biobank to identify shared and non-shared genetic risk loci of childhood-onset and adult-onset asthma.

Savenije JACI 2014[3]
A candidate-gene study in PIAMA (n=2007) and ALSPAC (n=7247) in which wheezing phenotypes and asthma diagnosis at age 8 were chosen as the outcome. Candidate-genes were from pathophysiological or immunological pathways of IL-33, IL1RL1, IL1rAcP, TIRAP, IL-1 en TRAF6.

Moffatt 2010 NEJM[4]

A GWAS (n=10,365 adults with asthma and 16,110 adults without asthma) in which they stratified for childhood-onset asthma.

Himes 2009 Am J Hum[5]
A GWAS in CAMP (n=359 children with asthma and 846 children without asthma) in which genes were identified related to childhood-onset asthma.

Torgerson Nat Genet 2011[6]

A meta-analysis of GWAS in 5,416 asthma cases representing European Americans, African Americans/African Caribbeans and Latinos, and replicated five regions among the most significant signals in 12,649 individuals from the same ethnic groups.

Moffatt 2007 Nature[7]
A GWAS (n=994 patients with childhood-onset asthma and 1,243 non-asthmatics) to identify associations with childhood-onset asthma and a replication in 2,320 German children and 2,320 British children.

Granell JACI 2013[8]
A candidate-gene study in ALSPAC (n=7045) in which was studied whether earlier associations with childhood asthma were related to specific childhood asthma phenotypes with a focus on the 17q21 region close to *ORMDL3*.

Supplementary information 2. Brief description of the analysis investigating sex moderation at age 3 and 7

We investigated sex moderation by testing whether the twin correlations (r) were different as a function of sex (rMZF = rMZM; rDZM = rDZF = rDZOS). The correlations did not differ, so we infer that there is no sex moderation at age 3 and age 7. To address this question, we fitted the 6 group twin model to estimate the tertrachoric correlations separate in the following groups:

group	correlation	thresholds
MZM	rMZM	tM
MZF	rMZF	tF
DZM	rDZM	tM
DZF	rDZF	tF
DZMF	rDZMF = rDZFM	tM, tF
DZFM	rDZFM = rDZMF	tF, tM

In the full model we estimate 5 tetrachoric correlations, and two thresholds. Note that we analysed the two phenotypic separately (asthma at age 3 and asthma at age 7).

We tests the hypotheses:

H_1: rDZM=rDZF=rDZMF=rDZFM (a two DF test) (no sex moderation of DZ phenotypic correlations)
H_2: rMZM=rMZF (a one DF test) (no sex moderation of MZ phenotypic correlations)
H_3: rDZM=rDZF=rDZMF=rDZFM and rMZM=rMZF (a 3 DF test) (no sex moderation)

We test each three hypothesis at age 3 with an alpha of .05/3 = 0.0167
We test each three hypothesis at age 7 with an alpha of .05/3 = 0.0167
(This is a compromise: .05 per test is too liberal, but .05/6 per test is too strict)

Results Age 3
Tetrachoric correlations in the 6 groups, no constraints, i.e., 5 correlations (MZM, MZF, DZF, DZF, DZFM=DZMF)

group	correlation
MZM	0.952034
MZF	0.9646008
DZM	0.6014834
DZF	0.5690056
DZMF=DZFM	0.5653507

Likelihood ratio tests (LRTs):
H_1: rDZM=rDZF=rDZMF=rDZFM (a two DF test) (no sex moderation of DZ phenotypic correlations)
LRT=0.566 (p=.753; alpha=.0167)
H_2: rMZM=rMZF (a one DF test) (no sex moderation of MZ phenotypic correlations)
LRT=1.336 (p=.247; alpha=.0167)
H_3: rDZM=rDZF=rDZMF=rDZFM and rMZM=rMZF (a 3 DF test) (no sex moderation)
LRT=1.910 (p=.5912; alpha=.0167)

Conclusion: no sex moderation.
Correlations in the model without sex moderation:

group	correlation
MZM=MZF	0.9589639
DZM=DZF=DZMF=DZFM	0.5742706

Results Age 7
Tetrachoric correlations in the 6 groups, no constraints, i.e., 5 correlations (MZM, MZF, DZF, DZF, DZFM=DZMF)

group	correlation
MZM	0.9063577
MZF	0.9094317
DZM	0.527179

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DZF          0.3973618
DZMF=DZFM    0.3474596
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Likelihood ratio tests (LRTs):
H_1: rDZM=rDZF=rDZMF=rDZFM (a two DF test) (no sex moderation of DZ phenotypic correlations)
LRT=7.209 (p=.0271; alpha=.0167)
H_2: rMZM=rMZF (a one DF test) (no sex moderation of MZ phenotypic correlations)
LRT=0.019 (p=.888; alpha=.0167)
H_3: rDZM=rDZF=rDZMF=rDZFM and rMZM=rMZF (a 3 DF test) (no sex moderation)
LRT=7.231 (p=.0.648; alpha=.0167)

Conclusion: no sex moderation.
Correlations in the model without sex moderation:

group	correlation
MZM=MZF	0.9080032
DZM=DZF=DZMF=DZFM	0.4027951

Supplementary table 1. Selection of single nucleotide polymorphisms based on previous genetic studies

SNP	position (Build38)	risk allele	reference allele	HWE p-value	Allele frequency ref. allele	Info	Gene	Study
rs67551275	1:9296617	C	T	0.27	0.55	0.94	*SPS1*	Ferreira et al. 2019 Am J Hum Genet[1]
rs61816761	1:152313385	A	G	0.32	0.98	0.81	*FLG, HRNR, FLG2*	Pividori et al. Lancet Resp Med 2019[2]
rs7518129	1:173194429	G	A	0.99	0.68	0.99	*TNFSF4, TNSF18, PRDX6*	Pividori et al. Lancet Resp Med 2019[2]
rs10208293	2:102349850	A	G	0.63	0.73	1.00	*IL1RL1*	Savenije et al. JACI 2014[3]
rs13424006	2:102350776	C	T	0.75	0.63	1.00	*IL1RL1*	Savenije et al. JACI 2014[3]
rs10204137	2:102351752	G	A	0.74	0.63	1.00	*IL1RL1*	Savenije et al. JACI 2014[3]
rs3771166	2:102369762	A	G	0.95	0.63	1.00	*IL18R1*	Moffatt et al. NEJM 2010[4]
rs10187276	2:227805721	A,C	T	0.59	0.27	0.80	*SLC19A3, CCL20*	Ferreira et al. 2019 Am J Hum Genet[1]
rs12634152	3:188403231	T	C	0.28	0.51	0.96	*LPP, FLJ42393, LPPAS1*	Pividori et al. Lancet Resp Med 2019[2]
rs1588265	5:60073967	G	A	0.39	0.69	1.00	*PDE4D*	Himes et al. Am J Hum Genet 2009[5]
rs1544791	5:60143255	A	G	0.41	0.69	0.99	*PDE4D*	Himes et al. Am J Hum Genet 2009[5]
rs1837253	5:111066174	C	T	0.37	0.28	0.99	*TLSP/GSDMA*	Torgerson et al. Nat Genet 2011[6]
rs1295686	5:132660151	C	T	0.00	0.21	0.98	*IL13*	Moffatt et al. NEJM 2010[7]
rs2051809	5:132721182	A	C	0.23	0.73	0.97	*KIF3A, IL4, CCNI2*	Pividori et al. Lancet Resp Med 2019[2]
rs274943	9:23585841	C	T	0.62	0.54	0.98	*DMRTA1, ELAVL2*	Ferreira et al. 2019 Am J Hum Genet[1]
rs1342326	9:6190076	C	A	0.20	0.84	0.99	*IL33*	Moffatt et al. NEJM 2010[4]

rs12365699	11:118872577	G	A	0.03	0.18	1.00	*CXCR5, DDX6*	Pividori et al. Lancet Resp Med 2019[2]
rs1887704	13:99322238	G	C	0.81	0.31	0.98	*UBAC2*	Ferreira et al. 2019 Am J Hum Genet[1]
rs3785356	16:27337847	T	C	0.00	0.70	0.97	*IL4R*	Ferreira et al. 2019 Am J Hum Genet[1]
rs9303277	17:39820216	C	T	0.24	0.51	1.00	*IKZF9*	Granell R et al. JACI 2013[8]
rs11557467	17:39872381	T	G	0.35	0.49	0.99	*ZPBP2*	Granell R et al. JACI 2013[8]
rs4795399	17:39905186	T	C	0.34	0.45	0.99	*GSDMB, ZPBP2, ORMDL3*	Pividori et al. Lancet Resp Med 2019[2]
rs2305480	17:39905943	A	G	0.35	0.54	0.99	*GSDML*	Granell R et al. JACI 2013[8]
rs3902025	17:39963001	A, C, T	G	0.37	0.42	0.99	*GSDM1*	Granell R et al. JACI 2013[8]
rs3894194	17:39965740	C	T	0.81	0.46	0.98	*ORMDL3*	Moffatt et al. Nature 2007[7]
rs2284033	22:37137994	G	A	0.24	0.44	0.99	*IL2RB*	Moffatt et al. NEJM 2010[7]

HWE: Hardy Weinberg Equilibrium; info: imputation quality of the SNP

Supplementary table 2. Demographics of individual children at age 3 and 7

	asthma-like symptoms at age 3 (n=3,087)	no asthma-like symptoms at age 3 (n=27,939)	asthma at age 7 (n=2,273)	no asthma at age 7 (n=22,890)
Zygosity				
MZ	1,053 (34.1%)	9,238 (33.1%)	774 (34.1%)	8,244 (36.0%)
DZ same-sex	1,027 (33.3%)	9,408 (33.7%)	758 (33.3%)	7,396 (32.3%)
DZ opposite-sex	1,006 (32.6%)	9,260 (33.1%)	741 (32.6%)	7,238 (31.6%)
missing	1 (0.0%)	33 (0.1%)	0 (0.0%)	12 (0.1%)
Gender				
Male	1,834 (59.4%)	13,643 (48.8%)	1,329 (58.5%)	11,197 (48.9%)
Breastfeeding				
None	1236 (40.0%)	9,333 (33.4%)	1,024 (45.1%)	8,671 (37.9%)
< 2 wk	287 (9.3%)	2,464 (8.8%)	182 (8.0%)	1,859 (8.1%)
2-6 wk	374 (12.1%)	4,004 (14.3%)	232 (10.2%)	2,908 (12.7%)
6 wk – 3 mnths	325 (10.5%)	3,289 (11.8%)	232 (10.2%)	2,573 (11.2%)
3-6 mnths	240 (7.8%)	2,562 (9.2%)	167 (7.3%)	1,944 (8.5%)
> 6 mnths	219 (7.1%)	2,614 (9.4%)	141 (6.2%)	1,840 (8.0%)
missing	406 (13.2%)	3,673 (13.1%)	295 (13.0%)	3,095 (13.5%)
Outside home child care				
none	219 (7.1%)	1,961 (7.0%)	208 (9.2%)	2,130 (9.3%)
1-4h week^{-1}	359 (11.6%)	2,673 (9.6%)	234 (10.3%)	2,058 (9.0%)
5-8h week^{-1}	713 (23.1%)	5,935 (21.2%)	553 (24.3%)	5,485 (24.0%)
9-16h week^{-1}	612 (19.8%)	5,230 (18.7%)	309 (13.6%)	3,238 (14.1%)
17-24h week^{-1}	479 (15.5%)	4,258 (15.2%)	259 (11.4%)	2,607 (11.4%)
>24h week^{-1}	183 (5.9%)	1,621 (5.8%)	112 (4.9%)	1,065 (4.7%)
Missing	522 (16.9%)	6,261 (22.4%)	598 (26.3%)	6307 (27.6%)
Educational attainment mother				
≤ 9 years	210 (6.8%)	951 (3.4%)	166 (7.3%)	1,140 (5.0%)
10-12 years	820 (26.6%)	6700 (24.0%)	715 (31.5%)	6,486 (28.2%)
< 2 years tertiary	1,366 (44.3%)	11,906 (42.6%)	877 (38.6%)	9,214 (40.3%)
≥ 2 years tertiary	681 (22.1%)	8,313 (29.8%)	507 (22.3%)	5,986 (26.2%)
missing	10 (0.3%)	69 (0.2%)	8 (0.4%)	64 (0.3%)
Educational attainment father				
≤ 9 years	224 (7.3%)	1,426 (5.1%)	199 (8.8%)	1,374 (6.0%)
10-12 years	929 (30.1%)	6,871 (24.6%)	689 (30.3%)	6,091 (26.6%)
< 2 years tertiary	1,060 (34.3%)	9,936 (35.6%)	723 (31.8%)	7,714 (33.7%)
≥ 2 years tertiary	784 (25.4%)	9,141 (32.7%)	611 (26.9%)	7,277 (33.7%)
missing	90 (2.9%)	565 (2.0%)	51 (2.2%)	434 (1.9%)
Atopy	777 (25.2%)	3,358 (12.0%)	737 (32.4%)	3,003 (13.1%)
missing	1,038 (33.6%)	8,374 (30.0%)	583 (25.6%)	4,756 (20.8%)
Older siblings				
None	1,167 (37.8%)	11,044 (39.5%)	1,026 (45.1%)	9,917 (43.3%)
missing	856 (27.7%)	7,873 (28.2%)	417 (18.3%)	3,886 (17.0%)

Supplementary table 3. Tetrachoric correlations and estimates for asthma at age 3 and 7, estimates for the model with asthma polygenic risk score

	MZ (n)	MZ cor	DZ same-sex (n)	DZ opposite-sex (n)	DZ cor	proportion due to A heritability	proportion due to C	proportion due to E	explained variance (APRS) (%)
						standardised liability variance components			
age 3	7,329	0.954	7,177	7,035	0.555	0.797	0.156	0.046	0
age 7	7,329	0.904	7,177	7,035	0.452	0.903	0*	0.096	0
						liability covariance			
age 3 and 7	$r_{liability}$ (including APRS): 0.746					R(A) = 0.806	NA	R(E) = 0.934	NA
contribution to $r_{liability}$						0.684	NA	0.062	NA
proportions						0.916	NA	0.083	NA

APRS: asthma risk score, MZ: monozygotic, DZ: dizygotic, n: number of twin pairs including twins with missing data (6,612 children with SNP data), cor: correlation, C: shared environment component, E: non-shared environment component, NA: not applicable, R(E): environmental correlation, R(A): genetic correlation. *Fixed to zero. Adjusted for gender.

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