

## Rationale and design of the multi-ethnic Pharmacogenomics in Childhood Asthma (PiCA) consortium

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### Abstract

**Aim:** International collaboration is needed to enable large-scale pharmacogenomics studies in childhood asthma. Here, we describe the design of the Pharmacogenomics in Childhood Asthma [PiCA] consortium.

**Material & Methods:** Investigators of each study participating in PiCA provided data on the study characteristics by answering an online questionnaire.

**Results:** Twenty-one studies, including 14,227 children/young persons (58% male), from 12 different countries are currently enrolled in the PiCA consortium. Fifty-six percent of the patients are Caucasians. In total 7,619 were inhaled corticosteroid [ICS] users. Among patients from 13 studies with available data on asthma exacerbations, one third reported exacerbations despite ICS use. In the future pharmacogenomics studies within the consortium, the pharmacogenomics analyses will be performed separately in each center and the results will be meta-analyzed.

**Conclusions:** PiCA is a valuable platform to perform pharmacogenetics studies within a multi-ethnic pediatric asthma population.

**Keywords:** *asthma, children, consortium, genetics, pharmacogenomics, treatment*

### 1 Introduction

Asthma is the most common chronic disease in childhood. Although it cannot be cured, effective treatments are available to decrease the symptoms, maintain lung function and prevent future exacerbations (1). Standard treatment regimens for persistent asthma include regular use of inhaled corticosteroids [ICS] combined with long-acting  $\beta_2$  agonists [LABA] and short-acting  $\beta_2$  agonists [SABA] as needed (2). There is heterogeneity in response to treatment; approximately 30-40% of the patients receiving ICS, do not show an improvement lung function and remain uncontrolled(3–6). Uncontrolled asthma is associated with low quality of life for patients and can be life threatening (7,8). Furthermore, unscheduled physician visits and hospital admissions due to exacerbations are responsible for almost half of the costs of asthma management (9,10).

Poor adherence to medication, continuous environmental exposures, disease severity and misdiagnosis influence response to treatment in asthmatic patients. In addition, it has been shown that genetic variation contributes to the heterogeneity in treatment response (11). To date, a large number of candidate gene studies and several genome-wide association studies [GWAS] have been conducted to study the pharmacogenomics of childhood asthma (12,13). However, one of the main unmet needs for pediatric asthma management is the lack of clinically available biomarkers (for example pharmacogenetic markers) to guide asthma treatment. Genetic associations have been reported with three commonly used outcome measures (i.e. asthma exacerbations, asthma symptoms and lung function) (14,15). Different outcomes might reflect different aspects of asthma control and the heterogeneity in the outcome measures complicates the comparison of study results. In addition, most studies have been performed in relatively small study populations. There is a need for international collaboration in the field of pharmacogenomics of asthma to obtain large sample sizes of well-phenotyped asthmatic children to perform large scale meta-analysis to assess the clinical value of genetic markers for asthma management and identify markers that can guide asthma treatment. (16,17). There have been successful efforts to establish consensus on diagnosis and management of asthma (18,19). The Pharmacogenomics in Childhood Asthma [PiCA] consortium was initiated in December 2013 and brings together asthma studies that have genetic data and treatment outcome measures. The main goals of the PiCA consortium are to create a platform to identify new pharmacogenomic markers in asthma by conducting GWAS meta-analyses. To replicate these new and also previously identified loci that are associated with treatment response, and finally, to develop pharmacogenetics-guided (PG) algorithms to guide asthma therapy to improve symptoms and reduce/prevent future exacerbations. This is the first consortium that focuses on

pharmacogenomics in childhood asthma. In this study, we describe the characteristics of the study populations currently included in the PiCA consortium, assess the outcome measures that can be used to study treatment response within the consortium and describe the design of the pharmacogenomics studies that will be performed within PiCA

### Methods

#### *PiCA consortium*

The PiCA consortium was established in December 2013 by the pharmacogenomics research group of Prof. dr. AH Maitland van der Zee (Utrecht University, The Netherlands) by expanding existing and new collaborations. Studies were identified from the literature, at conferences and by references of other PiCA collaborators. Studies were eligible to participate in the PiCA consortium if:

- Data of asthmatic children or young persons were collected;
- DNA samples were collected or could be collected;
- Data were collected on asthma drug use;
- Data were collected on treatment outcome.

PiCA is a growing consortium and new studies can join the consortium if they meet the inclusion criteria ([www.pica-consortium.org](http://www.pica-consortium.org)).

#### *Data collection:*

An online questionnaire (created using [www.surveymonkey.com](http://www.surveymonkey.com)) was sent to the investigators of each cohort to collect information about the patients and design of the studies.

#### *Characteristics of the studies and study populations*

Information was collected on the following characteristics of the studies: study design (i.e. asthma cohort, clinical trial and (high risk) birth cohort), country where the study was conducted and location of patient enrollment (type of health care centers: primary, secondary or tertiary care). Per study, the following data were collected on the study populations: the age range (in yrs.), number of male asthmatics, and the number of patients in distinct ethnic groups (i.e. Caucasians, African-Americans, Hispanics and Asians). In order to assess the potential of PiCA to perform pharmacogenomics studies, the numbers of patients with

a reported use of asthma medication (ICS, SABA, LABA, Leukotriene modifiers [LTMs], Anti-IgE and Oral corticosteroids [OCS]) were collected per study. It was also ascertained whether data regarding environmental exposures and atopy were collected. The source for the DNA collection (i.e. blood, saliva) and availability of whole genome genotyping data was assessed.

### *Outcome measures and treatment response*

The presence of information on exacerbations, asthma symptoms and lung function was assessed for each study. A severe exacerbation was considered as a short course (3-5 days) OCS use or a hospitalization/emergency room [ER] visit according to the American Thoracic Society/European Respiratory Society [ATS/ERS] 2009 statement (20). The presence of information on unscheduled General Practitioner [GP] visits or asthma-related absences from school was also assessed. The two outcomes have been used as indicators of exacerbations in several pharmacogenomics studies. For asthma symptoms, presence of information on validated asthma symptom questionnaires (asthma control questionnaire [ACQ] or Asthma Control Test [ACT]) was assessed within the studies. The comparability of the results of these two questionnaires has been shown previously (21). Patients with ACQ scores  $\geq 0.75$  and ACT scores  $< 20$  were considered to have poor asthma control. In addition, availability of information on asthma symptoms based on guidelines (i.e. Global initiative for Asthma [GINA] and ATS/ERS) was also assessed. According to the availability of data in each study, the number of patients with exacerbations despite regular use of ICS was collected. For observational studies, the presence of any of these outcomes in the preceding six or twelve months was gathered. Asthma diagnosis is difficult in infants and pre-school children. Hence from birth cohorts within the PiCA consortium, we collected outcomes of children  $\geq 6$  years of age with physician-diagnosed asthma. Cohen's Kappa statistic was calculated per study, to show the overlap between patients experiencing exacerbations and asthma symptoms (22). This was calculated for those studies in which both outcomes were available. The analysis was performed in R (Package 'irr')(23).

Furthermore, since lung function measures are widely used as a response outcome in asthma, it was ascertained whether data regarding lung function measurements, especially changes in FEV<sub>1</sub> from baseline over time (before and after treatment) and changes in FEV<sub>1</sub> after SABA use were also collected within the studies included in the consortium.

## Results

### *Baseline characteristics of the studies and patients*

Currently, 21 asthma studies from 12 different countries are enrolled in the PiCA consortium. PiCA includes 15 asthma cohorts, three birth cohorts, two high-risk birth cohorts (inclusion of infants based on allergic history of the mother) and one clinical trial (Table 1).

In total, PiCA includes data of 14,227 asthmatic patients up to 25 years of age. In 17 studies (80%), asthma was based on physician-diagnosis and/or hospital records. For three studies asthma diagnosis was based on parental-reported asthma diagnosis. PACMAN included children with a regular use of asthma medication. Analysis of PiCA children showed that 58% are male. From almost all patients within PiCA (97%) information was available on ethnic background. The majority of the asthmatic patients in PiCA are Caucasian (56%), 12% are Asian, 22% are Hispanic, and 8% have an African/African-American background and the remaining (2%) has mixed/other ethnic backgrounds (Figure 1). In the PiCA consortium studies, data on medication use was collected based on parental/patient reports (17 studies), pharmacy records (nine studies), and physician's prescriptions (five studies). Medication data was available for 12,736 patients. Most of the patients in the studies were treated with ICS (n=7,619) and SABA (n=8,571). Furthermore, 2,050 patients received LABA, and 2,132 used LTRA. OCS as a maintenance medication was used in 568 patients (Figure 2). In line with clinical asthma guidelines, most patients were treated with a combination of different asthma medications.

### *Outcome measures and treatment response*

Thirteen studies had information on exacerbations and approximately one third of the patients had severe exacerbations despite ICS treatment. In eleven studies (including 5,769 patients) data were available on OCS use as rescue medication despite ICS treatment. The prevalence of OCS use ranged between 7-67% in different studies, and in total 1,929 (33%) PiCA patients on ICS had received rescue OCS in the preceding 6-12 months of the study visit. Thirteen studies had data available on asthma-related ER visits or hospitalizations despite ICS (n=6,095). The prevalence of ER visits/hospitalizations ranged between 7-67%. In total 1,806 (29%) patients reported asthma-related ER visits or hospitalizations. Data on asthma-related school absences despite ICS use were available for 2,587 patients in six studies. Furthermore, data on unscheduled general practitioner (GP) visits were available for 1,479 patients in six studies (Figure 3). The total number of patients experiencing exacerbations in each study is shown in supplementary table 1.

Validated scaled questionnaires to assess current asthma symptoms (ACQ and ACT) were used in five studies (DUCHA, ESTATE, PACMAN, PAGES and Singapore Cross Sectional Genetic Epidemiology Study) (in a total of 2,070 patients). In this population, 37% (n=766) of the patients had ACQ scores  $\geq 0.75$  or ACT scores  $<20$  indicating poor asthma control. Furthermore, a modified version of the 1978 American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire (24) was used to assess current asthma control in GALA II and SAGE II in 1,725 patients; 41% had uncontrolled asthma symptoms based on this questionnaire. In addition to these scaled questionnaires, several other categorical measures of symptoms were used in studies. Modified GINA definition for long-term asthma control was used in BAMSE (n=226), with 34% of the patients having poor asthma symptoms. In the PIAMA study (n=110), 43% of the patients using inhaled steroids had uncontrolled asthma at age eight. Guidelines of the Dutch Pediatric Society (NVK), which follow the GINA guidelines, were used to define uncontrolled asthma(25). Regarding lung function measurements, changes in FEV<sub>1</sub> after bronchodilator were measured in seven studies and changes in FEV<sub>1</sub> from baseline were measured in four studies. Information on asthma severity was available for 5,608 PiCA patients. The number of severe asthmatics according to ATS/ERS, GINA and British Thoracic Society/Scottish Intercollegiate Guidelines Network [BTS/SIGN] (step 4 or higher) guidelines was 838.

### *Overlap between exacerbations and asthma symptoms:*

In three studies (GALA II, PACMAN and SAGE II), we could assess the overlap between exacerbations (defined by OCS use) and patients with asthma symptoms. In all three patient populations, there was only a slight to fair agreement between these two outcomes (kappa: 0.03-0.21); 46-72% of the patients with reported OCS use as a rescue medication also had uncontrolled asthma symptoms according to the asthma questionnaire. The overlap between patients with ER visits/hospitalizations in the past 6/12 months and uncontrolled asthma symptoms in four studies (BAMSE, GALA II, PACMAN, and SAGE II) was also poor (Kappa: 0.03 to 0.22); 41-55% of the patients with ER visits/hospitalizations had uncontrolled asthma symptoms (supplementary table 2).

### *Pharmacogenomic studies in PiCA:*

DNA samples have been collected in 20 studies, and for one study the DNA collection is still ongoing. The source of DNA per study is shown in table 1.



A protocol written by the research center interested in a specific research question will be sent to the Principal investigators [PI] of the consortium for review. Next, the protocol will be sent to all PiCA studies. Centers that are willing to participate will perform the association analysis and the results will be sent to research center that initially initiated the research proposal. In case, individual study lack resources or expertise to perform the analyses, other PiCA collaborators will help to perform the analysis.

### *GWAS in PiCA:*

Currently GWAS data is available for 13 studies (n= 6,743) (table 2). In addition, 1,967 DNA samples from 5 studies will be genotyped; BAMSE (n=400), BREATHE (n=92), PAGES (n=514), GoShare (n=561) and SLOVENIA (n=400).

In the discovery phase of the GWAS, genotyped samples will be imputed with the Michigan imputation server (Available at: <https://imputationserver.sph.umich.edu>). After imputation and quality check association analysis will be performed with EPACS (efficient and parallelizable association container toolbox. Available at: <http://genome.sph.umich.edu/wiki/EPACTS>). Principal component analysis and adjustment for gender and age will be performed when necessary. GWAS meta-analysis will be performed by METASOFT (26). In the replication phase, association analysis will be performed for the top hits identified in the discovery phase.

### *Candidate gene approach in PiCA:*

Candidate gene studies will be conducted for newly identified SNPs from GWAS meta-analyses and for previously identified SNPs in GWAS of childhood asthma onset and pharmacogenomics of asthma and SNPs that might associate with treatment response based on biological pathways.

Association analysis will be performed in the studies that have genotype or imputed data with high quality. The results of the association analysis will be meta-analyzed.

### Discussion

The PiCA consortium is a unique initiative that brings together data from 14,227 asthmatic children/young adults from 12 different countries worldwide. In genetic association studies, replication of the results across populations with different ethnic backgrounds is of high importance in order to support the findings of the pharmacogenomics analysis (27). The PiCA consortium is a novel platform to study the pharmacogenomics of uncontrolled childhood asthma despite asthma treatment.

It is important to study pharmacogenomics of childhood asthma in addition to adult asthma, since asthma phenotypes differ between children and adults and findings in adult studies cannot be translated directly to the pediatric asthma population (28). For example, a genetic variant influencing *FBXL7* expression has been found by the CAMP group to associate with improvement in asthma symptoms in response to ICS in two pediatric populations, but it failed to replicate in adults (13). Several GWAS of response to asthma medication have been published by the CAMP study group (29–31) and they can be found in the National Human Genome Research Institute [NHGRI] and the European Bioinformatics Institute [EMBL-EBI] GWAS catalog (32). In addition, variation in the *ADRB2* gene has been associated with altered LABA response, but mainly in pediatric populations (33–36). Hence, it is important to study treatment response in asthmatic children. However, assessing treatment response in asthmatic children remains a challenging subject, as symptoms may vary over time. Different measures of uncontrolled asthma (i.e. exacerbations, symptoms, or lung function) might reflect distinct dimensions of the disease. It has been previously shown that demographic characteristics and biomarker profiles of children with severe exacerbations were different from children with persistent symptoms (15), and children without asthma symptoms can be prone to severe exacerbations(37). Furthermore, It has been shown that the definition of treatment response influences the genetic risk profile associated with drug response (38,29,39). Calculated Kappa values showed only minimal to moderate agreements between asthma symptoms and exacerbations. Since different dimensions of uncontrolled asthma include different patient populations and overlap only partly, distinct outcome measures need to be studied separately. An important strength of PiCA is the collection of well-defined asthma outcomes in > 14.000 individuals for future pharmacogenomics studies within the PiCA consortium, we will perform analyses using distinct measures of poor treatment response that reflect different dimensions of asthma.

Within the PiCA consortium, we included study designs such as observational asthma cohorts and (high risk) birth cohorts. An observational study (cohort or case-control) is a common approach to assess pharmacogenomics and should not be undervalued. Observational studies can provide valuable evidence

for clinically relevant pharmacogenomics markers. Once identified, the next step would be further replication and developing a prognostic biomarker test with additional replication for generalizability and investigating the functional biology to interrogate the mechanistic aspect of the replicated findings.

Major strengths of the design of the PiCA consortium are inclusion of patients from mild to severe asthmatics with thoroughly investigated outcome and phenotype data (i.e. exacerbations and asthma symptoms), and the coverage of the broad spectrum of pediatric asthmatic medication users, which will make it possible to assess the value of pharmacogenetics for subgroups of patients. Study heterogeneity makes it possible to assess the generalizability of findings across multiple designs and/or multiple ethnicities. Sensitivity analyses can be used to assess for which group a certain marker might have the highest clinical value.

In addition to large-scale pharmacogenomics studies, which are the main goal of this consortium, PiCA also has potential to study other factors influencing treatment outcomes, such as continued exposure to allergens or epigenomics. However, obtaining additional biological samples or data might be complicated for some PiCA studies, this might only be possible in part of the PiCA population. Several potential limitations of this consortium should be acknowledged. One of the limitations of PiCA could be population stratification. However, this heterogeneity will help us to identify different genetic markers associated with the treatment response in patients with different ethnicities. Furthermore, it will help us to discover pharmacogenomics markers that are associated with the treatment response in asthmatics regardless of the ethnic background of the patients. In genome-wide association analyses, we will adjust the results of each cohort by principal components when necessary. In candidate gene studies, the analyses will be performed separately for each study and the results will be meta-analyzed. Furthermore, we will also perform sensitivity analysis by conducting separate analysis for patients with different ethnic backgrounds. The results of these analyses will be compared and in the presence of a significant difference, they will be reported. Another limitation could be the wide age range of the patients included in PiCA, although this does reflect the general asthma population in clinical practice, infant onset asthma might be a different phenotype from asthma in teenagers (40). In addition, asthma diagnosis is complicated at a young age, and infants and pre-school children can suffer from symptoms (such as wheezing) similar to those caused by asthma. In PiCA we will only include children that were still suffering from asthma symptoms at  $\geq 6$  years of age. In the majority of the PiCA studies (17 out of 21), asthma was based on physician-diagnosis and/or hospital records. Although criteria for physician-diagnosis might differ between countries, this difference reflects current clinical practice.

1 This is the first large effort to unite childhood asthma studies with a common interest in  
2 pharmacogenetics. Various studies within PiCA have collected detailed information on asthmatic children  
3 and followed children prospectively, making PiCA a unique platform for collaboration and validation.  
4 Several other studies (Asthma Genetics in Hungary [AGH], EUROPA from the Netherlands, GoShare from  
5 the UK and the Canadian asthma cohort) are still in the stage of recruiting patients, data and genotyping  
6 DNA samples, and will participate in the future projects of the PiCA consortium. In other fields, such as in  
7 cardiovascular pharmacogenomics, large research consortia have delivered key discoveries (41–44). PiCA  
8 is a growing consortium and it provides the opportunity to study pharmacogenetics on a large scale,  
9 paving the way for precision medicine in asthma.

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**Table 1. PiCA characteristics: Study design and patient characteristics**

Study name (Ref in this article)	Country	Study design	Recruiting centers	Asthmatic patients(N)	Age (Range, yrs.)	Male N, (%)	Mean (SD) FEV1% predicted baseline	Medication				DNA source
								ICS	LABA	SABA	LTRA	
<b>BAMSE</b> [1]	Sweden	General birth cohort	Primary care	420	0-16	242 (57.6)	103 (11.0)	226	57	218	-	Peripheral blood§
<b>BREATHE</b> [2]	UK	Asthma cohort	Primary and secondary care	1570	3-22	1017 (64)	96.6 (15.5)	959	62	1505	210	Saliva§
<b>British Columbia Childhood Asthma Cohort</b>	Canada	Asthma cohort	Tertiary/quaternary referral center	343	1-18	223 (65)	-	343	54	343	79	Buccal cell and Saliva
<b>CAMP</b> [3]	USA	RCT	Tertiary care	1041	5-12	621 (59)	95.6±18	311	-	418	-	Peripheral blood§
<b>COPSAC2000</b> [4]	Denmark	High risk birth cohort	Written invitation	43	0-7	22(51)	94.4 (12.1)	43	*	43	*	Peripheral blood§
<b>COPSAC2010</b>	Denmark	General birth cohort	Written invitation	90	0-5	52(57)	97.1 (12.1)	90	0	90	*	Peripheral blood§
<b>COPSACSevere*</b>	Denmark	Asthma cohort	Registry based	1173	0-25	791 (67)	-	*	*	*	*	Peripheral blood
<b>DUCHA</b>	Greece	Asthma cohort	Tertiary care	193	5-14	179 (92)	101.2 (12.8)	193	56	18	25	Peripheral blood
<b>ESTate</b>	Netherlands	Case-control	Primary care	111	4-19	67 (60)	-	110	42	111	2	Saliva§
<b>followMAGICS</b> [5]	Germany/Austria	Asthma cohort	Secondary and tertiary care	313	7-25	194 (62)	-	150	104	107	27	Peripheral blood§
<b>GALA II</b> [6]#	USA	Case-control	Secondary care, community and clinic-based recruitment	2377	8-21	1288 (54)	90.8 (16.2)	1174	368	1900	610	Peripheral blood and Saliva§
<b>Generation R#2</b> [7]	Netherlands	Population-based birth cohort	Primary, secondary and tertiary care	399	fetal-ongoing	249 (62.4)	100 (12.8)	200	50	280	10	Umbilical cord blood§



## Design of the Pharmacogenomics in Childhood Asthma consortium

<b>GOASC</b> [8] <sup>#</sup>	Spain	Asthma cohort	Secondary and tertiary care	125	2-18	76 (60)	94.6 (15.2)	125	78	14	107	Peripheral blood and Saliva
<b>PACMAN</b> [9]	Netherlands	Asthma cohort	Primary care	995	4-12	616 (61)	-	844	229	819	87	Saliva§
<b>PAGES</b> [10]	UK	Asthma cohort	Primary, secondary and tertiary care	701	2-18	519 (74)	94 (16)	648	347	696	286	Saliva
<b>PASS</b> [11]	UK	Asthma cohort	Tertiary care	525	5-18	307 (58)	-	525	395	525	369	Peripheral blood and Saliva§
<b>PIAMA</b> [12]	Netherlands	General birth cohort/ high risk birth cohort	Primary care	428	8	254 (59.3)	105.4 (12.2)	208	28	210	5	
<b>SAGE II</b> [6] <sup>#</sup>	USA	Case-control	Secondary care, community and clinic-based recruitment	987	8-21	503 (51)	98.7 (14.1)	670	171	822	96	Peripheral blood and Saliva§
<b>Singapore Cross Sectional Genetic Epidemiology Study</b> [13] <sup>#</sup>	Singapore	Asthma cohort	Tertiary care	1450	18-25	600 (41)	76.9 (12.8)	394*	*	*	*	*
<b>Slovenia</b> [14]	Slovenia	Asthma cohort	Tertiary care	350	5-19	162 (46)	89.9 (14.85)	193	*	*	86	Peripheral blood
<b>Study of asthma in Puerto Rican children (HPR)</b> [15]	USA	Case-control	Tertiary care and population based probabilistic sampling design	593	6-14	320 (53.9)	88.5 (16.5)	213	9	452	133	Peripheral blood§
<b>Total: 21 studies</b>	12 countries			14,227				7,619	2,050	8,571	2,132	

1 - Data not available, \* Data collection ongoing, # patient inclusion ongoing. §Studies with GWAS data available. #2 Patient follow-up ongoing, numbers based on  
2 participation until April 1<sup>st</sup>, 2015, aged 9 years. BAMSE, Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology. CAMP, Childhood Asthma Management  
3 Program. COPSAC, The Copenhagen Prospective Study on Asthma in Childhood. DUCHA, . ESTATE, Effectiveness and Safety of Treatment with Asthma Therapy in children.  
4 GALA II, Genes-Environment and Admixture in Latino Americans. GOASC, Genetics of Asthma in Spanish Children. ICS, inhaled corticosteroids. LABA, Long-acting Beta2  
5 agonist. LTRA, Leukotriene Receptor Antagonists. MAGICS, Multicenter Asthma Genetics in Childhood Study. PACMAN, Pharmacogenetics of Asthma Medication in Children:  
6 Medication with Anti-inflammatory effects. PAGES, Paediatric Asthma Gene Environment Study. PASS, Pharmacogenetics of adrenal suppression. PIAMA, The Prevention and  
7 Incidence of Asthma and Mite Allergy. SABA, Short-acting Beta2 agonists. SAGE II, Study of African Americans, Asthma, Genes Environments. RCT, randomized controlled trial  
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**Table 2. Studies with GWAS**

Study	Asthmatic patients, (n)	Genotyping chip	Genotyped SNPs*
<b>BAMSE</b>	122	Illumina, Infinium 610 Quad Chip	582,892
<b>BREATHE</b>	222	Illumina Infinium Exome-24 BeadChip	172,660
<b>CAMP</b>	124	Illumina, HumanHap550v3 Genotyping BeadChip	486,706
<b>COPSAC2000</b>	43	Illumina Infinium HumanOmniExpressExome Bead chip	657,699
<b>COPSAC2010</b>	90	Illumina Infinium HumanOmniExpressExome Bead chip	657,699
<b>COPSACsevere</b>	1173	Illumina Infinium HumanOmniExpressExome Bead chip	657,699
<b>ESTATe</b>	103	Illumina, Infinium CoreExome-24 BeadChip	538,267
<b>followMAGICS</b>	311	Illumina Sentrix HumanHap300 BeadChip	309,560
<b>GALA II</b>	1,900	Affymetrix, Axiom™ LAT1 array, World Array 4	742,201
<b>HPR</b>	593	Illumina HumanOmni2.5 BeadChip	1,300,000
<b>PACMAN</b>	842	Illumina, Infinium CoreExome-24 BeadChip	518,648
<b>PASS</b>	403	Illumina Omni Express 8v1	654,246
<b>SAGE II</b>	817	Affymetrix, Axiom™ LAT1 array, World Array 4	759,124
<b>Total</b>	6,743		

\*Number of SNPs after quality control: SNPs with MAF >5%, failure rate <5% and Hardy-Weinberg p-value <  $1 \times 10^{-4}$ .

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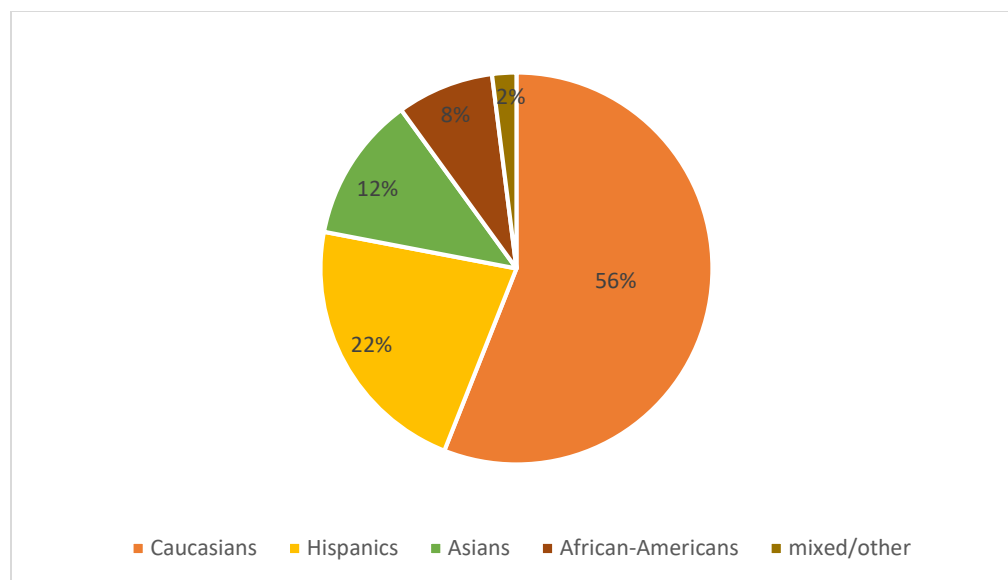


Fig 1. Ethnic backgrounds of the asthmatic patients included in the PiCA consortium

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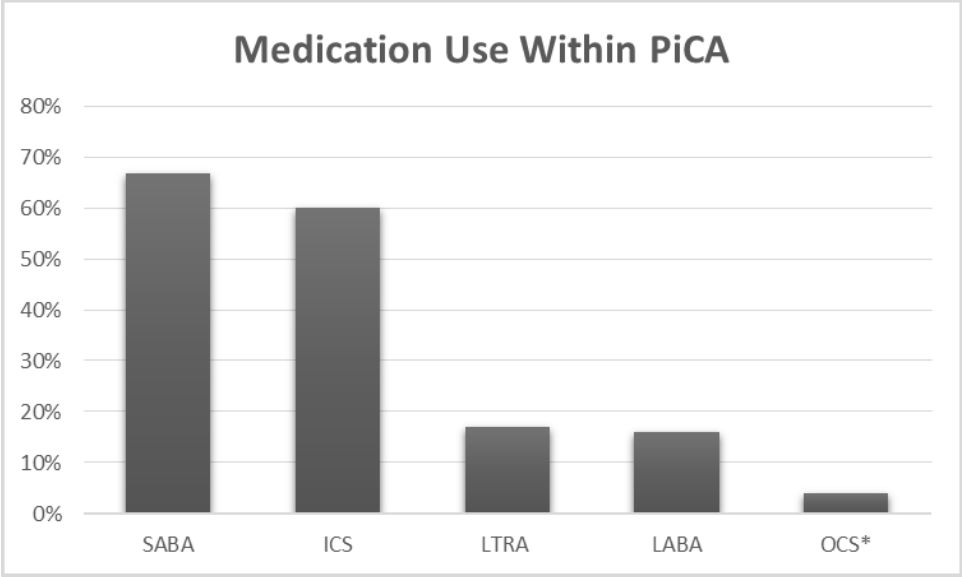


Fig 2. Physician or patient/parental reported medication use in PiCA. \*OCS considered as long-term therapy.

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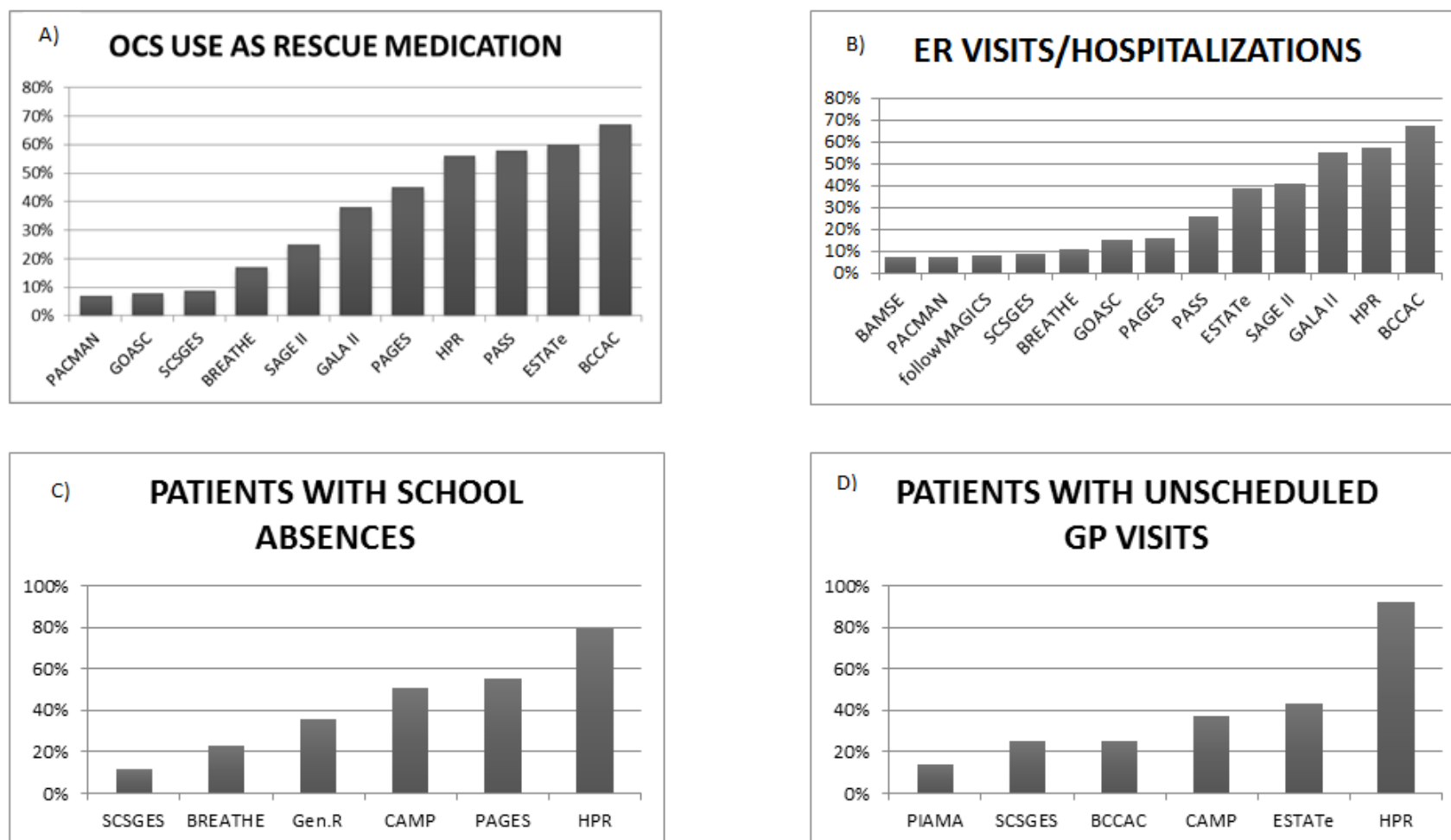


Fig 3. Exacerbations despite regular use of ICS in the preceding six months or year. A) Percentage of OCS users as a rescue medication in 11 PiCA studies. B) Percentage of patients with ER visit/hospitalization in 13 PiCA studies. C) Percentage of patients with asthma-related school absences in 6 PiCA studies. D) Percentage of patients with unscheduled GP visits in 6 studies. BCCAC; British Columbia Childhood Asthma Cohort, Gen.R; Generation R, SCSGES; Singapore Cross Sectional Genetic Epidemiology Study. In PASS and BREATHE exacerbation data were available in the preceding 6 months.

**Supplementary Table 1. PICA characteristics: Treatment outcomes within the total population**

Study	Asthma exacerbations					Poor asthma symptoms	
	OCS use <sup>1</sup> N (%)	ER <sup>1</sup> N (%)	Hospitalizations <sup>1</sup> N (%)	School absences <sup>1</sup> N (%)	GP visits <sup>1</sup> N (%)	ACQ N (%)	ACT N (%)
BAMSE	-	<b>32 (7.6)</b>	<b>4 (1.0)</b>	-	-	-	-
PIAMA	2 (0.4)	3 (0.7)	2 (0.4)	-	75 (17)	-	-
PAGES	<b>668 (95)</b>	-	<b>289 (41)</b>	-	-	-	64 (9)
PACMAN1	60 (6)	61 (6.1)	-	-	61/953 (6.4)	406 (40)	-
followMAGICS	-	<b>12 (4)</b>	<b>6 (2)</b>	<b>75 (24)</b>	<b>108 (35)</b>	-	-
GALA II	<b>745 (31)</b>	<b>1144 (48)</b>	<b>1195 (50)</b>	-	-	-	-
SAGE II	<b>187 (18)</b>	<b>335 (33)</b>	<b>48 (4)</b>	-	-	-	-
GOASC	<b>11 (8)</b>	<b>16 (12)</b>	<b>2 (1.6)</b>	-	-	-	-
BREATHE	468 (29)	-	<i>299(19)</i>	<i>605 (38)</i>	-	-	-
Singapore Cross Sectional Genetic Epidemiology Study	38 (2.6)	<b>120 (8)</b>	<b>34 (2.3)</b>	<b>170 (11)</b>	<b>309 (21)</b>	-	92 (6)
DUCHA	-	-	-	-	-	-	56 (29)
British Columbia Childhood Asthma Cohort	<b>232 (67)</b>	<b>214 (62)</b>	<b>67 (19)</b>	-	<b>91 (26)</b>	-	-
PASS	<i>309 (58)</i>	-	<i>141 (26)</i>	-	-	-	-
CAMP	538 (51)	183 (17)		564 (54)	479 946)	-	-
HPR	<b>229 (38)</b>	<b>279 (47)</b>	<b>98 (16)</b>	<b>355 (59)</b>	<b>467 (78)</b>	-	-
ESTATE	<b>39 (35.1)</b>	<b>13 (11.7)</b>	-	-	<b>37 (33)</b>	-	<b>32 (29)</b>

- Data not available, \* data not analyzed. 1 number of children with this outcome during past 6 months (italic font) or past 12 months of cohort studies (bold font), currently in the birth cohort (underlined), or during the trial (standard font). ACQ-score  $\geq 0.75$  and ACT-score  $\leq 19$  is considered not well controlled asthma. #2 patient follow-up ongoing, numbers based on participation until April 2015, aged 9 years. N.a. not applicable at current stage.

**Supplementary table 2. Cohen's Kappa values for different definitions of uncontrolled asthma**

	Uncontrolled symptoms & OCS use	Uncontrolled symptoms & ER visits and/or hospitalizations
<i>Calculated values of Cohen's Kappa</i>		
HPR		
BREATHE		
GALA II	0.21	0.19
PACMAN	0.03	0.03
SAGE II	0.16	0.2
BAMSE		0.22

