Models of Child Health Appraised

(A Study of Primary Healthcare in 30 European countries)

Work Package 1: Identification of models of children's primary care: **Systematic Review and Meta-analysis of the Literature – Part 2**

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Commission Deliverable: Report on systematic review and meta-analysis for MOCHA WP1 Part 2.

Systematic Review and Meta-analysis of the Literature

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Note

This edition of the deliverable meets the purpose and objectives as set out in the Description of Activity of the MOCHA project. However, given the necessity to limit the number of conditions studied, and the likelihood of new publications during the lifetime of the project, this deliverable will be refreshed with later editions. Such further work is likely to reinforce and refine the findings in this edition, rather than to change them fundamentally. Thus this edition forms a sound building block for other MOCHA activities.

Introduction

This deliverable addresses one of the aims of the WP1 "Identification of Models of Children's Primary Health Care". In order to describe the different models of care provided in member states, Norway and Iceland We have pursued a systematic review of the literature and meta-analysis of the evidence for different models by selecting three different aspects each of which reflects a different perspectives of the primary care health system:

1. making an early diagnosis (Autistic spectrum disorder, Attention –Deficit/Hyperactivity disorder)
2. prevention (immunization)
3. optimizing care for a child with a chronic condition (asthma)

The first topic focused on the age of first diagnosis of **Autistic Spectrum Disorder (ASD)** (in particular: Autism/ autistic disorder; Asperger's syndrome; Pervasive developmental disorder not otherwise specified; Childhood disintegrative disorder) and **Attention-Deficit/Hyperactivity Disorder (ADHD)** in children and young people.

The second topic concentrated on the coverage of **immunisation** of children (in particular: measles, mumps and rubella).

These two topics have been addressed in the D2 deliverable submitted to the European Commission in February 2016. This deliverable deals with the remaining aspects, namely and **ADHD** and **asthma**, as indicated in the previous D2 deliverable.

The ADHD, similarly for ASD, focused on the age at first diagnosis.

The control of asthma in over 5s focused on:

1) Accident & Emergency Department/Room visits for asthma;

2) Hospital admissions for asthma;

3) Unscheduled primary care visits for asthma;

4) The availability of the spirometry at a primary care level.

Background

Attention Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD), referred also as Attention deficit disorder and Hyperkinetic disorder, is a psychiatric disorder of the neurodevelopmental type marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (American Psychiatric Association, 2013).

People with symptoms of inattention may often:
• Overlook or miss details, make careless mistakes in schoolwork, at work, or during other activities • Have problems sustaining attention in tasks or play, including conversations, lectures, or lengthy reading • Not seem to listen when spoken to directly • Not follow through on instructions and fail to finish schoolwork, chores, or duties in the workplace or start tasks but quickly lose focus and get easily sidetracked • Have problems organizing tasks and activities, such as what to do in sequence, keeping materials and belongings in order, having messy work and poor time management, and failing to meet deadlines • Avoid or dislike tasks that require sustained mental effort, such as schoolwork or homework, or for teens and older adults, preparing reports, completing forms or reviewing lengthy papers • Lose things necessary for tasks or activities, such as school supplies, pencils, books, tools, wallets, keys, paperwork, eyeglasses, and cell phones • Be easily distracted by unrelated thoughts or stimuli • Be forgetful in daily activities, such as chores, errands, returning calls, and keeping appointments

People with symptoms of hyperactivity-impulsivity may often:
• Fidget and squirm in their seats • Leave their seats in situations when staying seated is expected, such as in the classroom or in the office • Run or dash around or climb in situations where it is inappropriate or, in teens and adults, often feel restless • Be unable to play or engage in hobbies quietly • Be constantly in motion or “on the go,” or act as if “driven by a motor” • Talk nonstop • Blurt out an answer before a question has been completed, finish other people’s sentences, or speak without waiting for a turn in conversation • Have trouble waiting his or her turn • Interrupt or intrude on others, for example in conversations, games, or activities

Some people with ADHD only have problems with one of the behaviours, while others have both inattention and hyperactivity-impulsivity.

Table 1: Types of ADHD

Types of ADHD		
Combined	Inattentive	Hyperactive/impulsive
All three core features are present and ADHD is diagnosed when ≥6 symptoms of hyperactivity/impulsivity and ≥6 symptoms of inattention have been observed for ≥6 months	Diagnosed if ≥6 symptoms of inattention (but <6 symptoms of hyperactivity/impulsivity) have persisted for ≥6 months	Diagnosed if ≥6 symptoms of hyperactivity/impulsivity (but <6 symptoms of inattention) have been present for ≥6 months

Most children have the combined type of ADHD.

Diagnosis of ADHD requires a comprehensive evaluation by a licensed clinician, such as a paediatrician, psychologist, or psychiatrist with expertise in ADHD (National Institute for Mental Health-Index). For a person to receive a diagnosis of ADHD, the symptoms of inattention and/or hyperactivity-impulsivity must be chronic or long-lasting, impair the person's functioning, and cause the person to fall behind normal development for his or her age. The doctor will also ensure that any ADHD symptoms are not due to another medical or psychiatric condition. Most children with ADHD receive a diagnosis during the elementary school years. For an adolescent or adult to receive a diagnosis of ADHD, the symptoms need to have been present prior to age 12.

ADHD symptoms can appear as early as between the ages of 3 and 6 and can continue through adolescence and adulthood. Symptoms of ADHD can be mistaken for emotional or disciplinary problems or missed entirely in quiet, well-behaved children, leading to a delay in diagnosis. ADHD symptoms can change over time as a person ages. In young children with ADHD, hyperactivity-impulsivity is the most predominant symptom. As a child reaches elementary school, the symptom of inattention may become more prominent and cause the child to struggle academically. In adolescence, hyperactivity seems to lessen and may show more often as feelings of restlessness or fidgeting, but inattention and impulsivity may remain. Many adolescents with ADHD also struggle with relationships and antisocial behaviours. Inattention, restlessness, and impulsivity tend to persist into adulthood.

Attention Deficit/Hyperactivity Disorder diagnosis

For a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should meet the diagnostic criteria in Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or International Statistical Classification of Diseases and Related Health Problems (ICD).

The DSM classification of disease systems is now in its fifth edition and is the standard classification of 'mental disorders' used by mental health professionals in the United States of America.

The following table describes the diagnostic criteria from DSM IV, DSM IV TR and DSM V.

Table 2: DSM diagnostic criteria

DSM edition	Description
DSM IV	A. Either (1) or (2): (1) inattention: six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities (b) often has difficulty sustaining attention in tasks or play activities (c) often does not seem to listen when spoken to directly (d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions) (e) often has difficulty organizing tasks and activities (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools) (h) is often easily distracted by extraneous stimuli (i) is often forgetful in daily activities (2) hyperactivity-impulsivity: six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: Hyperactivity (a) often fidgets with hands or feet or squirms in seat (b) often leaves seat in classroom or in other situations in which remaining seated is expected (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) (d) often has difficulty playing or engaging in leisure activities quietly (e) is often "on the go" or often acts as if "driven by a motor" (f) often talks excessively Impulsivity (g) often blurts out answers before questions have been completed (h) often has difficulty awaiting turn (i) often interrupts or intrudes on others (e.g., butts into conversations or games) B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years. C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home). D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

	E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder). Code based on type: **314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:** if both Criteria A1 and A2 are met for the past 6 months **314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:** if Criterion A1 is met but Criterion A2 is not met for the past 6 months **314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type:** if Criterion A2 is met but Criterion A1 is not met for the past 6 months **Coding note:** For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified. (American Psychiatric Association, 1994)
DSM IV – TR	A. Either (1) or (2): (1) inattention: six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities (b) often has difficulty sustaining attention in tasks or play activities (c) often does not seem to listen when spoken to directly (d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions) (e) often has difficulty organizing tasks and activities (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools) (h) is often easily distracted by extraneous stimuli (i) is often forgetful in daily activities (2) hyperactivity-impulsivity: six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: Hyperactivity (a) often fidgets with hands or feet or squirms in seat (b) often leaves seat in classroom or in other situations in which remaining seated is expected (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) (d) often has difficulty playing or engaging in leisure activities quietly (e) is often "on the go" or often acts as if "driven by a motor" (f) often talks excessively

	Impulsivity (g) often blurts out answers before questions have been completed (h) often has difficulty awaiting turn (i) often interrupts or intrudes on others (e.g., butts into conversations or games) B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years. C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home). D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning. E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder). Code based on type: **314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:** if both Criteria A1 and A2 are met for the past 6 months **314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:** if Criterion A1 is met but Criterion A2 is not met for the past 6 months **314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type:** if Criterion A2 is met but Criterion A1 is not met for the past 6 months **Coding note:** For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified. (American Psychiatric Association, 2000)
DSM IV	As in DSM-IV, symptoms will be divided into two categories of inattention and hyperactivity and impulsivity that include behaviours like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, fidgeting, or an inability to remain seated in appropriate situations. Children must have at least six symptoms from either (or both) the inattention group of criteria and the hyperactivity and impulsivity criteria, while older adolescents and adults (over age 17 years) must present with five. While the criteria have not changed from DSM-IV, examples have been included to illustrate the types of behaviour children, older adolescents, and adults with ADHD might exhibit. The descriptions will help clinicians better identify typical ADHD symptoms at each stage of patients' lives. Using DSM-5, several of the individual's ADHD symptoms must be present prior to age 12 years, compared to 7 years as the age of onset in DSM-IV. This change is supported by substantial research published since 1994 that found no clinical differences between children identified by 7 years versus later in terms of course, severity, outcome, or treatment response. DSM-5 includes no exclusion criteria for people with autism spectrum

	disorder, since symptoms of both disorders co-occur. However, ADHD symptoms must not occur exclusively during the course of schizophrenia or another psychotic disorder and must not be better explained by another mental disorder, such as a depressive or bipolar disorder, anxiety disorder, dissociative disorder, personality disorder, or substance intoxication or withdrawal. (American Psychiatric Association, 2013)

The World Health Organization ICD contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. The latest revision of the ICD, ICD-10, was updated in 2015 (ICD-10 Version 2015). The ICD-10 classification of Hyperkinetic disorders, such as Attention-deficit hyperactivity disorder is schematically organised as the following:

F90-Hyperkinetic disorders

A group of disorders characterized by an early onset (usually in the first five years of life), lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. Several other abnormalities may be associated. Hyperkinetic children are often reckless and impulsive, prone to accidents, and find themselves in disciplinary trouble because of unthinking breaches of rules rather than deliberate defiance. Their relationships with adults are often socially disinhibited, with a lack of normal caution and reserve. They are unpopular with other children and may become isolated. Impairment of cognitive functions is common, and specific delays in motor and language development are disproportionately frequent. Secondary complications include dissocial behaviour and low self-esteem.

Excluding: anxiety disorders (F41.-)
mood [affective] disorders (F30-F39)
pervasive developmental disorders (F84.-)
schizophrenia (F20.-)

F90.0-Disturbance of activity and attention

Attention deficit:
disorder with hyperactivity
hyperactivity disorder
syndrome with hyperactivity

Excluding: hyperkinetic disorder associated with conduct disorder (F90.1)

F90.1-Hyperkinetic conduct disorder

Hyperkinetic disorder associated with conduct disorder

F90.8-Other hyperkinetic disorders

F90.9-Hyperkinetic disorder, unspecified

Hyperkinetic reaction of childhood or adolescence NOS

Hyperkinetic syndrome NOSF84-Pervasive developmental disorders

Epidemiology of Attention Deficit/Hyperactivity Disorder

Although there is no global consensus on the prevalence of ADHD in children, adolescents and adults, meta-regression analyses have estimated the worldwide prevalence at between 5.29% (Polanczyk, 2007) and 7.1% in children and adolescents (Willcutt, 2012), and at 3.4% (range 1.2–7.3%) in adults (Hayyad, 2007).

ADHD prevalence rates may vary depending on several factors:

- Age – whilst ADHD was once considered to be a childhood disease with a decline in symptoms during maturation to adulthood (Biederman, 2000), it is now acknowledged to persist into adulthood in an estimated 50–66% of individuals (Barkley, 2002).
- Gender – a higher prevalence of ADHD is often reported in males (Murphy, 1996; Nøvik, 2006).
- Presentations of ADHD – the combined inattentive-hyperactive-impulsive presentation of ADHD is considered most prevalent in children, adolescents and adults (Faraone, 1998; Wilens, 2009).

ADHD is often present alongside comorbidities such as oppositional defiant disorder, conduct disorder, anxiety disorder, personality disorders and depression (Kessler, 2006; Piñeireo-dieguez, 2014; Steinhausen, 2006), which may further complicate understanding of true prevalence rates.

Early diagnosis of ADHD allows for prompt behavioural management and medication to be commenced and monitored. Early diagnosis and treatment improves the outcome for the child in terms of intrafamilial and school peer/teacher relationships and optimises educational attainment.

Asthma

Asthma is the commonest chronic disease in childhood. Due to the various different phenotypes of childhood asthma, it has been difficult to agree on a clear definition of the condition and instead an operational description is used: 'Asthma is heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.' (1). Asthma can start at any time of life, but is likely to begin in childhood.

Symptoms

Symptoms and airflow limitation may resolve spontaneously or in response to medication, and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community. Asthma is usually associated with airway hyper responsiveness to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment (GINA, 2016). Symptoms occur often at night or in the early morning. Sometimes symptoms can worsen over hours or minutes, leading to a severe obstruction of the airways known as an asthma attack. Acute asthma is the most frequent cause of admission to hospital in children of all ages. Deaths from asthma are low and over recent years the number has deceased across Europe. Research suggests that 9 out of 12 deaths from asthma are due to anaphylaxis with asthma caused by food allergy. (European Lung Foundation) However, in children <5 years of age, clinical symptoms of asthma are variable and nonspecific, and a symptoms-only approach that defines various wheezing phenotypes has been recommended (ERS, 2016).

Causes

Asthma results from an interaction between environmental factors and genetic factors.

Environmental

The environmental influences begin during pregnancy: allergic sensitization has been described before birth, and several studies have demonstrated reduced lung function in newborn infants of smoking mothers compared to those of non-smoking mothers. Smoking increases the risk of both asthma and poorer lung function throughout childhood. All children should have the right to an environment free from tobacco smoke products both before and after birth.

Respiratory virus infections are the major cause of acute bronchiolitis in infancy and of acute asthma attacks among older asthmatic children. From 2 years of age and especially during school years, inhalant allergy becomes increasingly important for childhood asthma. Approximately 60% of all school-aged asthmatic children are allergic. The most important allergens vary according to climate, but in all European countries animal dander is among the most frequent allergens in asthma. In a warm and humid climate, house dust mites and moulds are also of major importance, and, depending upon climate, the seasonal allergens (birch, grass and mugwort pollen) play a role. Allergen exposure may cause acute asthma exacerbations, and even in the absence of an exacerbation, may increase airway inflammation and bronchial hyper responsiveness.

Occupational agents play a minor role during childhood, but several types of allergy may influence the choice of education in relationship to later working life. Kindergartens and schools are the working environment of children, and the need for a healthy indoor environment in such institutions should be emphasized. Special consideration should be given to the increased risk of respiratory infections, especially in kindergartens. In schools, precautions may be taken to reduce allergen exposure for allergic asthmatic children. Emphasis should also be put upon mastering exercise-induced asthma in gymnastic lessons and physical training.

Genetic

Asthma, and one of its major causes, allergy, have strong hereditary traits. During recent years, much effort has been put into genetic family studies in order to identify genetic markers. A large number of markers with possible relationships to asthma and airway inflammation have already been identified, but these vary between populations. There has also been increased focus upon epigenetics: the finding that environmental influences may cause DNA methylation and histone formation, and thus change and inactivate the influence of specific genes, has given insight into how the environment may interact with genes, and has shown that this interaction may even be transferred from mother to child. Furthermore, hereditary traits have been found to influence the response to asthmatic drugs.

Exercise

Throughout childhood, but increasingly during school age, exercise is an important cause of asthma exacerbations (exercise-induced asthma). However, if exercise is managed properly, it can be a great benefit to help children manage their symptoms.

Morbidity

Asthma morbidity is a major burden for the child, his/her family and the community. Asthma attacks are very frightening for the child and due to the resulting disruption of life and reduced

physical ability there is an emotional, as well as economic, impact of the disease. The social burden of asthma is considerable, not only on the sick child but also on parents, siblings and the household in general (lots of parents take time off from work because of the child's asthma and some had given up their jobs completely). In assessing quality of life in asthmatic children, it is important also to assess the quality of life of the caregivers.

Direct healthcare costs for childhood asthma arise from consultations in both primary and secondary care, as well as hospital admissions and treatment costs. In some, but not all, countries, hospital admissions have fallen in recent years, but greater use of both inhaled and oral agents has increased the expenditure on asthma drugs. A number of new drugs have recently been introduced, thereby increasing the drug-related cost. In particular, the use of inhaled steroids has increased markedly in recent years (ERS, 2016)

Phenotypes

Many phenotypes have been identified (Bel EH, 2004; Moore WC, 2010; Wenzel SE, 2012). Some of the most common include:

- Allergic asthma: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy.
- Non-allergic asthma: some adults have asthma that is not associated with allergy.
- Late-onset asthma: some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic.
- Asthma with fixed airflow limitation: some patients with long-standing asthma develop fixed airflow limitation that is thought to be due to airway wall remodelling.
- Asthma with obesity: some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.

Treatment

There is no widely used test to diagnose asthma. In children, it is often identified when the child displays common symptoms of wheeze, a tight chest or cough.

Medications for treatment include:

- Controller medication: This medication is taken regularly to build up a protective effect against asthma symptoms. Among controlling treatments, inhaled corticosteroids are the most important drugs and enable most children and adolescents with asthma to lead a normal life. In most cases, inhaled corticosteroids also control exercise-induced asthma, allowing participation in physical activity and sports. High doses of inhaled

steroids may impair growth but only to a small extent (1–2 cm in height at most), and usually in the early phase of treatment.

- Reliever medication: These are taken to relieve asthma symptoms. They relax the muscles surrounding the narrowed airways and can be used in the event of an asthma attack or worsening of symptoms. These are usually in the form of short-acting β-agonists.

Children should be monitored carefully to assess the response to treatment, and treatment that proves to be ineffective should be stopped.

Asthma care involves more than just drugs. Participation in activity and exercise is very important in childhood asthma and is encouraged.

Guidelines

Asthma is a common condition that produces a significant workload for general practice, hospital outpatient clinics and inpatient admissions. It is clear that much of this morbidity relates to poor management particularly the under use of preventative medicine.

A number of guidelines on the management of asthma have been developed, including the GINA (GINA, 2016) (supported by unrestricted educational grants from non-pharmaceutical and pharmaceutical companies) and the Expert Panel Report 3 (CRD, 2009) developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), co-ordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. In the UK, in 1999 the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) agreed to jointly produce a comprehensive new asthma guideline, both having previously published guidance on asthma. The original BTS guideline dated back to 1990 and the SIGN guidelines to 1996. The guidelines provide recommendations based on current evidence for best practice in the management of asthma in adults, including pregnant women, adolescents and children.

An important test of the quality of the primary care system is its ability to keep children out of hospital and provide careful monitoring of symptoms and signs, regular review of medication requirements and the provision of age appropriate education and written materials e.g. asthma plans.

Materials and methods

Search strategy

A comprehensive electronic search was performed using PubMed.

For ADHD the following key words have been set for the search in the title or in the abstract: (ADHD OR "Attention deficit" OR "Hyperactivity disorder" OR "Attention disorder"); moreover ((age) AND (diagnosis OR onset)) was set for the search in the full-text.

The filters "Text availability: Full text" and "Languages: English" were set.

For asthma, the word "asthma" was searched in the title or in the abstract, in combination with the following key words searched in the text: (emergency OR emergency department OR unschedul*) AND (admission* OR care OR visit*), using the filters humans.

A second search was undertaken using the word "spirometer" and "availability" in the text.

All potentially eligible articles were screened at title, abstract, and full-text stages in order to sequentially identify the study country and the availability of the investigated outcomes.

The PubMed search was supplemented with hand-searching of reference lists of all potentially eligible full-text articles.

Eligibility criteria for a study

Types of study design: Any types of study design have been included in the search; however the search identified mainly observational studies, either cross-sectional or longitudinal.

Reference year: all paper published in the range of years 2000-2016.

Authors' affiliations: only European affiliated authors were included.

Outcomes investigated:

a) ADHD age at onset.
b) In asthmatic children the % or number of:
   b1) Accident & Emergency Department/Room visits for asthma;
   b2) Hospital admissions for asthma;
   b3) Unscheduled primary care visits for asthma;
   b4) the availability of the spirometry at a primary care level.

Data extraction

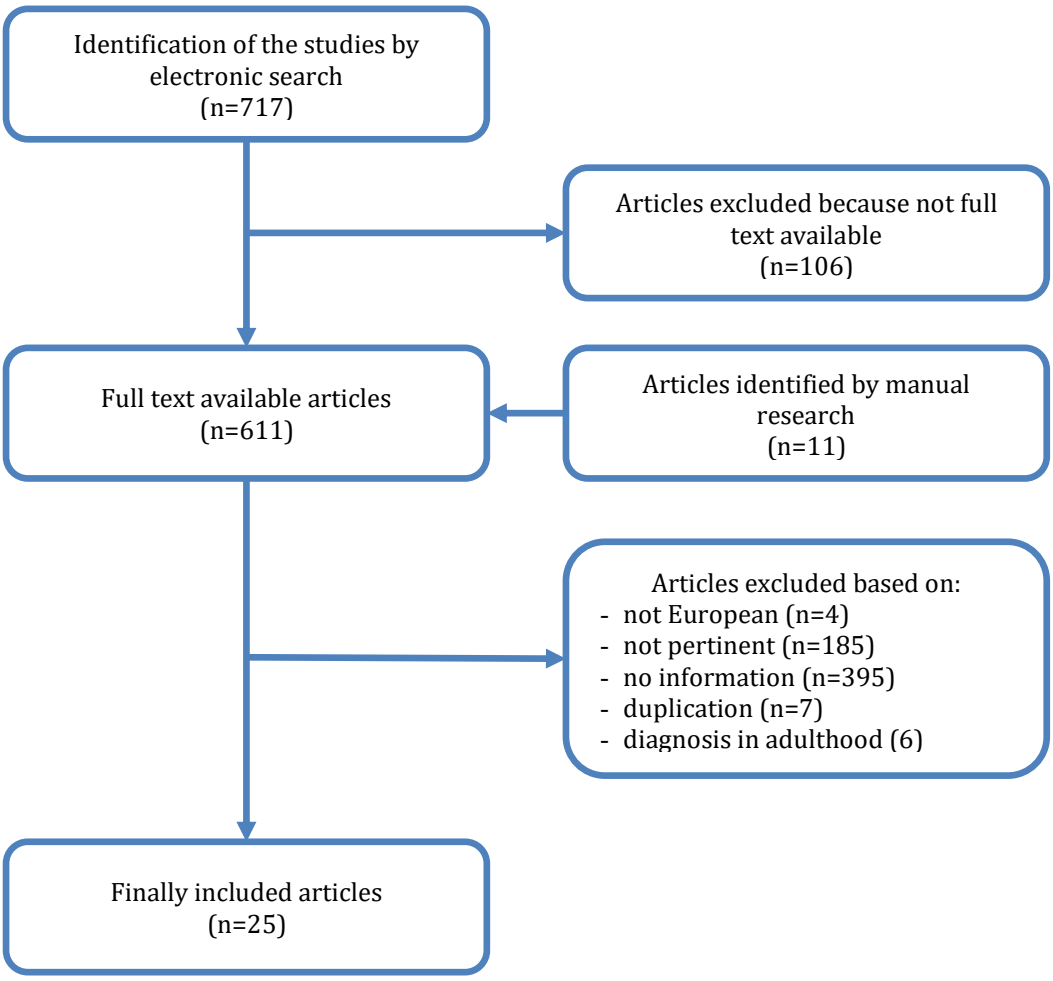
The following data was extracted from all included papers: the first author's last name, publication year, country where the study was conducted, the outcome measures investigated, the sample size, the age of reference, and gender.

Summary of the study selection process

The following figures show the different steps of the selection process for ADHD and asthma, respectively.

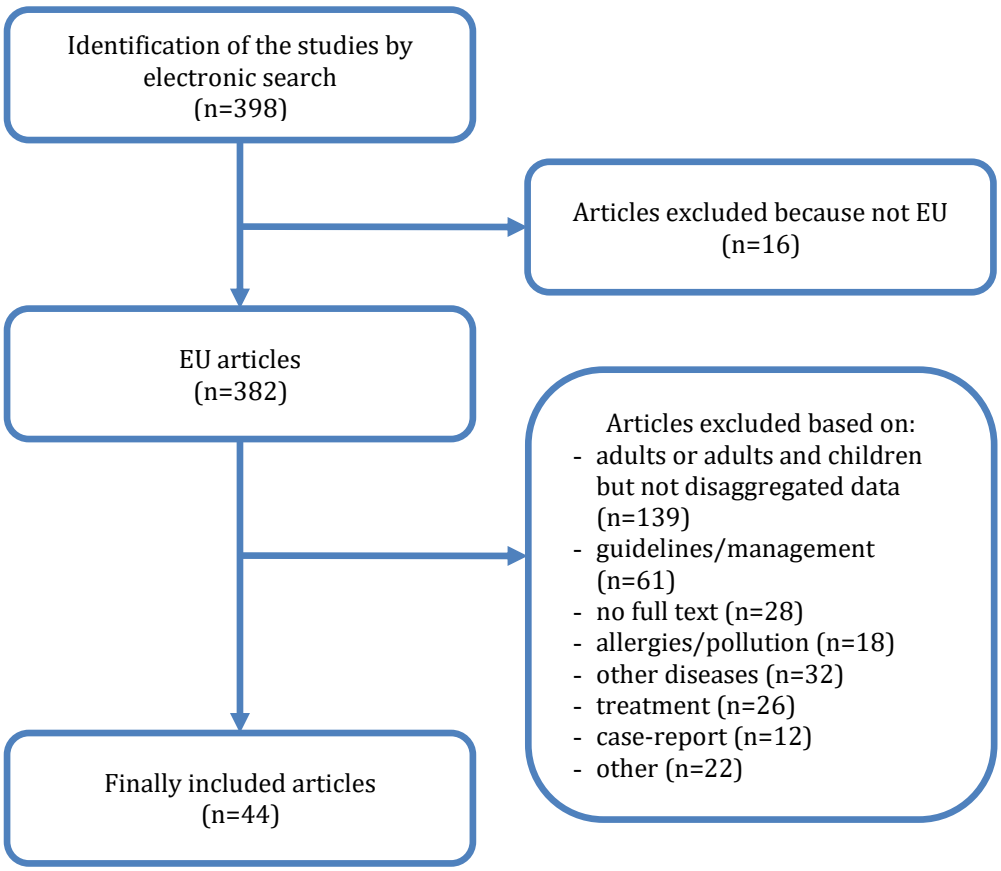
The PubMed search retrieved 717 articles on ADHD from year 2000 to 2016 (Fig. 1). Fifteen percent of these papers (106/717) have been excluded since the full text of the articles was not available. Eleven articles have been retrieved manually, leading to 622 articles read as a full text. Out of these, only 25 have been included in our systematic review (3.5%).

Figure 1. Flow chart age at ADHD diagnosis



The PubMed search retrieved 398 articles on asthma for the ED/hospital/unscheduled primary care visits, from year 2000 to 2016 (Fig. 2). Although the restriction on authors' affiliation, 16 of these papers have been excluded since the research was not carried out in a European Country. The full-text reading of the 382 articles lead to 44 articles to be included in our systematic review.

Figure 2. Flow chart asthma



The PubMed search retrieved 15 articles on spirometry instrument, but only 4 of them reported the %/absolute number of available spirometers at a primary care level.

Meta-analysis

In our search the primary interest lies in the descriptive estimates, as opposed to comparative estimates that arise naturally for Randomized Controlled Trials studies or cohort studies (where exposed are compared with the unexposed) or case-control studies (where people with the condition are compared with people without the condition).

Investigated outcomes have been combined in a pooled estimate, using the method of the inverse of the variance, that is the weighing assigned to the different studies is related with the inverse of the standard error and therefore indirectly to the sample size. This implies that studies with smaller standard error and larger sample size are given more weight in the calculation of the pooled estimates. Fixed effects or random effects model have been used, according to the presence of heterogeneity which was tested by means of the Cochrane's Q test and the Higgins I^2 statistic which was interpreted as follows: I^2 of 25 % = low heterogeneity. I^2 of 50 % = medium heterogeneity. I^2 = 75 % = high heterogeneity. The results of the different studies and the overall estimate with its 95% Confidence Interval (95%CI) are illustrated in a graph called a "forest plot".

Type of care: country classification

The EU countries have been classified according to their primary care system defined as: Paediatrician mainly oriented (Ped); General Practitioner mainly oriented (GP); Mixed. This classification is the outcome of the MOCHA classification working group based on the Country Agent investigations upon a specific request from the WP leaders on a case study.

Table 4 reports the description of the health system given by the Country Agents, the findings from Van Esso et al. (2010) and the MOCHA classification working group.

Table 3: Type of primary care for each EU country

Country	Description of type of primary care	From Van esso et al. Arch Dis Child 2010; 95:791-5	MOCHA Classification
Austria	GP and paediatrician	Combined	Mixed
Belgium	Family doctor or 1st line paediatrician	Combined	Mixed
Bulgaria	GP for those with health insurance. Pre 2000 was mandatory to have a community paed for children up to 18; This generation now retiring and GPs only have 9 weeks paeds	GP	GP

	training.		
Croatia	Primary care doctor / paediatrician	-	Ped
Cyprus	Private paediatrician or public funded GP who will refer to hospital Paed if necessary	Ped	Mixed
Czech Republic	"registering paediatrician" accessed via triage nurse	Ped	Ped
Denmark	-	GP	GP
Estonia	GP	GP	GP
Finland	GP	GP	GP
France	Family physician or GP who is either a Paediatrician or a GP	GP	Mixed
Germany	Paediatrician	GP	Ped
Greece	GP or Paediatrician chosen from insurance co list Usually paediatrician up to 18 years old.	Ped	Ped
Hungary	-	Combined	Mixed
Iceland	One family doctor from a health care centre or private paediatrician	Combined	Mixed
Ireland	GP	GP	GP
Italy	0-14 have paediatrician or GP if none locally. Max 800 children per paediatrician	Mixed	Ped
Latvia	GP / family doctor or a paediatrician	GP	Mixed
Lithuania	Family doctor or paediatrician	Combined	Mixed
Luxembourg	Family doctor. Paediatrician up to the age of 2 years.	Combined	Mixed
Malta	Family doctor (private) or walk in community health centre	-	GP
Netherlands	GP (Triaged by nurse)	GP	GP
Norway	GP	GP	GP
Poland	GP or Paediatrician chosen from insurance company list	GP	Mixed
Portugal	GP (80%) or private paediatrician	GP	GP
Romania	Family doctor	-	GP

Slovakia	-	Ped	Ped
Slovenia	-	Ped	Ped
Spain	Family doctor in health care centre or a paediatrician	Ped	Mixed
Sweden	Child health care nurse up to age 6; school health nurse afterwards. GP/Paeds in hospital contacted by nurse	GP	Mixed
United Kingdom	GP as a named accountable professional	GP	GP

The Ped/GP/Mixed MOCHA classification was used to perform the meta-analysis for each type of primary care and allow some speculations on possible difference across types of primary care systems.

Sweden reported a system based on a child health nurse and for our purposes was classified as Mixed; Luxembourg reported a Ped if the child was under two years and a GP if was over 2 years and our purposes was classified as Mixed.

Results

Attention Deficit/Hyperactivity Disorder

Appendix 1 shows the main characteristics of the identified studies for ADHD. A total of 25 studies have been identified. The age of reference reported in the studies ranges from 0 to 60 years and the sample size from 14 to 20742. The majority of the studies had been carried out in one country, with the exception of Caci (2014) and Hodgkins (2013) that considered 6 EU countries. Most of the studies (26.9%) have been carried out in Germany, followed by The Netherlands (15.4%), UK (11.5%), Denmark, France, Ireland and Spain (7.7%), and Finland, Greece, Italy and Sweden (3.8%).

The articles that do not indicate the mean age at diagnosis and/or its standard error but which provide the tools to calculate them have been included in the meta-analysis.

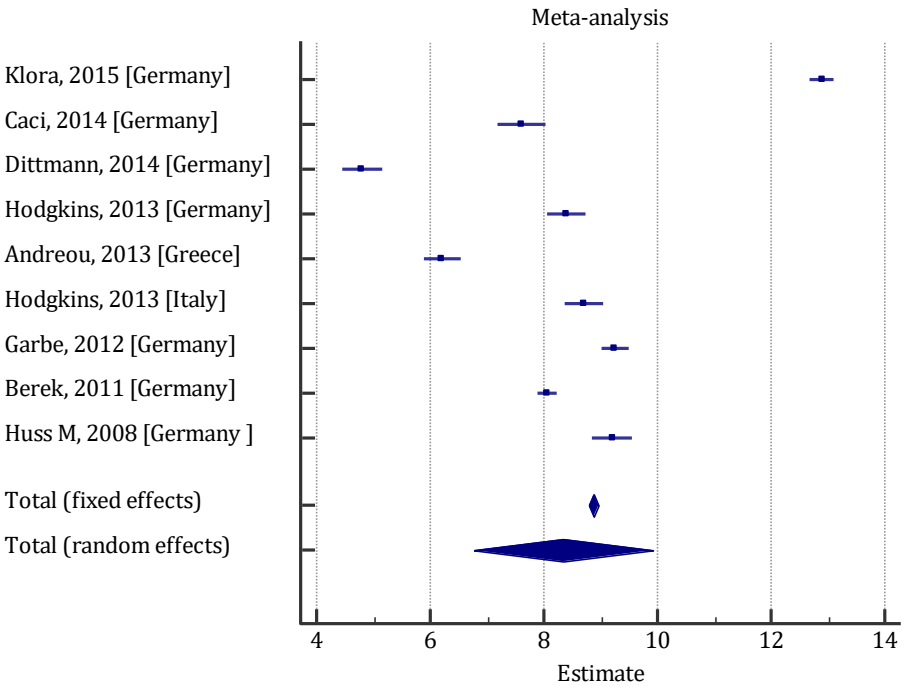
5 articles have been excluded because the calculation of the standard error was not feasible.

The meta-analysis was performed by the MOCHA classification type of primary care in each country. Paediatrician included 3 countries (Germany, Greece and Italy), GP included 5 countries (Denmark, Finland, Ireland, Netherland, and UK), and mixed included 3 countries (France, Iceland, Spain and Sweden).

For the calculation of the pooled estimate of the mean age at onset for ADHD, a random effect model was used, due to the presence of heterogeneity in Paediatrician (Q=2323.9; p-value<0.0001; I^2=99.66%), in GP (Q=11021.7; p-value<0.0001; I^2=99.90%) and in mixed (Q=1927.1; p-value<0.0001; I^2=99.79%).

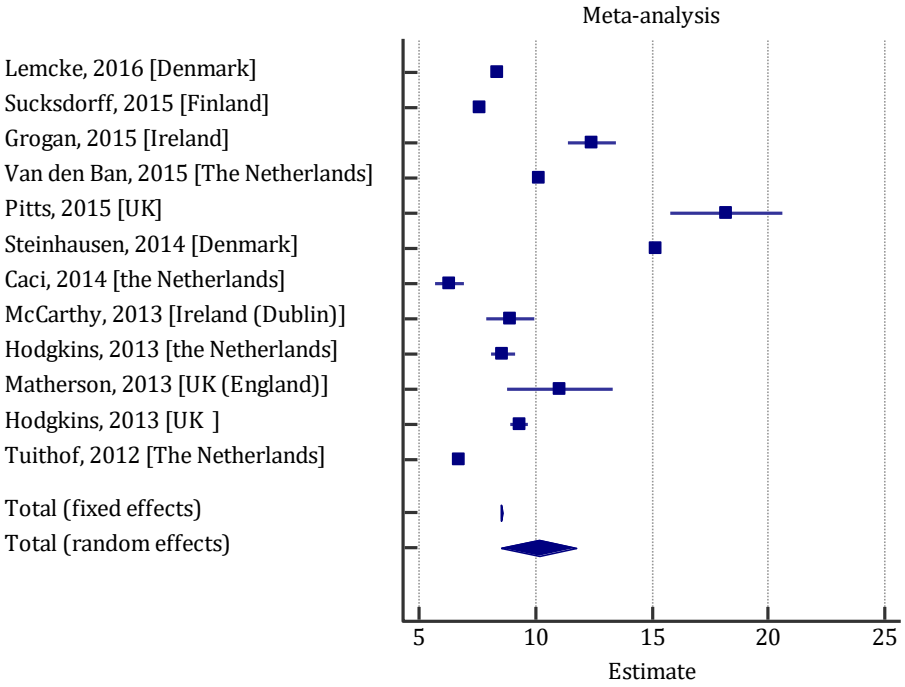
The pooled estimated of age at onset for ADHD was 8.3 years with a 95% CI = (6.8-9.9) in a Paediatrician primary care system, as presented in fig.3.

Figure 3. Meta-analysis for mean age at onset of ADHD, Paediatrician primary care system.



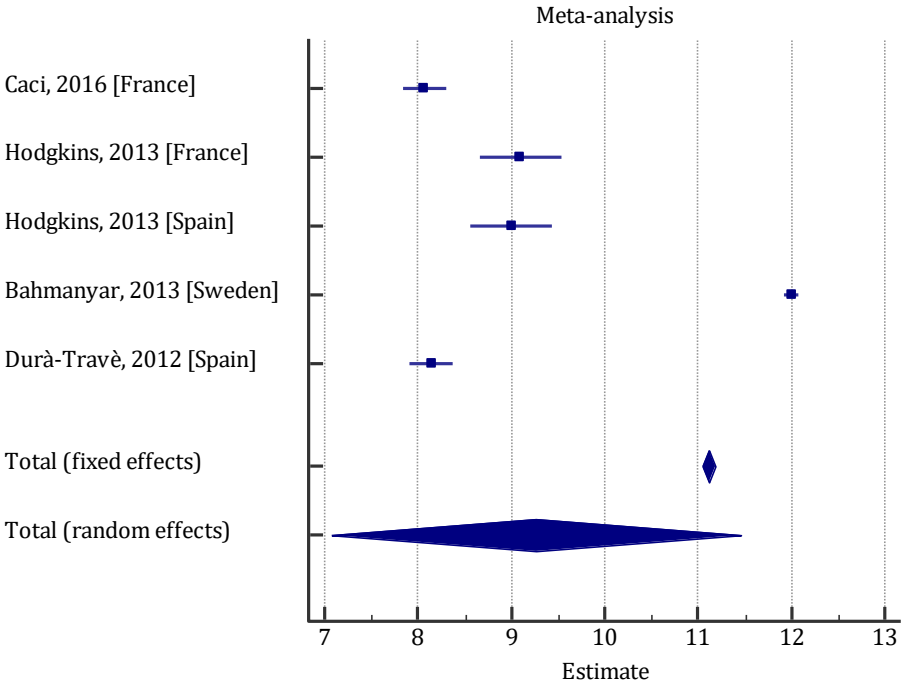
The pooled estimated of age at onset for ADHD was 10.1 years with a 95% CI= (8.5-11.7) in a GP primary care system, as presented in fig.4.

Figure 4. Meta-analysis for mean age at onset of ADHD, GP primary care system.



The pooled estimated of age at onset for ADHD was 9.3 years with a 95% CI= (7.1-11.4) in a Mixed primary care system, as presented in fig. 5.

Figure 5. Meta-analysis for mean age at onset of ADHD, Mixed primary care system.



Asthma

Appendix 2 shows the main characteristics of the identified studies for asthma regarding Accident & Emergency Department/room visits, hospitalizations and unscheduled primary care visits. A total of 18 studies have been identified, between them the majority investigated the Accident & Emergency Department/room visits for asthma (16), 9 concerned the hospital admissions for asthma and 6 looked at unscheduled primary care visits that were asthma related. Most of the retrieved papers looked at more than one of our outcomes.

The most represented country is United Kingdom with 5 papers, followed by France, Germany, Italy, the Netherlands, and Sweden with 2 paper each, and Finland, Portugal and Spain with 1 paper each.

For the meta-analysis 26 studies have been excluded. The majority of them were excluded because the studies were focus on Accident & Emergency Department/room visits, hospitalizations and/or unscheduled primary care visits only, so no percentage could be calculated.

The meta-analysis was performed by the MOCHA classification type of primary care in each country for the remaining papers. Based on the information retrieved, for each type of primary care the following countries were included for meta-analyses:

- Paediatrician 2 countries (Germany, Italy);
- GP 4 countries (Finland, the Netherland, Portugal, United Kingdom);
- mixed 3 countries (France, Spain, Sweden).

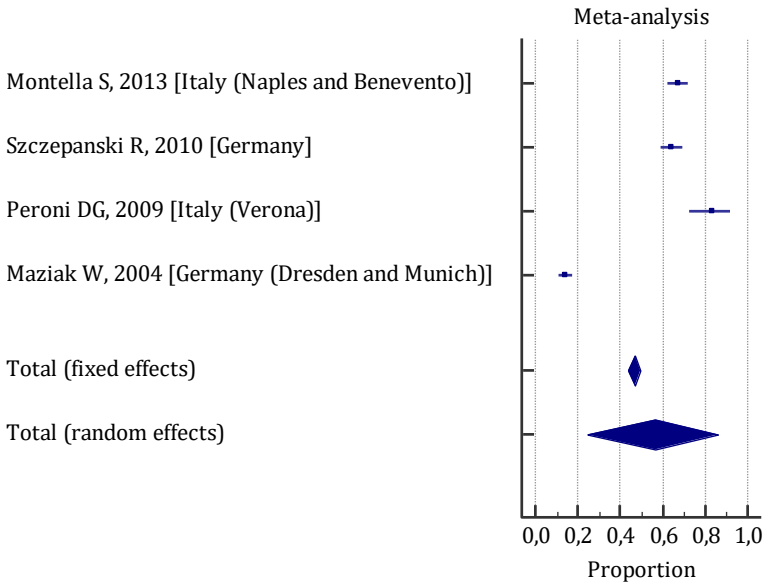
Appendix 3 shows the main characteristics of the identified studies for asthma regarding the availability of spirometry at primary care level. Only 4 studies were found, 3 from Spain and one from United Kingdom. Two of the Spanish studies sampled health care centres that routinely evaluated adult patients and are based on the same survey. In the other two studies the target population was not specified. Due to this low number of studies, no meta-analysis could be performed for this topic.

Accident & Emergency Department/room visits for asthma

The pooled estimate of Accident & Emergency Department/room visits was calculated by a random effect model, due to the presence of heterogeneity in Paediatrician (Q=390,6; p-value<0.0001; I^2=99,23%), in GP (Q=3276,1; p-value<0.0001; I^2=99.76%) and in Mixed (Q=190.8; p-value<0.0001; I^2=98.95%).

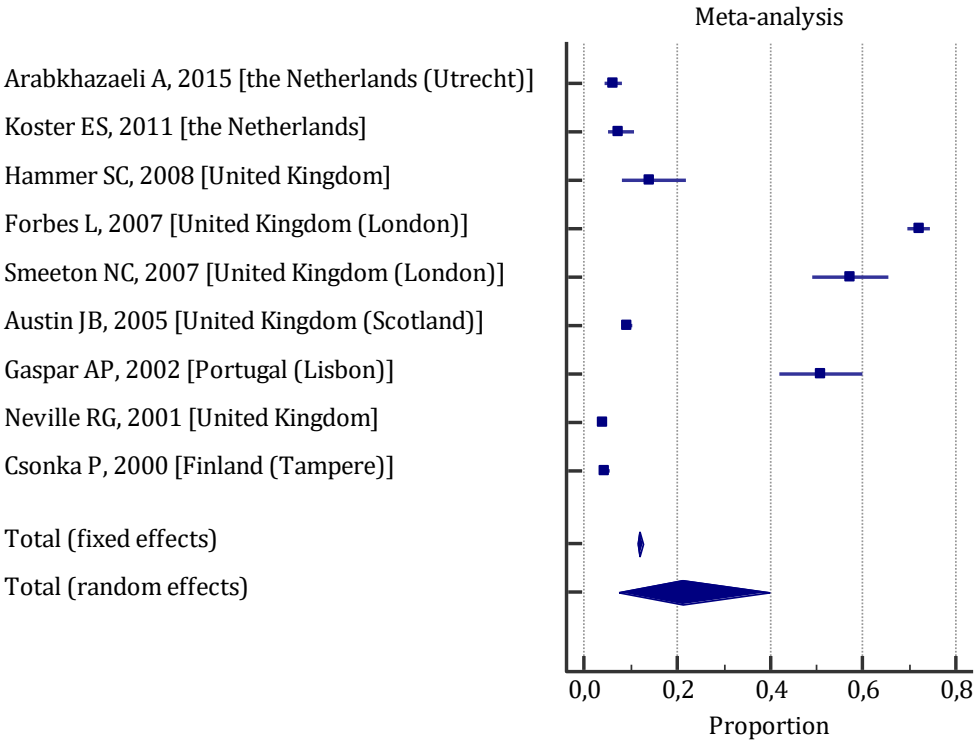
The pooled estimated of Accident & Emergency Department/room visits was 56.6% with a 95% CI = (24.6-85.8) in a Paediatrician primary care system, as presented in fig. 6.

Figure 6. Meta-analysis Accident & Emergency Department/room visits, Paediatrician primary care system.



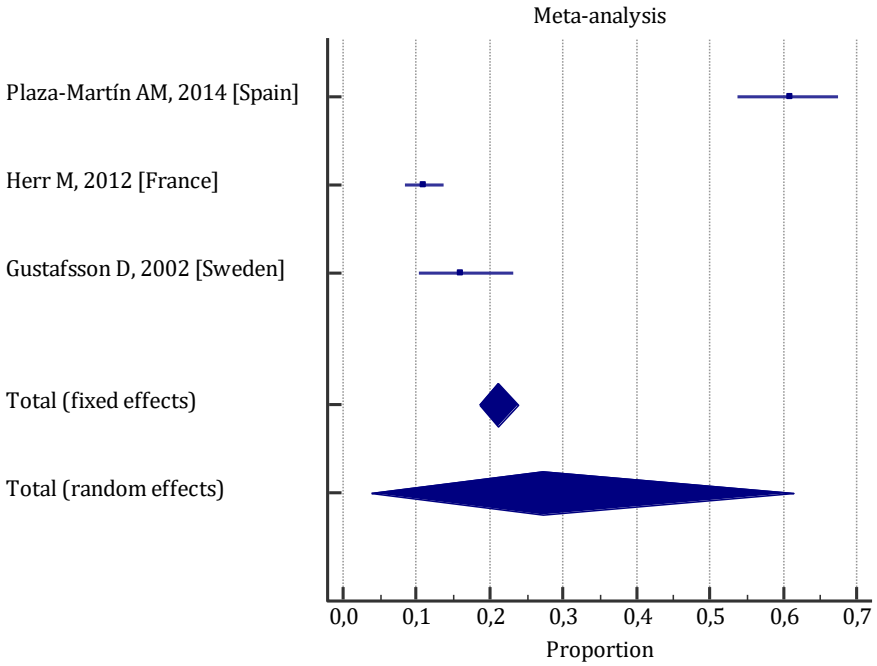
The pooled estimated of Accident & Emergency Department/room visits was 21.2% with a 95% CI = (7.4-39.8) in a GP primary care system, as presented in fig. 7.

Figure 7. Meta-analysis Accident & Emergency Department/room visits, GP primary care system.



The pooled estimated of Accident & Emergency Department/room visits was 27.2% with a 95% CI = (3.8-61.4) in a Mixed primary care system, as presented in fig. 8.

Figure 8. Meta-analysis Accident & Emergency Department/room visits, Mixed primary care system.

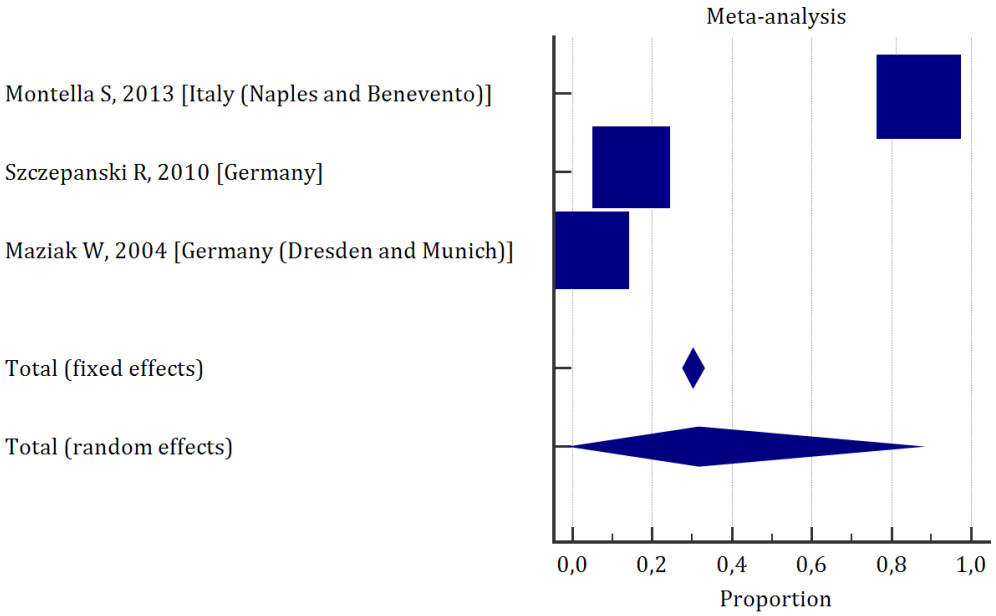


Hospitalizations visits for asthma

The pooled estimate of hospitalizations visits was calculated by a random effect model, due to the presence of heterogeneity in Paediatrician (Q=840.0; p-value<0.0001; I^2=99.76%), in GP (Q=26.3; p-value<0.0001; I^2=92.38%) and in Mixed (Q=19.3; p-value<0.0001; I^2=89.62%).

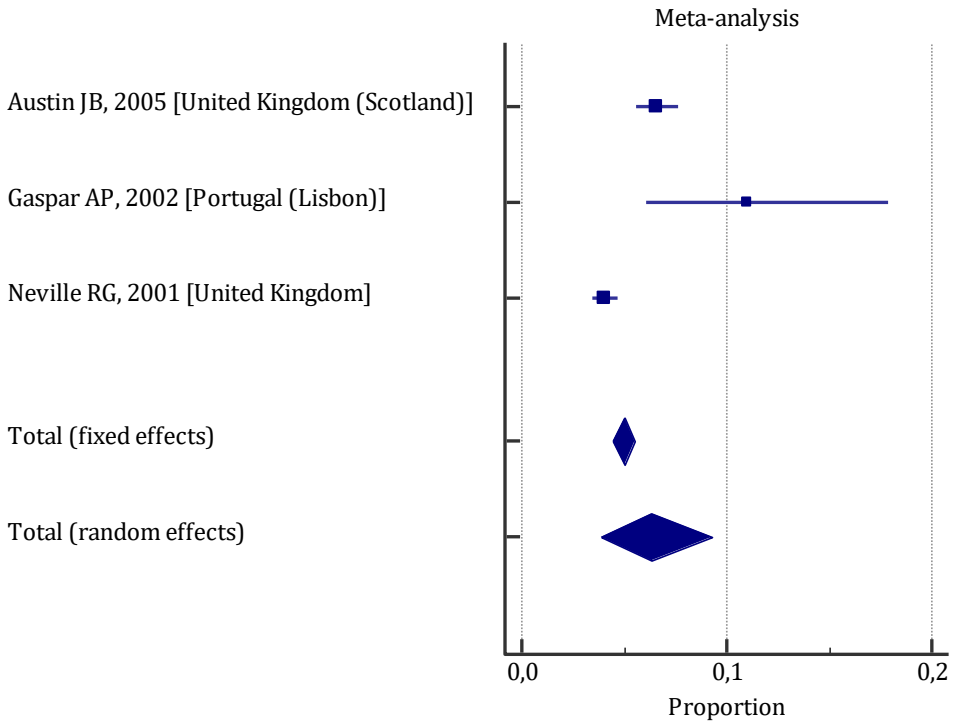
The pooled estimated of hospitalizations visits was 31.6% with a 95% CI = (0.0-86.1) in a Paediatrician primary care system, as presented in fig. 9.

Figure 9. Meta-analysis hospitalizations visits, Paediatrician primary care system.



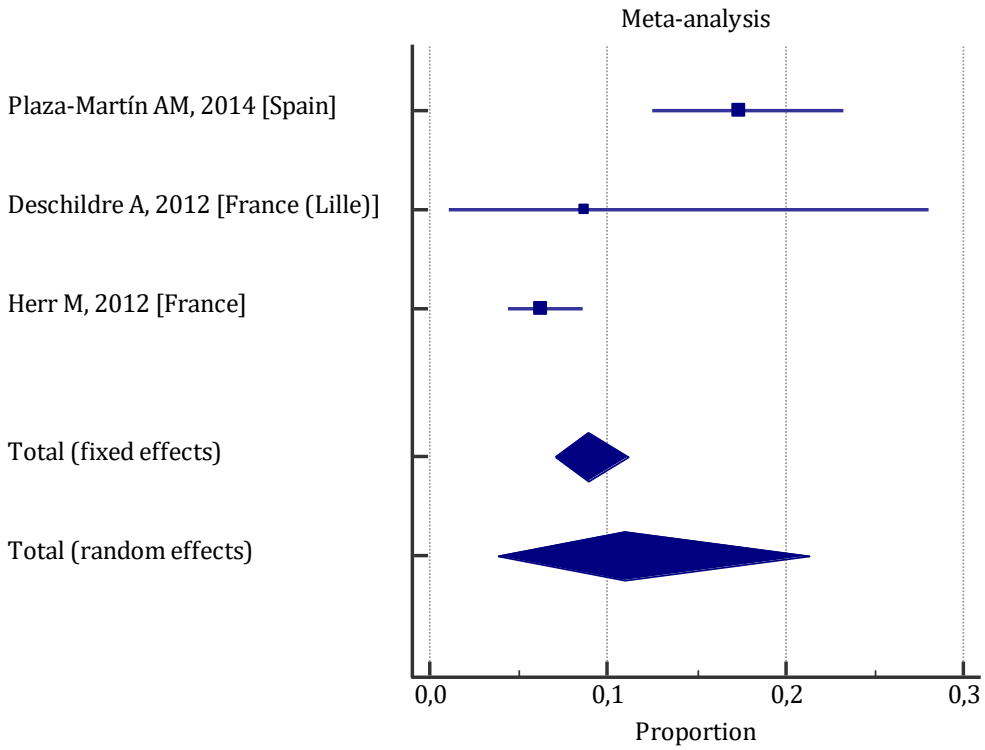
The pooled estimated of hospitalizations visits was 6.28% with a 95% CI = (3.8-9.3) in a GP primary care system, as presented in fig. 10.

Figure 10. Meta-analysis hospitalizations visits, GP primary care system.



The pooled estimated of hospitalizations visits was 11.0% with a 95% CI = (3.8-21.3) in a Mixed primary care system, as presented in fig.11.

Figure 11. Meta-analysis hospitalizations visits, Mixed primary care system.

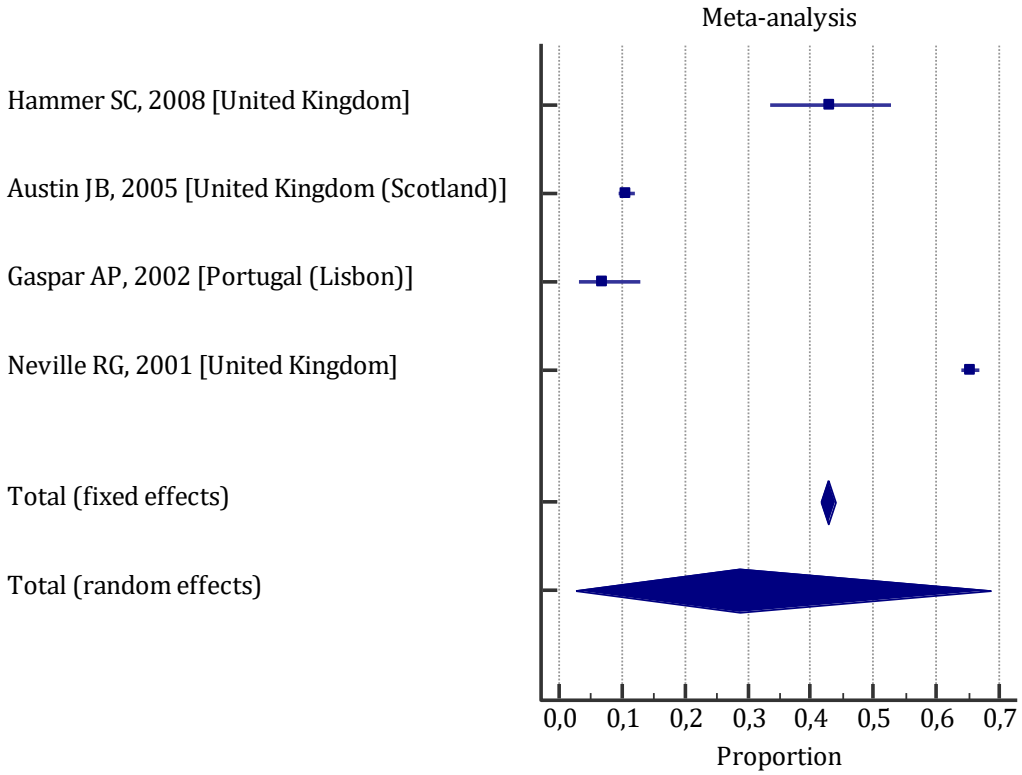


Unscheduled primary care visits for asthma

The pooled estimate of unscheduled primary care visits was calculated by a random effect model, due to the presence of heterogeneity in GP (Q=2247.0; p-value<0.0001; I^2=99.87%) and in Mixed (Q=221.2; p-value<0.0001; I^2=99.55%). For the Paediatrician primary care system no papers was found.

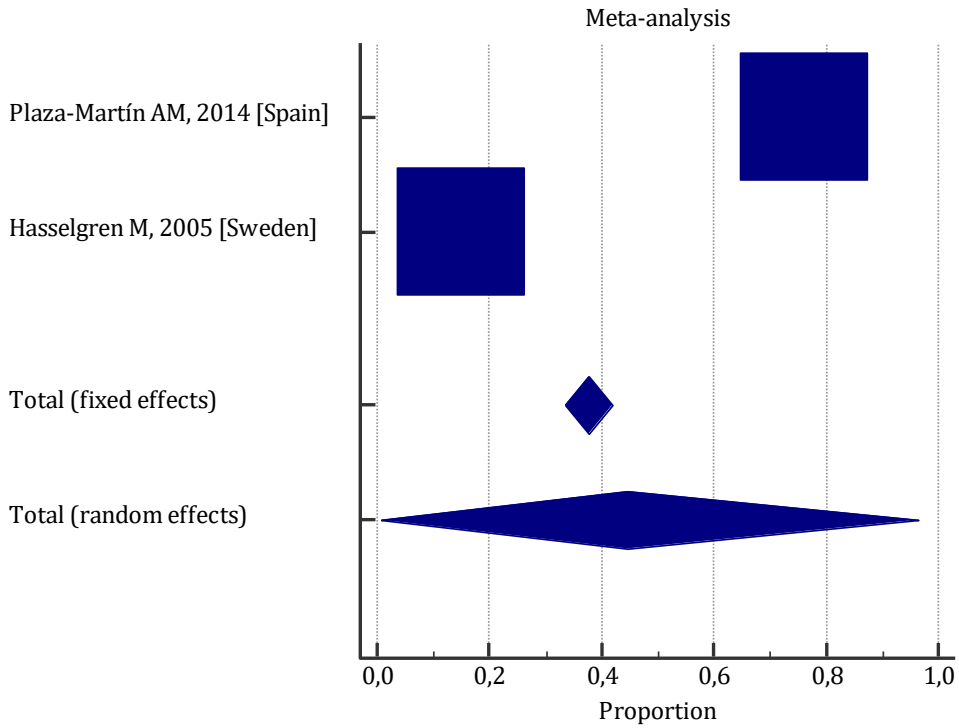
The pooled estimated of unscheduled primary care visits was 28.8% with a 95% CI = (2.5-68.6) in a GP primary care system, as presented in fig. 12.

Figure 12. Meta-analysis unscheduled primary care visits, GP primary care system.



The pooled estimated of unscheduled primary care visits was 44.5% with a 95% CI = (0.7-96.3) in a Mixed primary care system, as presented in fig. 13.

Figure 13. Meta-analysis unscheduled primary care visits, Mixed primary care system.



Conclusions

The meta–analysis performed according to the primary care classification revealed some similarities and some differences in the investigated outcomes (table 5).

The ADHD mean age at onset ranged from an 8.3 to 10.1 years, with no statistical difference across the three classifications.

The percentage of children with Accident & Emergency Department/room visits for asthma is more than 50% for Ped system while around 25% for GP and Mixed systems, but this difference is not statistically significant.

The hospitalizations visits for asthma is lower for GP system (6.3%), around 11% for Mixed system and 32% for Ped, but again no statistically significant.

No article was found for asthma' related unscheduled primary care visits in the Ped system. The percentage of unscheduled primary care visits in GP was 29% while for the Mixed system 45, but the difference is not statistically significant.

Table 5. Summary of the meta-analysis findings.

	Type of care primary care system			**Note**
	Ped	GP	Mixed	
Mean age at onset and 95% CI				
ADHD	8.3 (6.8-9.9)	10.1 (8.5-11.7)	9.3 (7.1-11.4)	No difference
Asthma (%) and 95% CI				
Accident & Emergency Department/room visits	56.6 (24.6-85.8)	21.2 (7.4-39.8)	27.2 (3.8-61.4)	No difference
Hospitalizations visits	31.6 (0.0-86.1)	6.3 (3.8-9.3)	11.0 (3.8-21.3)	No difference
Unscheduled primary care visits	No article found	28.8 (2.5-68.6)	44.5 (0.7-96.3)	No difference

Strength and limitations

The meta-analysis is the statistical part of the systematic review process and carries some advantages. Meta-analysis includes more participants than the single constituent study, whose implication lies in a reduction of the random errors and in the increase of the power. Moreover, the meta-analysis is capable of exploring variations between studies. However, we have some limitations of both the primary studies and the systematic review.

For ADHD, depending on the age-range of the analysed sample, the age at diagnosis of ADHD could be susceptible of bias. For example, a study considered children up to 16 years of age, while another study involved subjects between 15 and 55 years. In the meta-analysis of the Paediatric system, out of 9 studies included 7 were from Germany.

For asthma, the majority of the papers (17/44) found with the systematic review were "case-only", meaning that the study investigated some characteristics of children with asthma admitted to hospital or who had an ED visit asthma-related. Therefore these studies provided only the absolute number of children and did not allow the computation of the prevalence. In some papers the access to ED/hospital in the previous/following 12 months was reported, but again this information could not have been used in the meta-analysis, since it represented a "second hospitalised/admission".

Within the GP system, of the 9 papers retrieved, 5 were from the United Kingdom.

For the Paediatric system model regarding unscheduled primary care visits for asthma, the systematic review search did not identify any studies eligible for the meta-analysis.

Due to the lack of studies, the meta-analysis on the availability of spirometry at primary care level could not be performed.

Finally, the MOCHA country classification of type of primary care is based on the actual health system running in the country, whereas the retrieved articles for the systematic review refer to preceding years during which the health system may have had a different legislation and regulation.

APPENDIX 1. Main characteristics of the identified studies: ADHD							
Year of publication	**1st author**	**Country**	**Age of reference**	**Year of the study**	**Sample size**	**Age at diagnosis**	**Notes**
2016	Caci	France	Mean=11.0	2013-2014	473	Mean= 8.07; SD= 2.59	
2016	Lemcke	Denmark	Between 8 and 14	1996-2012	2034	Mean= 8.4; SD= 1.98	
2015	Grogan	Ireland	Between 18 and 70	2014	63	Mean= 12.44; SD= 4.165	
2015	Klora	Germany	Mean= 12.9; SD= 10.3	2006-2007	9083	Mean= 12.9; SD= 10.3	
2015	Pitts	UK	Mean= 32.1; SD= 11.5		89	Mean= 18.2; SD= 11.5	
2015	Sucksdorff	Finland	Between 6 and 20	1991-2011	10321	Mean= 7.6; SD= 2.9	
2015	Van den Ban	The Netherlands	<=19	1999-2000	817	Mean= 10.14; SD= 3.5	
2014	Caci	Italy France UK Germany the Netherlands Spain Total	<=20	2010	79 79 86 94 98 99 535	 Mean= 6.4 Mean= 6.3; SD= 2.1 Mean= 7.6; SD= 3.1 Mean= 7.0; SD= 2.8	
2014	Dittmann	Germany	Mean= 9.6; SD= 2.6		504	Age Mean= 9.6; SD= 2.6 Time since disease onset Mean= 4.8; SD= 3.0	
2014	Steinhausen	Denmark	Between 3 and 60	1994-2010	20742	Mean= 15.20; SD= 10.08	
2013	Bahmanyar	Sweden	below 19	2005-2007	7931	Mean= 12.0; SD= 3.7	
2013	Hodgkins	Italy France UK Germany the Netherlands Spain Total	Between 6 and 17	2004-2007	144 130 146 151 74 134 779	Mean= 8.7; SD= 2.1 Mean= 9.1; SD= 2.5 Mean= 9.3; SD= 2.3 Mean= 8.4; SD= 2.1 Mean= 8.6; SD= 2.6 Mean= 9.0; SD= 2.3 Mean= 8.9; SD= 2.6	
2013	Matherson	UK (England)	Between 15 and 55		15	Mean= 11.07; SD= 4.50	Subsample with ADHD diagnosis in childhood
2013	McCarthy	Ireland (Dublin)	Mean= 24.5 years		16	Mean= 8.9; SD= 2.1	

2012	Durà-Travè	Spain	Mean= 8.14; SD= 1.60	2009	187	Mean= 8.14; SD= 1.60	
2012	Garbe	Germany	Between 3 and 17	2005-2008	6210	3-5 yrs: 8.7% 6-8 yrs: 36.0% 9-11 yrs: 32.5% 12-14 yrs: 17.2% 15-17 yrs: 5.6%	
2012	Kirov R	Germany (Göttingen)	Between 8 and 15		20	Mean= 5.9; Range= [4-8]	
2012	Tuithof	The Netherlands	Between 18 and 44; Mean= 28.9; 95% I.C.=(26.6-31.2)		74	Mean= 6.7; 95% I.C.=(5.4-8.0)	
2011	Berek	Germany	Between 6 and 18		785	Mean= 8.06; SD= 2.48	
2008	Huss M	Germany	Mean= 21 years and 9 months; SD= 4 years and 8 months		215	Mean= 9 years and 2 months; SD= 2 years and 7 months	
2007	Kirov R	Germany (Goettingen)	Mean= 10.94; SD= 1.99 Mean= 11.10; SD= 2.31		18 18	Mean= 6.1; Range= [4-8] Mean= 5.9; Range= [4-7]	ADHD-only (children with attention-deficit/ hyperactivity disorder) ADHD + TD (children with attention-deficit/ hyperactivity disorder + children with tic disorder)
2006	Masi G	Italy (Pisa)	Mean= 12.0; SD= 2.9		37	Mean= 3.7; SD= 1.1	A series of 98 children and adolescents consecutively referred to our Paediatric Psychopharmacology Service during a 4-year period with a current diagnosis of BD were included in the study.
2003	Masi G	Italy (Pisa)	Between 7 and 18		14	Mean= 4.07; SD= 0.7	This was a naturalistic study based on a clinical database of 59 consecutive patients with BD, 35 inpatients and 24 outpatients, followed for a mean period of 15.9 months (range, 1 to 48 months).
2003	Parr JR	UK (Wirral)	16 or under	2000	391	Mean= 8.7	

APPENDIX 2. Main characteristics of the identified studies. Asthma related Accident & Emergency Department/room visits, hospitalizations and unscheduled primary care visits.

Year of publication	1st author	Country	Years of study	Sample	Sample size	%	N	Other measure	Age reference	Notes
2015	Altzibar JM	Spain (Basque Country)	2009-2011	asthma exacerbations (AEs) requiring ED visits or hospitalisations			21307	2583,7°	<15 years	Emergency Department visits [°Incidence Rate per 100000]
							13084	4046,4°	<5 years	Emergency Department visits [°Incidence Rate per 100000]
							8223	1640,2°	5-14 years	Emergency Department visits [°Incidence Rate per 100000]
			1996-2010	hospitalisations for asthma			7160	182,2°	<15 years	Hospital admission [°Incidence Rate per 100000]
							4330	316,8°	<5 years	Hospital admission [°Incidence Rate per 100000]
							2839	110,5°	5-14 years	Hospital admission [°Incidence Rate per 100000]
2015	Arabkhazaeli A	the Netherlands (Utrecht)	01/04/2009 data collection	cross-sectional analysis of asthmatic children included in the baseline of the PACMAN study with complete data on allergies	703	6.3			4-12 years	Asthma-related ED visit in the past year
2015	Black M	United Kingdom (Scotland)	Jan 2015	retrospective cohort, followed up until Jan 2015, of all live births in first-time mothers between Jan 1993 and Dec 2007			461			asthma requiring hospital admission in planned caesarean delivery
							1964			asthma requiring hospital admission in unscheduled caesarean delivery
							8624			asthma requiring hospital admission in vaginal delivery
2014	Julian V	France (Clermont-Ferrand)	nov 2010-feb 2011	prospective clinical study of children admitted with a clinical diagnosis of asthma exacerbation			143		1-16 years	admitted to the department with a clinical diagnosis of asthma exacerbation
2014	Plaza-Martín AM	Spain		patients with severe asthma according to the physicians' criteria	207	16.9	35		10,8 (2,3)	1-4 hospitalisations asthma in the previous six months
					207	0.5	1		10,8 (2,3)	>4 hospitalisations in the previous six months
					207	54.1	112		10,8 (2,3)	1-5 Emergency Room visits in the previous six months
					207	6.8	14		10,8 (2,3)	>5 Emergency Room visits in the previous six months
					207	37.2	77		10,8 (2,3)	1-3 Unscheduled primary care

										visits in the previous six months
					207	27.1	56		10,8 (2,3)	4-7 Unscheduled primary care visits in the previous six months
					207	8.7	18		10,8 (2,3)	8-10 Unscheduled primary care visits in the previous six months
					207	3.4	7		10,8 (2,3)	>10 Unscheduled primary care visits in the previous six months
2013	Belgrave DC	United Kingdom		population-based birth cohort					<8 years	
2013	Millett C	United Kingdom (England, Hospital Episode Statistics (HES))	April 1, 2002 and November 30, 2010	Interrupted time series study on emergency hospital admission with a principle diagnosis of asthma			217381			all unplanned (emergency) hospital admissions with a principle diagnosis of asthma, to assess the implementation of English Smoke-free legislation in July 2007
2013	Montella S	Italy (Naples and Benevento)	Jan-March 2009	children with current doctor-diagnosed wheeze, defined as a history of at least one physician-diagnosed wheezing episode lasting more than 24 hr in the past year	376	67			1-5 years (32.8 (0.8) months)	ED visits
						86			1-5 years (32.8 (0.8) months)	Hospital admissions
2012	Deschildre A	France (Lille)	Jan 2003-Dec2007	12-months prospective, randomised, controlled trial on children with severe allergic asthma	50	24			10,9 years (mean age)	hospitalised at least twice during the previous year
					50	12			10,9 years (mean age)	history of intensive care unit hospitalisation for asthma
					21			5,0 (3,0-7,0)^	6-16 years	unscheduled visits for telemonitoring (HM) group [^median (IQR)]
					21		2		6-16 years	hospitalisation for telemonitoring (HM) group
					23			3,0 (2,0-7,0)^	6-16 years	unscheduled visits for monitoring according to guidelines (CT) group [^median (IQR)]
					23		2		6-16 years	hospitalisation for monitoring according to guidelines (CT) group
2012	Herr M	France	2003-2006	birth cohort on wheezers	560	11	61		18 months	emergency room visits
					560	6.4	35		18 months	hospitalisation

2012	Santus P	Italy (Milan)	Jan 2007-Dec 2008	case cross-over based on POEMI (Pollution and Emergencies in Milan) study			821		0-4 years	daily Emergency Room Admissions (ERAs) for acute respiratory diseases
							601		5-19 years	daily Emergency Room Admissions (ERAs) for acute respiratory diseases
2011	Fuhrman C	France	Nov 2006-Nov 2007	prospective study: children with asthma exacerbation	498	57	284		3-17 years	Previous hospitalization for asthma exacerbation (lifetime)
					498	25.5	127		3-17 years	Hospital admission in the previous year
					498	14.9	74		3-17 years	1 unscheduled visit for asthma (GP or ED) (previous year)
					498	28.5	142		3-17 years	2-3 unscheduled visit for asthma (GP or ED) (previous year)
					498	30.7	153		3-17 years	4 or more unscheduled visit for asthma (GP or ED) (previous year)
					498	27.3	136		3-17 years	Emergency department visit for asthma (previous year)
2011	Koster ES	the Netherlands		PACMAN (Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) cohort study on asthmatic children	386	7.6			4-12 years	Emergency Department visits related to asthma during the preceding 12-months
		United Kingdom (Scotland)		BREATHE study, children and young adults (3-22 years) with physician-diagnosed asthma	939	12.3			3-22 years	asthma-related hospital admission during the preceding 6-months
2011	Samoli E	Greece (Athens)	2001-2004	daily counts of paediatric asthma emergency admission, for at least one over-night stay			3601		0-14 years	admission for acute asthma-related diagnoses
2010	Dehò A	United Kingdom (London)	Aprl 2005-March 2007	retrospective reviewed of retrieved to paediatric intensive care unit (PICU) with a diagnosis of acute asthma	60	18.3	11		2-16 years	Previous PICU admission for asthma
2010	Giovannini M	Italy (Milan)	Jan 2007-Dec 2008	observational study considered the hospital admissions for respiratory conditions occurred after emergency room visits			110		<=14 years	admission for asthma
								0.23 (0.46)*	<=14 years	January Number of admission/day for asthma [Mean (SD)]
								0.10 (0.30)*	<=14 years	February Number of admission/day for asthma [Mean (SD)]
								0.14 (0.39)*	<=14 years	March Number of admission/day for asthma [Mean (SD)]
								0.15 (0.40)*	<=14 years	April Number of admission/day for asthma [Mean (SD)]

								0.21 (0.48)*	<=14 years	May Number of admission/day for asthma [Mean (SD)]
								0.16 (0.42)*	<=14 years	June Number of admission/day for asthma [Mean (SD)]
								0.03 (0.17)*	<=14 years	July Number of admission/day for asthma [Mean (SD)]
								0.08 (0.27)*	<=14 years	August Number of admission/day for asthma [Mean (SD)]
								0.21 (0.45)*	<=14 years	September Number of admission/day for asthma [Mean (SD)]
								0.11 (0.32)*	<=14 years	October Number of admission/day for asthma [Mean (SD)]
								0.18 (0.39)*	<=14 years	November Number of admission/day for asthma [Mean (SD)]
								0.11 (0.32)*	<=14 years	December Number of admission/day for asthma [Mean (SD)]
2010	Szczepanski R	Germany		multicentre study on children with an asthma diagnosis made by their paediatricians	338	64.3			24-60 months	Pre-intervention emergency visits (One or more in the half year before randomization)
					288	43.1			24-60 months	Post-intervention emergency visits (One or more in the half year before randomization)
					338	14.7			24-60 months	Pre-intervention hospitalization (Only single hospitalizations)
					288	6.9			24-60 months	Post-intervention hospitalization (Only single hospitalizations)
2009	Indinnimeo L	Italy	March-June 2005	multicentre, prospective, randomized controlled trial on newly diagnosed intermittent or mild persistent asthma			60	1.75 (2.11)*	6-14 years	Education group: How many times during the past year did your child need an emergency department? [Mean (SD)]
							60	0.30 (0.86)*	6-14 years	Education group: How many times was your child hospitalized for asthma during the past year? [Mean (SD)]
							63	1.65 (2.31)*	6-14 years	Control group: How many times during the past year did your child need an emergency department? [Mean (SD)]
							63	0.26 (0.67)*	6-14 years	Control group: How many times was your child hospitalized for asthma during the past year? [Mean (SD)]

2009	Orazzo F	Italy (Ancona, Bologna, Padua, Varese and Gallarate< Florence, Naples)	1996-2000	information on daily ER visits for wheezing			1337	0.7 (1.0)*	0-2 years	daily counts of ER visits in Ancona, [Mean (SD)]
			1996-2000				6526	3.6 (3.4)*	0-2 years	daily counts of ER visits in Bologna, [Mean (SD)]
			1996-2002				4776	1.9 (2.2)*	0-2 years	daily counts of ER visits in Florence, [Mean (SD)]
			1996-2000				33501	18.3 (9.1)*	0-2 years	daily counts of ER visits in Naples, [Mean (SD)]
			1996-1998				5299	4.8 (4.9)*	0-2 years	daily counts of ER visits in Padua, [Mean (SD)]
			1996-2000				1833	1.0 (1.3)*	0-2 years	daily counts of ER visits in Varese-Gallarate, [Mean (SD)]
2009	Peroni DG	Italy (Verona)		cross-sectional study with random selection from the complete sampling frame of all private kindergartens of the area	66	83.3	55		3-5 years	children referred to hospital emergency visits for respiratory problems in wheezing children with doctor's asthma diagnosis
					103	82.5	85		3-5 years	children referred to hospital emergency visits for respiratory problem in wheezing children without doctor's asthma diagnosis
2008	Cunningham S	United Kingdom (Edinburgh)	Aug 2004-Feb2005	cluster-randomized trial on all hospital emergency department (ED) visits with acute asthma/wheeze			322		2-16 years	visits with acute asthma/wheeze
2008	Davies G	United Kingdom	1998-2005	large audit of children admitted to paediatric units with acute wheeze/asthma each November			1175		1-18 years	Number of admissions audited 1998
							1040		1-18 years	Number of admissions audited 1999
							961		1-18 years	Number of admissions audited 2000
							1612		1-18 years	Number of admissions audited 2001
							1313		1-18 years	Number of admissions audited 2002
							850		1-18 years	Number of admissions audited 2003
							1371		1-18 years	Number of admissions audited 2004
							1106		1-18 years	Number of admissions audited 2005
2008	Halonen JI	Finland (Helsinki)	1998–2004	hospital emergency room visits			4807		< 15 years	daily asthma hospital emergency room visits

2008	Hammer SC	United Kingdom		children with doctor-diagnosed asthma, and known at the paediatric outpatient clinic for at least 6 months randomly selected from the population of children attending the clinic for a normal routine visit	112	43			6-16 years	Unscheduled care visit during last year
					112	14			6-16 years	Emergency visits during last year
				AIRE (Asthma Insights and Reality in Europe) surveys	753	36			children and adults	Unscheduled care visit during last year
					753	18			children and adults	Emergency visits during last year
2008	Laurent O	Francia (Strasbourg metropolitan area (SMA))	Jan 2000-Dec 205	each call regarding an asthma attack			954		0-19 years	numbers of emergency asthma calls
2007	Forbes L	United Kingdom (London)	cases: Feb 1999 -Feb 2000/controls: summer 1999	case-control study on asthmatic children who had/had not attended A&E for asthma over the course of 1 year	1412		1018		3-14 years	asthmatic children who had attended A&E for asthma over the course of 1 year
2007	Smeeton NC	United Kingdom (London)		asthmatic children of a large multi-ethnic population and a high proportion of South Asian (Indian and Pakistani)	148	57.4			3-9 years	use of accident & emergency (A&E) service in the previous 12 month
2006	Atkinson RW	United Kingdom (London)	1992-1994	Daily counts of the number of GP consultations, visits to A&E departments, and number of hospitalisations for asthma			13,2 (8,9)*		0-14 years	GP visits (n/day; [Mean (SD)])
							16,2 (8,5)*		0-14 years	A&E visits (n/day; [Mean (SD)])
							22,6 (13,8)*		0-14 years	Admission (n/day; [Mean (SD)])
2006	Massin MM	Belgium	Jan-Dec 2003	prospective indexed of all patients who presented to paediatric emergency department (PED)			179			number of visits for asthma
2005	Austin JB	United Kingdom (Scotland)	Jan-March 2002	Adopted ISAAC protocol, including the self-completed questionnaire previously used in 1995. From 4665 only 2262 with lifetime wheeze and/or asthma were extracted	2262	10.6	240		12-15 years	a required a doctor visit
					2262	9.2	208		12-15 years	had attended an accident and emergency department (A&E)
					2262	6.5	148		12-15 years	had had hospital admissions in the last 12 months

2005	Benito-Fernández J	Spain	1993-2003							number of acute asthma exacerbation episodes, the number of children admitted to the observation unit for a maximum of 24 h, and the number of children hospitalized
2005	Hasselgren M	Sweden		random sample of patients in paediatric or primary care for their asthma	320	15			15-18 years	unscheduled, urgent care visits
2004	Benito-Fernandez J (a)	Spain	May 2002	comparative prospective-retrospective cohort study	259				<14 years	prospective cohort that included all consecutive children younger than 14 years with acute asthma exacerbation treated in the paediatric emergency department of an acute-care teaching hospital
					259		28			observation unit
					259		4			hospital admission
					259		15			return for medical care
			May 2001	comparative prospective-retrospective cohort study	321				<14 years	retrospective historic cohort of all consecutive children younger than 14 years with acute asthma exacerbation treated in the paediatric department
					321		30			observation unit
					321		5			hospital admission
					321		24			return for medical care
2004	Benito-Fernandez J (b)	Spain	Dec 2001-Dec 2002	prospective cohort study of random sample of patients with acute asthma exacerbations treated in the paediatric emergency department of an acute-care teaching hospital	258		28		4 months-14 years	returned for medical care at the emergency department
							4			required hospitalization
2004	Maziak W	Germany (Dresden and Munich)	1995-1996	cross-sectional survey according to ISAAC phase II protocol on the occurrence and severity of wheezing episodes during the 12 months prior to the survey	441	13.8	61		5-11 years	emergency department visits on children with asthma diagnosis ever within current wheezers
					441	4.3	19		5-11 years	hospital admissions on children with asthma diagnosis ever within current wheezers

2004	Migliaretti G	Italy (Turin)	Jan 1997-Dec 1999	case-control residents admitted to city hospitals paediatric patients			1060		<15 years	cases: admitted for asthma (ICD-9 code 493)
							25523		<15 years	controls: age-matched patients admitted for causes other than respiratory diseases (ICD-9 codes 460–487, 490–492, 494–496, and 500–519) or heart diseases (ICD-9 codes 390–405 and 410–429)
2004	Mihailidou H	Greece		asthmatic children	118		112		1-14 years	total number of hospital admissions due to asthma as well as asthma exacerbations during the 12 months before regular follow-up care at the special paediatric pulmonary outpatient clinic
							19			total number of hospital admissions due to asthma as well as asthma exacerbations during the 12 months after regular follow-up care at the special paediatric pulmonary outpatient clinic
2003	Harvey S	United Kingdom (London)	Dec 1998-Feb 1999	weekly computerised searches of A&E asthma related records	255				3-14 years	
2002	Gaspar AP	Portugal (Lisbon)	1995-1996	Matched inpatient/outpatient. Inpatient: all children admitted to the hospital for acute asthma symptoms. outpatients: with clinical diagnosis of asthma, was selected randomly observed during the first appointment	124	73			1-10 years	inpatients: frequent asthma emergency room visits
					124	43			1-10 years	inpatients: prior asthma hospitalizaton
					124	33			1-10 years	inpatients: last year asthma admission
					124	51			1-10 years	outpatients: frequent asthma emergency room visits
					124	11			1-10 years	outpatients: prior asthma hospitalizaton
					124	7			1-10 years	outpatients: last year asthma admission
2002	Gustafsson D	Sweden	Jan-Dec 1996	170 children with a diagnosis of asthma and attending our outpatient clinic	139	16	22		4-13 years	Attended the emergency room in the last year for asthma?

2002	Stevens CA	United Kingdom (Manchester)	Feb 1998-March 1999	prospective, randomised, partially blinded, controlled trial of children admitted to ward or attended at either an accident and emergency (A&E) department or the children's (emergency) assessment unit (CAU at LRI) with a primary diagnosis of acute severe asthma or wheezing	99				18 months-5 years	intervention group: received a general education booklet about asthma in pre-school children (excluding babies); a written guided self management plan; and two 20 minute structured educational sessions given on a one to one basis by a specialist respiratory nurse with a diploma in asthma care to the parent(s) and child
					97		26			intervention group: number of inpatient admissions
					97		17			intervention group: A&E/CAU attendance
					101					control group
					99		19			control group: number of inpatient admissions
					99		19			control group: A&E/CAU attendance
2001	Neville RG	United Kingdom	1994-1995	spectrum of severity of patients diagnosed with asthma, whether managed in hospital, general practice or both	597	81	486		<5 years	Patient-initiated consultations
						75	446			Practice review consultations
						11	63			A&E attendance
						16	93			Hospital outpatient
						13	80			Hospital admissions
					3362	63	2107		5-15 years	Patient-initiated consultations
						72	2426			Practice review consultations
						3	94			A&E attendance
						5	180			Hospital outpatient
						2	78			Hospital admissions
2000	Csonka P	Finland (Tampere)		cross-sectional, questionnaire-based survey, modified from ISAAC questionnaire	1816	4.6			6-13 years	Proportion of children treated for acute wheezing in an emergency room or hospital ward in the past year
						10.2			<3 years	
						9.1			3-6 years	

2000	Rabe KF	France, Germany, Italy, the Netherlands, Spain, Sweden, UK	25 Feb-21 April 1999	Patients with current asthma were identified as those with asthma diagnosed by a physician who were currently taking medication for their asthma or had asthma attacks and symptoms during the past year	753	36			<16 years	Unscheduled urgent care visits during last year
						18				Emergency visits during last year

APPENDIX 3. Main characteristics of the identified studies. Availability of spirometry at primary care level.

Year of publication	1st author	Country	Years of study	Sample	Sample size	%	N	Notes
2015	Márquez-Martín E	Spain	Jan-March 2012	study of 970 primary care centres in Spain that routinely evaluated adult patients with respiratory disease	549		103	Rural Centres: Do not have spirometry
							55	Rural Centres: Have spirometry but not using it
					421		46	Urban Centres: Do not have spirometry
							19	Urban Centres: Have spirometry but not using it
2013	López-Campos JL	Spain	Jan-March 2012	cross-sectional telephone survey of Primary Care and Secondary Care health-care centres in Spain where adult outpatient respiratory patients are routinely evaluated	970		149	Primary Care: Do not have spirometry
					289		17	Secondary Care: Do not have spirometry
2006	Hueto J	Spain (Navarre)	Oct-Nov 2004	primary health care centres	55	90.9	50	Have spirometer
					50	22		Never been used
2005	Bolton CE	United Kingdom (Wales)	July-Dec 2003	questionnaire-based survey of randomly selected general practices	227	82.4	187	Have spirometer
					187		27	Have spirometry but not using it

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