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Estimating the incidence, prevalence and true cost of asthma in the UK: secondary analysis of national stand-alone and linked databases in England, Northern Ireland, Scotland and Wales—a study protocol

Mome Mukherjee, Ramyani Gupta, Angela Farr, Martin Heaven, Andrew Stoddart, Bright I Nwaru, Deborah Fitzsimmons, George Chamberlain, Amrita Bandyopadhyay, Colin Fischbacher, Christopher Dibben, Michael Shields, Ceri Phillips, David Strachan, Gwyneth Davies, Brian McKinstry, Aziz Sheikh, on behalf of the Burden and True Cost of Asthma in the UK Research Team

ABSTRACT

Introduction: Asthma is now one of the most common long-term conditions in the UK. It is therefore important to develop a comprehensive appreciation of the healthcare and societal costs in order to inform decisions on care provision and planning. We plan to build on our earlier estimates of national prevalence and costs from asthma by filling the data gaps previously identified in relation to healthcare and broadening the field of enquiry to include societal costs. This work will provide the first UK-wide estimates of the costs of asthma. In the context of asthma for the UK and its member countries (ie, England, Northern Ireland, Scotland and Wales), we seek to: (1) produce a detailed overview of estimates of incidence, prevalence and healthcare utilisation; (2) estimate health and societal costs; (3) identify any remaining information gaps and explore the feasibility of filling these and (4) provide insights into future research that has the potential to inform changes in policy leading to the provision of more cost-effective care.

Methods and analysis: Secondary analyses of data from national health surveys, primary care, prescribing, emergency care, hospital, mortality and administrative data sources will be undertaken to estimate prevalence, healthcare utilisation and outcomes from asthma. Data linkages and economic modelling will be undertaken in an attempt to populate data gaps and estimate costs. Separate prevalence and cost estimates will be calculated for each of the UK-member countries and these will then be aggregated to generate UK-wide estimates.

Ethics and dissemination: Approvals have been obtained from the NHS Scotland Information Services Division’s Privacy Advisory Committee, the Secure Anonymised Information Linkage Collaboration Review System, the NHS South-East Scotland Research Ethics Service and The University of Edinburgh’s Centre for Population Health Sciences Research Ethics Committee. We will produce a report for Asthma-UK, submit papers to peer-reviewed journals and construct an interactive map.

INTRODUCTION

Asthma is a common long-term condition that is associated with considerable morbidity, avoidable mortality and substantial costs. 

Strengths and limitations of this study

- This is so far the first study to estimate the UK-wide and country-specific burden and cost of asthma using available stand-alone and linked routine data.
- This study will form the basis for creating the UK Asthma Observatory for timely monitoring of the burden of asthma.
- On the basis of our scoping search for data sources, several of the data sets may be available only at the aggregate, but not individual level, example, Quality and Outcomes Framework data.
- Our scoping data search also indicates that not all outcome measures have data available across the different nations in the UK.
- Finally, all potential data gaps will be identified and we will recommend ways of overcoming these for future research work.
to the National Health Service (NHS) and society.\textsuperscript{1,2} Our previous work on the epidemiology and burden of allergy in the UK, driven mainly by asthma, has provided important insights into asthma epidemiology and resource utilisation and also demonstrated that the UK ranks among the countries with the highest prevalence in the world with a spend in excess of £1 billion in direct healthcare expenditure in England and Wales and an excess of £130 million in Scotland for asthma/allergy.\textsuperscript{1-4} A recent systematic review investigating the economic burden of asthma found that the costs associated with asthma are increasing globally.\textsuperscript{5}

There were, however, some important shortcomings in our previous work.\textsuperscript{1-4} These include the fact that the analyses undertaken related to England and Wales or Scotland only, rather than the whole of the UK. Furthermore, some healthcare data were not studied in the previous works, for example, outpatient and accident and emergency department (A&E) utilisation and their associated costs. Moreover, estimates of the previous works are now several years out of date.\textsuperscript{2,3} There is therefore a need for a more comprehensive, contemporaneous picture of asthma epidemiology, healthcare utilisation, outcomes and costs for the whole of the UK.

In this study, we seek to describe the epidemiology, healthcare utilisation and costs of asthma for the UK as a whole and its member countries by analysing secondary data available from national surveys and routine administrative data sources across England, Northern Ireland, Scotland and Wales. More specifically, we will estimate for the UK as a whole and its member countries for asthma the:

1. Incidence and prevalence.
2. Healthcare utilisation, including general practitioner (GP) and nurse consultations, prescriptions, out-of-hours calls, attendances at A&E services, ambulance services, outpatient consultation, day case and inpatient care and intensive care unit (ICU) provided by the NHS and care provided at the patient’s home.
3. Healthcare costs due to (2) above.
4. Societal costs of asthma, including (3) above, and the wider costs to society due to school absenteeism, work absenteeism, disability living allowance (DLA), care-at-home and mortality.
5. Where available, we will describe how each of these estimates varies by age, gender, socioeconomic status (SES) and ethnicity and over time.

\section*{Methods}

\subsection*{Ethical considerations and permissions}

Since some patient-level data are to be used in Scotland and Wales, approval was obtained from the Information Services Division—NHS Scotland’s Privacy Advisory Committee and the Secure Anonymised Information Linkage (SAIL) Collaboration Review System, respectively (see online supplementary appendices 1a, 1b). For the anonymised, aggregated data in Scotland, the NHS South-East Scotland Research Ethics Service confirmed that ethical review was not required (see online supplementary appendix 1c). For the entire work, on behalf of all the participating Universities, we have processed this application through The University of Edinburgh’s Centre for Population Health Sciences Research Ethics Committee; this self-assessment revealed that no further ethical permissions were required.

\subsection*{Study period}

We will describe the incidence and prevalence of asthma and healthcare utilisation during the period 2001 and 2012, which will be presented by financial years (ie, April to March of the next year). Cost estimates of asthma will be presented only for 2011–2012, since the aim here is to estimate the latest costs of asthma for the latest financial year.

\subsection*{Study populations}

The study population for each of the study outcomes will be derived from the population of the respective data set. Asthma will be defined according to the diagnostic definition available in the respective data set. The denominator in each data set will be based on the total sample of people in the data set or the total population in cases where the data set covers the entire population.

\subsection*{Assessment and definition of asthma}

With respect to each data set, patients with asthma will be defined as follow:

1. being diagnosed with asthma in primary care based on relevant Read codes (see online supplementary appendices 2 and 3) or the International Classification of Disease (ICD) revision-9 code 493;\textsuperscript{6}
2. respondents in health surveys who marked ‘yes’ for doctor-diagnosed asthma or have reported having symptoms suggestive of asthma;
3. dispensed asthma prescriptions prescribed by their GP for asthma, where prescriptions are coded using British National Formulary (BNF) codes (see online supplementary appendix 4);\textsuperscript{7}
4. used the NHS outpatient clinic or out-of-hours service or ambulance service or A&E for asthma;
5. had a primary diagnosis of asthma with Read codes (see online supplementary appendix 3) or the ICD-10 code of J45 for asthma or J46 for status asthmaticus,\textsuperscript{8} at discharge from hospital, at admission to the ICU and on registration of death;
6. claimed DLA for asthma.\textsuperscript{9}

\subsection*{Outcome measures}

\paragraph*{Incidence}

Our primary aim is to measure healthcare utilisation; therefore, our primary focus is to estimate asthma incident spells that have generated a contact with primary care (see description for England below); second, where possible, we will also estimate the incidence of first occurrence of asthma (incident cases; see description
for Scotland and Wales below). However, considering that an asthma episode may present in secondary care and that most UK primary and secondary care data are not linked, it will be challenging to identify with certainty if an asthma episode presenting in secondary care represents the first occurrence of the asthma case.

In England, the weekly incidence of asthma will be estimated by averaging new weekly episodes recorded by the Weekly Returns Service (WRS) of the Royal College of General Practitioners.\textsuperscript{10} WRS receives notifications of weekly episodes and numbers of consultations for asthma using ICD-9 code 493 from about 90 GP practices covering over 800 000 people in England. WRS is available by age groups and gender for each quarter and year.

We could not identify any GP database in Northern Ireland that could be used to estimate annual onset of asthma by new GP consultation within the available budget for this work.

In Scotland, Practice Team Information (PTI), a GP database comprising a sample of 60 general practices representing about 6\% of Scottish general practices and around 6\% of the Scottish patient population, will be used to measure the onset of asthma resulting in new GP consultation.\textsuperscript{11} PTI data include GP and nurse consultations and diagnoses using Read codes, along with demographics (see online supplementary appendix 2). PTI was established in 2003–2004. We will use the year 2003–2004 as the starting point of follow-up for 5 years and define onset of asthma by new GP consultation in patients who were consistently in PTI since 2003–2004 and did not consult their GP for asthma for those 5 years, but consulted their GP for asthma after 2008–2009. This assumes that patients who consulted their GP for asthma before 2003 would come to see their GP at least once in those 5 years.

In Wales, onset of asthma resulting in new GP consultation will be estimated from the SAIL database, which currently collects data from 42\% of the GP practices in Wales.\textsuperscript{12} There are data on demographics and diagnoses based on Read codes. Only patients who had not deregistered from the participating GP practices and did not consult a GP for asthma between 1996–1997 and 2000–2001 will be taken into account.

Prevalence

We will estimate the annual and lifetime prevalence of asthma,\textsuperscript{13} based on (a) national health surveys for the: (i) patient’s report of symptoms indicative of asthma (usually wheezing); (ii) patient’s report of doctor-diagnosed asthma and (iii) patient’s report of doctor-diagnosed asthma and doctor-treated asthma; and (b) primary care for GP-diagnosed asthma and GP-treated asthma.

We also aim to estimate the prevalence of asthma that is likely to be allergic in origin, on the basis of the patient having anaphylaxis, conjunctivitis, eczema, food allergy, allergic rhinitis and urticaria (see online supplementary appendix 5). Since up to 15\% of patients with chronic obstructive pulmonary disease (COPD) may also have asthma, we will also estimate the prevalence of COPD in those with asthma aged 40 years and above (see online supplementary appendix 6). Since smoking is the key risk factor for COPD, past and current smoking status will be queried (see online supplementary appendix 7).

The health surveys to be used are the: Health Survey for England (HSE) of 2001, 2004 and 2010; Northern Ireland Health and Social Wellbeing Survey and the Northern Ireland Health Survey of 2001, 2005/2006, 2010/2011 and 2011/2012; Scottish Health Survey (SHeS) of 2003, 2008 and 2010; and the Welsh Health Survey (WHS) of 2003, 2007, 2008, 2010 and 2011. These surveys are of randomly selected samples of people broadly representative of the respective general population. They involve the collection of information on health and utilisation of health services. Survey data will be obtained from the UK Data Service.\textsuperscript{15}

The prevalence estimates from the GP databases will come from WRS in England, PTI in Scotland, SAIL in Wales and the Quality and Outcomes Framework (QOF) database across the four countries. QOF data are available from 2004. QOF is a fundamental part of the UK General Medical Services contract, whereby general practices are rewarded by incentives for providing quality care to their patients.\textsuperscript{15} QOF data are, however, aggregated numbers; hence, breakdown by age and gender is impossible.

Healthcare utilisation in primary care

GP and nurse consultations

For estimating GP and nurse consultations for asthma, WRS and HSE will be used for England, PTI and SHeS for Scotland and SAIL-GP for Wales. We have not been able to identify any suitable data source for Northern Ireland.

Prescriptions

Some treatments commonly used for asthma (see online supplementary appendix 4) may be used for the management of other disorders. Therefore, in order to establish the use of these medications for asthma, in Scotland, patient records from Prescribing Information System (PIS; available from 2009–2010) will be linked to SHeS respondents who had mentioned having doctor-diagnosed asthma.

For Wales, diagnosis and prescribing data will be queried using the SAIL-GP database. PIS information is on prescriptions dispensed, whereas SAIL-GP data are for prescriptions written by GPs, but which may not always have been dispensed. Dispensing is reported on a monthly basis for Wales by drug and GP practices. These totals can be reconciled against the prescribing by practice in the SAIL data to establish the proportions prescribed and not dispensed and to help with the costing estimates.


Open Access
Although patient-level prescribing data are available in Northern Ireland, diagnosis information is not available; we will therefore not be in a position to conclusively ascertain if treatments have been used for asthma or for other indications.

In addition to the above data sources, data on community prescriptions in each of the four countries will be presented detailing numbers of items and costs by BNF category available from Prescription Cost Analysis.17

Out-of-hours
Data on out-of-hours GP attendance will be obtained from relevant NHS entities, where available. In England, although an out-of-hours surveillance team exists, a breakdown by asthma is not available. We have not been able to identify any comparable service in Northern Ireland. Information on calls to out-of-hours using NHS-24, the national telephone triage and advice service for Scotland, is available from 2008 onwards.18 All out-of-hours calls triaged by a nurse using asthma-specific algorithm to support decision-making will be selected. The out-of-hours data in Wales are inconsistently collected across areas and hence will not be used.

Healthcare utilisation in secondary care

Outpatient clinics
Routine data on attendances in NHS outpatient clinics are available across the four nations; these data are, however, captured under the broader heading of ‘respiratory’ consultations, and it is therefore not possible to estimate the proportions of these consultations that are for asthma. This will be noted as a major data gap. In an attempt to fill this gap, we will use HSE 2001 for England and SHeS for Scotland from the respective questions: “How many times were you treated by (type of medical professional) for your asthma/wheezing/whistling in the last 12 months?” and “How many times were you treated by a consultant/specialist or other doctor at hospital outpatient for your (asthma/wheezing or whistling) in the last 12 months?”.19–22 For Wales, estimates will be obtained from the SAIL-Outpatient Database from which asthma patients’ GP referral and attendances to outpatient clinics for asthma will be extracted.

Ambulance service
Usage of the ambulance service due to asthma cannot reliably be estimated from the aggregated routinely collected data available in England, Northern Ireland and Wales; this will therefore be identified as a data gap. For England, a question from HSE 2010 will be used: “Have (Has) you (name) had an asthma attack at school which has involved any of these situations?... “An ambulance had to be called”.23 For Scotland, asthma data from the Scottish Ambulance Service, which uses the record “Emergency call-asthma selected”, will be used from 2008–2009 onwards.24

A&E services
In England and Northern Ireland, there are no accurate published data on A&E attendances for asthma. For England, a question in HSE 2001 “How many times were you treated by (type of medical professional) for your asthma/wheezing/whistling in the last 12 months?” will be used.19 In Scotland, the A&E data mart will be used for sites which report patient-level information from their A&E departments since 2010–2011.25 If the ‘disease code’ includes the ICD-10 codes above or ‘R062’ (family history of asthma) or if the ‘presenting complaint text’ or ‘diagnosis text’ referred to any of the terms asthma, wheezing, low saturation, chest tightness or shortness of breath, then those cases will be selected. In Wales, the SAIL Emergency Department Data-set, which contains data since 2009, will be used.26

Inpatient and day cases in hospitals
We will query the Hospital Episode Statistics for England,27 the Department of Health, Social Service and Public Safety in Northern Ireland,27 the General/Acute Inpatient and Day Case data set for Scotland and the SAIL Patient Episode Database for Wales,28 29 for a primary diagnosis of asthma with ICD-10 codes to identify all asthma episodes. Hospital-based prescribing is not, however, included in these data sets.

Intensive care units
Paediatric ICUs (PICU): The Paediatric Intensive Care Audit Network is a national audit which collects data on all critically ill children admitted to PICUs across the UK.30 It has data from PICUs from England and Wales from 2002, from Northern Ireland from 2008 and from Scotland from 2007, recorded in Read V.3 (see online supplementary appendix 3).18

Adult ICUs: For England, Northern Ireland and Wales, we will use Intensive Care National Audit & Research Centre data, which have been collected since 1996.31 For Scotland, the Scottish Intensive Care Society Audit Group data will be queried, which uses ICD-10 codes.32

Wider societal costs
Since there may be people with asthma who might not be using health services, but may be sustaining social and economic costs, we will investigate absenteeism, care-at-home, contacts made with the Department of Work and Pensions (DWP), the government agency providing national benefits and lost productivity due to early death.

School absenteeism
For England, HSE 2010 with the question “Over the last 12 months, how many days has your (name) asthma/wheezing/whistling in (your/his/her) chest caused (you/him/her) to be absent from school?” will be used among asthma respondents. We could not identify any suitable data source to investigate school absenteeism in Northern Ireland, Scotland or Wales.
Work absenteeism
For England, the HSE 2010 question “Over the last 12 months, how many days has your wheezing/whistling in your chest, shortness of breath or difficulty in breathing caused you to be absent from work?” will be used among asthma respondents. Sickness-leave data from the Northern Ireland civil service from the Department of Finance and Personnel will be used on workdays lost due to asthma.33 We were unable to find any suitable data sources for Scotland and Wales. Workdays lost due to occupational asthma will be obtained from 2005 onwards from The Health and Occupation Research Network, which collates data from a research network of over 2000 specialist physicians and specially trained GPs throughout the UK.34

Care-at-home
We have been unable to identify any suitable data to estimate costs of care-at-home for asthma from England, Scotland and Northern Ireland. The only data we have identified come from a recent project undertaken by the Swansea Centre for Health Economics in collaboration with the Swansea Social Services available in SAIL, detailing home-care service packages and costs to people aged 50 years and above and living within the city and county of the Swansea council area.35

Disability living allowance
There are aggregated data available from DWP on a number of people receiving DLA, total DLA amount and expenditure on people receiving DLA due to asthma for England, Scotland and Wales for 2011–2012.36 For Northern Ireland, there are data available from the Department for Social Development on the number of people with asthma receiving DLA and total amount by age group, gender and SES from 2008.37

Premature retirement
So far, no data source has been identified.

Mortality
Mortality data with a primary or secondary cause of asthma from death certificates, coded using ICD-10, are available from the Office of National Statistics for England and Wales,37 the Northern Ireland Statistics and the Research Agency and General Register Office for Scotland.38 39

Covariates
We aim to present the estimates of incidence, prevalence and healthcare utilisation by age, gender, SES and ethnicity, where data for these covariates are available, provided risks of individuals’ identity being disclosed is not compromised. For cost estimates, the covariates will be limited to the primary covariates of age and gender.

For age, estimates will be given for children (aged under 15 years) and adults (15 years and above). In addition, to facilitate comparisons of prevalence estimates with results from the International Study of Asthma and Allergies in Childhood, we will also present estimates of prevalence by age groups 6–7 and 13–14 years.1

Gender will be classified as male and female.

SES will be categorised into quintiles based on: the English Index of Multiple Deprivation in England40; Northern Ireland Multiple Deprivation Measure in Northern Ireland41; Scottish Index of Multiple Deprivation in Scotland42; and Welsh Index of Multiple Deprivation in Wales,43 as are available in the data sets.

Where available, ethnicity will be classified as per the 2011 censuses in the respective countries (see online supplementary appendix 8).44–47

Analysis
Incidence, prevalence, time trends and healthcare utilisation
The incidence of asthma for a specific year from the respective national GP data sets will be calculated as the number of new patients diagnosed with asthma in that year divided by the total number of patients registered with the participating GP practices at the beginning of that year. Lifetime prevalence of asthma for a specific year from respective national health surveys will be calculated as the number of respondents who reported ever having had asthma divided by the total number of respondents in that year. The annual prevalence of asthma from respective national data sets will be calculated as the number of patients who reported/were diagnosed to have asthma divided by the total number of participants in the respective data set for that specific year. The incidence, prevalence and healthcare utilisation estimates will be multiplied by 1000 to give estimates per 1000 of the population. These will be presented by financial years and, where possible, by age groups, gender, SES and ethnicity. The European standard population V.2013 will be used as the reference population to age standardise the rates for comparison across countries.48 Crude rates will be provided where age breakdowns are not available. All estimates will be accompanied by their respective 95% CI, where appropriate based on the Poisson approximation.49 Trends over time will be presented based on years of data availability.

Health and societal care costs of asthma
Healthcare costs will be estimated from an NHS perspective based on the healthcare utilisation detailed above. Where a given data set does not inherently include a cost estimate, standard UK weights will be applied. The majority of primary care price weights will be taken from the Personal and Social Services Research Unit annual unit costs.50 Inpatient care costs will be based on Healthcare Resource Grouping codes version-4 in the Department of Health reference costs or the Scottish National Tariff for Scotland.51 52 Costs of prescribing will be based on net ingredient costs from the prescribing databases of the respective countries. Societal costs will be estimated from a wider societal perspective including NHS costs as above, DLA and lost work productivity.
estimated using a Human Capital approach. The latter estimate will be undertaken by applying the national average wage rates by age group and gender to estimate lost productivity due to absenteeism and death (up to a conservatively assumed retirement age of 65). All costs will be estimated from a base year of 2011/2012 applying appropriate inflation indices where required.

Addressing data gaps

Data gaps can take three forms: (1) within the country—where no single data set in a given country holds sufficient variables to provide an estimate, but linkages between data sets may overcome this; (2) between countries—where data on the variable of interest (after allowing for linkages) are available in one member country, but not in another or (3) across the country—where no data (after allowing for linkages) from any member country are found for the variable of interest. Appropriate linkages will be explored for Type 1 data gaps. Type 2 will be addressed by mapping estimates of a given variable from one country where data are available to another, based on the age group and gender. Where this is not possible or where a gap is of Type 3, estimate from the wider literature may be used. As the time frame for the study does not permit a full systematic review to identify such parameters, this may be based on a simple literature search or parameters found in the Health Economic Evaluation Database, with the most appropriate parameter estimate selected based on expert judgement from the team.

Economic modelling

An economic model of the cost of asthma in the UK and its member countries will be built in Microsoft Excel 2010. This will be used to:

1. Apply the mapping techniques and synthesis of data with wider literature and price weights,

2. Sum up the cost estimates into the required groupings (e.g., NHS costs, wider societal costs each by the age and gender groupings described above), and estimate 95% CI around the joint distributions of each total cost estimate with each cost element and total presented as cost per 1000 population as well as an absolute figure. In order to estimate CI around the cost totals, the model will apply probability distributions based on the observed means and appropriate measures of uncertainty (such as SEs or SDs) for parameters of interest. The CI will be estimated by taking bootstrapped samples from the distributions applied to each parameter simultaneously and running the model based on this set of sampled parameter estimates, thus capturing their joint distribution within the bootstrapped sample. The required 95% CI will then be estimated using the percentile method based on these samples.

UK-wide estimates can be provided for the outcomes by pooled data analysis only if there is homogeneity. However, if among the individual countries there is excessive heterogeneity, then it will not be appropriate to pool national estimates.

Project timeline and current status

This project started in October 2013 and will end in December 2014. Currently, the teams are in the process of acquiring and analysing data.

Implications

The current project will, for the first time, generate reliable estimates of the incidence, prevalence, trends, healthcare utilisation and health and social care costs of asthma for the UK as a whole and for its individual member nations. The conclusion of this project will mark an important milestone in comprehensively appreciating the overall burden posed by asthma in the country. The project findings will serve as an important resource for policymakers in informing policy deliberations on effective service planning and provision for people with asthma.

This project should provide a summary of the key available data sources for asthma epidemiology, health and social services use and costs in the UK and its member countries. In this vein, identification of data gaps will assist deliberations on how to plug these gaps in order to develop a comprehensive picture of people living with long-term conditions. Furthermore, we will recommend possible ways of filling these gaps. Moreover, we are in the longer term in the process of creating a UK Asthma Observatory, which will represent a significant milestone in the field of asthma research in the UK through which real-time trends of asthma can be monitored, and this work should serve as an important foundation in this respect. Ultimately, this should serve as a motivation for setting up such observatories in other European countries.

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Collaborators Other members of the research team: Elisabeth Ehrlich, Chantelle Anandan, Colin Simpson and Ronan Lyons.

Contributors ASh conceived the idea for the study. MM carried out the initial exploration of the data availability. Data selections were made by MM for Scotland, Northern Ireland and UK-wide; RG for England, and AF, MH, AB and GC for Wales. MM wrote the initial manuscript apart from the cost analysis section which was written by ASH. The protocol has been developed by all authors. The manuscript has been reviewed by MM, RG, AF, MH, ASH, BM, BS, AB, GD, DF and CP. All authors have read the draft critically to make contributions and have approved the final version.

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Competing interests ASh was an adviser to the Scottish Health Survey.

Ethics approval NHS South-East Scotland Research Ethics Service, NHS Scotland Information Services Division’s Privacy Advisory Committee, Secure Anonymised Information Linkage Collaboration Review System and The University of Edinburgh’s Centre for Population Health Sciences Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This is a protocol and currently we are in the process of obtaining data. When the data are available, we aim to construct an interactive map for asthma in the UK, which will feed into the UK Asthma Observatory (UKAO). Both the interactive map and UKAO will be available on the web.

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Supplementary material can be found at: http://bmjopen.bmj.com/content/suppl/2014/11/04/bmjopen-2014-006647.DC1.html

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References

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