An innovative breath test for better care for children with asthma-like symptoms, ADEM2 (Asthma Diagnosis with Exhaled Markers)

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Objectives: 1) The development of an optimal point-of-care (POC) breath test for an early asthma diagnosis in preschool wheezing children; 2) To unravel important pathogenetic mechanisms in the early development of viral wheeze and asthma by…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON52377

Source
ToetsingOnline

Brief title
Asthma diagnosis by exhaled markers, ADEM2

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma, viral wheeze

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: ZonMW;TKI-LSH,Longfonds

Intervention

Keyword: Asthma, Early diagnosis, Exhaled breath, Viral wheeze

Outcome measures

Primary outcome

WP1: the main outcome measure is the discriminative exhaled VOCs between asthma, viral wheeze, and healthy controls. WP2: the primary outcome measure is the sensitivity, specificity, true positive and true negative rate of the various VOC sensing techniques for a diagnosis of asthma/viral wheeze in preschool children. WP3: The main outcome parameter is % of well controlled asthma-like symptoms after 1-year follow-up. The % well controlled asthma-like symptoms during the study period will be based on the validated TRACK questionnaire. This questionnaire is completed by the parents and doctors and specifically developed for use in this age group, independent of the diagnosis. A score of 80 or more is defined as well controlled disease. The TRACK score is sensitive and reliable, and an increase of 10 points was found to be the *minimally important difference*.

Secondary outcome

In WP1, secondary endpoints in blood are immunological cells, gene expression, epigenetics, and gene polymorphisms. Endpoints in faeces/nasopharyngeal swabs are microbiome and gene expression. In WP2, no secondary endpoints are present. WP3: Secondary outcome parameters are pharmacotherapy, growth retardation and other side-effects of medication, exacerbations/hospital admissions, quality of life, lung function, allergy, blood eosinophils, absence of school and work,

healthcare resource use and -costs (standard and extra clinical visits,

hospital admissions, referrals), costs outside healthcare, cost-effectiveness,

and asthma diagnosis at 6 years.

Study description

Background summary

Rationale: About 40% of all young children suffer from asthma-like symptoms, such as wheeze, chronic cough, breathlessness, and sputum. However, the majority (2/3 of this group) of wheezing children will not develop asthma but has so called *transient or viral wheeze*. They will outgrow their symptoms when they are 5-6 years and are overtreated with asthma medication. 1/3 of the group with asthma-like symptoms really has asthma and remains to have chronic symptoms at 5-6 years and over. Preschool children with asthma are frequently underdiagnosed and undertreated. Currently, it is not possible to discriminate between asthma and viral wheeze at preschool age: there is no accurate diagnostic test available. In the ADEM1 study, we proofed the principle that an exhaled breath test, based on exhaled inflammation markers (volatile organic compounds, VOCs) in combination with a simple clinical index (asthma predictive index, API) enabled a reliable asthma diagnosis in young wheezing children. In the current ADEM2 project, we proceed with the development and application of the breath test in wheezing preschool children. The first hypothesis of the ADEM2 study is that an early asthma diagnosis with the breath test will improve disease control, quality of life of children and parents, optimise treatment and thereby improve the prognosis of wheezing children. Moreover, we hypothesize that the use of the breath test will considerably reduce unnecessary burden and costs of the health care system by significantly reducing referral to secondary/tertiary care centres, diminishing use of asthma medication in *viral wheeze* children, and by reducing loss of asthma control/exacerbations/hospital admissions in children with asthma. Thereby, the asthma breath-test will be a sustainable health care solution in the large group of children with asthma-like symptoms. We used GC-MS for exhaled breath analysis in the ADEM1 study but more simple, cheaper, and faster VOC sensing techniques became available. Therefore, the second hypothesis is that the GC-MS breath test can be developed into a point-of-care breath test which provides immediate results and is affordable for both primary care and specialist care. Our third hypothesis is that the predictive VOCs of an early diagnosis (discovered in the ADEM1 study) point to important underlying pathogenetic pathways of an early asthma development.

Study objective

Objectives: 1) The development of an optimal point-of-care (POC) breath test for an early asthma diagnosis in preschool wheezing children; 2) To unravel important pathogenetic mechanisms in the early development of viral wheeze and asthma by studying predictive VOCs and applying a multi-omics approach; 3) To assess health gain (disease control, quality of life, reduction of exacerbations/hospital admissions), improvement of pharmacotherapy, and reduction in costs of care with the application of the breath test in wheezing preschool children;

Study design

The project will consist of several work packages (WP).
WP1: Aim: To assess potential pathogenetic pathways based on discriminative VOCs in the early development of asthma. Design: Observational study in 220 wheezing preschool children (2-3 years of age) and 100 non-wheezing preschool children. Samples of breath (VOCs), blood (immunological markers, gene-expression, epigenomics), and nasopharyngeal swabs (gene expression and microbiota) and faeces (microbiota) will be assessed at 2-3 yrs and 6 yrs and related to an algorithm based asthma diagnosis.

WP2: Aim: To assess feasibility, accuracy and reproducibility of VOC techniques (mentioned under WP2) for an early asthma diagnosis in comparison with the gold standard technique (GC-MS). Design: prospective 4-year observational study in 220 wheezing children. Breath samples will be collected and analysed for VOCs with SIFT-MS, sensors, and GC-MS (gold standard) to develop a point of care (POC) breath test. Exhaled VOCs will be related to an asthma diagnosis, based on the algorithm diagnosis of ADEM1.

WP3: Wheezing preschool children of WP1 and WP2 will be randomised in WP3. Aim: to assess the improvement in health gain, pharmacotherapy, and costs of care with the application of the breath test in wheezing preschool children. Design: Multicentre RCT in 220 wheezing preschool children during a maximum of 4 years. Exhaled breath will be collected and analysed with the gold standard (GC-MS). Based on the validated ADEM1 algorithm, a diagnosis of asthma or viral wheeze will be made. Children will be randomised into an intervention group (n=110), in which the doctors and parents will be informed about the diagnosis, or a *usual care* (control) group (n=110), in which the diagnosis is masked for the parents/treating doctors until the end of the trial. Children diagnosed with asthma in the intervention group will receive medication according to the asthma guidelines, whereas medication use and referral to a specialist can be avoided in children with a viral wheeze diagnosis. The usual care group will be treated according to the current clinical practice. Children will be followed up until 6 years of age, at which age a definite diagnosis (asthma versus viral wheeze) is made based on respiratory symptoms and extensive lung function measurements.

Intervention

In WP3, 220 children with asthma-like symptoms will be randomised in an intervention group and an usual care group. In the intervention group at the start of the study, the breath test will be taken in the children and the test result (asthma or *viral wheeze*) will be given within 1 week to the parents and the treating doctors. The breath test result will provide extra guidance to the treating doctors: In children with asthma, asthma drugs will be prescribed in accordance with (inter)national guidelines.In case of suboptimal asthma control, the next level of asthma treatment will be given. Preschool children with more severe asthma can be referred to a specialist (paediatrician or paediatric pulmonologist). In children with a *viral wheeze* diagnosis, use of asthma medication is allowed. However, in many viral wheeze children, asthma medication probably is not effective. When there is no improvement in symptoms with asthma medication (bronchodilators, inhaled corticosteroids, leukotriene antagonists), the treating doctors will stop this medication. Treating doctors will generally not refer children to secondary/tertiary care. Additional examinations like allergy testing, X-rays, and cultures of sputum or nasopharyngeal swabs are mostly not informative in these children and will be avoided. In the usual care group, no early diagnosis of asthma/viral wheeze will be available during the trial period. The care and treatment of these children will be in accordance with the (inter)national guidelines (*usual care or standard care*) and will be comparable to current clinical practice before the introduction of the breath test. The use of asthma medication is allowed.

Study burden and risks

The collection of exhaled breath is safe and non-invasive. At preschool age and at 6 years of age, blood and swabs will be collected, and lung function tests will be assessed which predominantly are non-invasive too. Children in the intervention group of the RCT will benefit from the early diagnosis followed by better treatment. Children of the usual care group will benefit too, but at a later phase.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Work package (WP)1: 320 children aged 2-3 yrs (n= 220 with asthma-like symptoms, n=100 healthy children)
WP2: 220 children aged 2-3 yrs with asthma-like symptoms
WP3: 220 children aged 2-3 yrs with asthma-like symptoms

Exclusion criteria

mental disability, cardiac abnormalities, congenital anomalies, other respiratory diseases, chronic inflammatory diseases (e.g. Crohns disease, rheumatoid arthritis), inability to perform the exhaled breath sampling and lung function tests properly.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-12-2019
Enrollment:	320
Type:	Actual

Ethics review

Approved WMO Date:	11-04-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64912.068.18