STUDY PROTOCOL

A COHORT STUDY ON THE ASSOCIATION BETWEEN ACID-SUPPRESSING DRUGS IN PREGNANCY AND ASTHMA IN THE OFFSPRING

Prepared by:

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Contents

1. PROTOCOL SYNOPSIS

Study title: A cohort study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring

AZ study identifier(s): D9612N00018 Nexium Children Asthma Epidemiology Study

Principal Investigator:

Co-Investigator:

Type of study, study design: Cohort study

Study objective(s): To estimate the association between prenatal exposure to proton pump inhibitors (PPIs) and the risk of asthma during childhood.

To estimate the association between prenatal exposure to H_2-receptor antagonists (H_2RAs) and the risk of asthma during childhood.

Setting: The Health Improvement Network (THIN) primary care database in the UK

Study population of mother-infant pairs: All women aged 18–45 years and with at least one pregnancy between 1 January 1995 and 31 December 2010 who have been enrolled with their PCP (Primary Care Physician) for at least 1 year and have had a health contact in the year prior to the last menstrual period (LMP) of the respective pregnancy. The final study population will include pregnancies that can be unequivocally linked with live birth(s) and only the first pregnancy ascertained during the study period for each woman will be retained. The offspring of these women will be then followed for up to 6 years.

Exposed cohort: Acid-suppressing drugs prenatally exposed cohort

All pregnancies in the study population with recorded use of acid-suppressing drugs (PPIs or H_2RAs) at anytime during pregnancy will be retained in the exposed group.

Non-exposed cohort: not prenatally exposed to acid-suppressing drugs cohort

Among all remaining pregnancies (first pregnancy for each woman during the study period) free of acid-suppressing drug use at any time during pregnancy, a cohort of 10,000 pregnancies frequency-matched by year and trimester of delivery to the exposed cohort, will constitute the unexposed comparison cohort.

All live-born children linked to an eligible pregnancy will be followed up starting when they turn one year old until first recorded entry of asthma, they reach the age of 6 years, die or end of study period (31 December 2010), whatever comes first. The earliest end of follow-up period will be 1 January 2002 (child born on 1 January 1996).

To ascertain the number of cases with a diagnosis of asthma, epidemiologists at will manually review the electronic medical records of patients, including free-text comments, with suppressed personal identifiers and information on drug use removed to allow for a blinded revision of patient profiles. A random sample of potential cases will be further validated for accuracy of diagnosis through questionnaires to the PCP.

Exposure definition: All prescriptions issued by the PCP are recorded in the database and a coded drug dictionary (Multilex) is used to record prescribed medicines. Details of every prescription issued include date, dosage, quantity dispensed, duration of therapy, and indication.

In mothers, medication use will be categorized as follows: *first trimester exposure* when the supply of a prescription overlapped with at least one week of first trimester; *second trimester exposure* when the supply of a prescription overlapped with at least one week of second trimester; *third trimester exposure* when the supply of a prescription overlapped with at least one week of third trimester: Non-use, when there was no prescription of the relevant medication ever during pregnancy.

In THIN, acid-suppressing drugs include PPIs: lanzoprazole, omeprazole, rabeprazol, pantoprazole, esomeprazole and H2RAs: cimetidine, famotidine, nizatidine, ranitidine

Outcome definition: Physician-diagnosed asthma defined as a child over one year of age with a code for asthma diagnosis in the electronic medical record confirmed by blinded (to exposure) review of the medical history around diagnosis.

Statistical analysis: Kaplan Meier survival curves for prenatally and non-prenatally exposed children from year one up to six years of life will be performed. Cox proportional hazard models will be used to estimate the relative risk and 95% CI of first asthma diagnosis associated with prenatal exposure to acid-suppressing drugs taking into account time to event. Adjustment for matching variable and other potential confounders will be introduced in the Cox regression model.

In addition, the cumulative risk of asthma diagnosis up to 6 years of age will be estimated among the subgroup of children with complete follow-up up to that age in the exposed and non exposed cohorts. Unconditional logistic regression will be used to compute multivariate adjusted odds ratios of asthma status at 6 years of age associated with prenatal exposure to acid-suppressing drugs.

Specific PPIs and specific timing of exposure during pregnancy (first, second and third trimester) will be considered. Several sensitivity analyses will be performed. One will characterize the use of acid-suppressing drugs between 12 and 3 months prior to the date of conception in mothers and evaluate the association with asthma in children. Another one will analyze the association between exposure in fathers in the time window corresponding to pregnancy and asthma in children.

Study strengths: A major strength of this study is that use of THIN enables analysis of a large population-based sample of PPI exposed pregnancies that are representative of the UK primary-care population, with a similar age and sex distribution to those in the national population supporting a broad external validity of the findings and generalizability. Sensitivity analyses to assess confounding, selection, and information

biases (e.g. subanalysis with exposure experience in “fathers”) will be conducted. In addition, the risk with another drug class (H_2RA) that shares similar treatment indication than PPI will be analyzed to verify the specificity of the results. Validation of asthma with the PCP will help to reduce the extent of outcome misclassification always present when working with automated databases.

Study Limitations: A potential limitation of the study is that PPI use could be misclassified in some instances. For example, the recording of a PPI prescription in THIN does not necessarily mean that the patient actually took the medication, although it is likely that patients with repeated prescriptions do take their medication. Also, lack of recording of OTC PPI is another source of misclassification. This misclassification of drug exposure will most likely be non-differential and thus will bias the effect estimates towards the null. Therefore, it should be noted that to the extent such misclassification occurs in our study population, effect estimates will tend to underestimate the true relative risk.

Outcome misclassification of asthma will be substantially reduced with our two step validation process: first obtaining free text comments for the review of the patient profiles and second the direct validation with the PCP. The extent of recording of comorbidity, medication use and life style habits in THIN will help to minimize as much as possible potential confounding by any of these variables.

2. INTRODUCTION

Proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) are widely prescribed acid-suppressive medications that in general have good safety profiles (Yang and Metz, 2010). During pregnancy, antacids are also among the most commonly used drugs.(Mitchell, Gilboa et al. 2011)

More than half of all women who become pregnant suffer from heartburn or gastroesophageal reflux (GERD), that can be resistant to control during pregnancy. (Olans and Wolf 1994; Richter 2005) Usually, physicians start treating GERD in pregnancy with conservative measures such as advising patients to eat smaller meals, or recommending antacids available over-the-counter, including products containing calcium carbonate (e.g., Tums®) and aluminium hydroxide/magnesium hydroxide (e.g. Mylanta®). Histamine H2-receptor antagonists are recommended in pregnant women whose symptoms can not be adequately controlled with lifestyle modification and antacids. (Katz, 1998) However, these methods are often ineffective, which might explain why physicians are increasingly prescribing PPIs. (Pasternak and Hviid 2010; Mitchell, Gilboa et al. 2011) Often GERD symptoms start early in pregnancy, when the fetus would be most vulnerable to any potential teratogenic effect of medications, which can lead not only to birth defects but also to developmental problems in the offspring.

Epidemiological studies (Brunner, Meyer et al. 1998; Kallen 1998; Lalkin, Loebstein et al. 1998; Nielsen, Sorensen et al. 1999; Ruizgómez, García Rodríguez et al. 1999; Kallen 2001; Diav-Citrin, Amon et al. 2005; Nava-Ocampo, Velazquez-Armenta et al. 2006; Pasternak and Hviid 2010) and systematic reviews (Richter 2005; Gill, O'Brien et al. 2009) have suggested that use of PPIs during pregnancy does not pose a teratogenic risk to the fetus. Gill and colleagues published a systematic review evaluating the risk of PPI use in pregnancy. Among 1530 PPI-exposed subjects compared with 133,410 controls, they found no association between major fetal malformations, spontaneous abortions, or pre-term delivery.

Some human studies have analyzed whether in utero exposure to PPIs might enhance the development of adverse health outcomes in the offspring later in life. In a recent Swedish registry-based cohort study, the use of maternal acid-suppressive medication, including PPIs was associated with an increased risk for the development of severe childhood asthma (3.7% in the population at large vs. 5.6% in exposed children; OR 1.51, 95% CI 1.35-1.69), but not for other allergic diseases. (Dehlink E et al 2009) At a recent conference, investigators from Denmark reported prenatal exposure to both PPIs and H2RAs to be associated with an increased risk of asthma in the offspring. The postulated mechanism, based on animal model data, is that acid suppression increases type 2 helper cell bias in their offspring, thus predisposing to increased atopy. However, the association was found for maternal postnatal use of PPIs, suggesting that the results may be affected by confounding by indication or other environmental or genetic factors. (Ane Birgitte Telén Andersen, et al. Abstract presented 27th ICPE, 2011)

Other prenatal exposures, including maternal asthma, use of asthma medications, and use of antibiotics have been speculated to be contributing causes of childhood asthma.(Yuan W, et al 2003: Benn CS, et al 2002) Early antibiotic use during childhood has also been associated with asthma and allergy at 6 years of age. (Risnes KR et al 2011)

Algert et al 2011 concluded that that the immune system response is the relevant factor rather than a specific organism for the increased risk of asthma in children. The season-associated risk is consistent with early pregnancy exposures such as the winter flu season or low vitamin D. Martel MJ et al. reported a significant increase in asthma risk among children whose mothers had poor control and increased severity of asthma during pregnancy, indicating that this element should be added to the expanding list of determinants of childhood asthma.

In summary, data suggest that the immediate fetal development risk of PPIs may be negligible. However, possible risks to the fetus that may only become manifest in childhood require further study. The study of prenatal exposures and childhood asthma is challenged methodologically by potential confounding due to genetic and environmental factors shared by the mother, father and the offspring during and after gestation. The proposed observational study will further investigate the hypothesized associations in clinical practice and contribute to quantify the risk of asthma in children associated with maternal use of acid-suppressing drugs (PPI and H2RA) during pregnancy.

3. STUDY OBJECTIVES

- To estimate the association between prenatal exposure to PPIs and the risk of asthma during childhood.

- To estimate the association between prenatal exposure to H_2-receptor antagonists (H2RAs) and the risk of asthma during childhood.

4. METHODS

4.1 Study design

A cohort study will be performed using The Health Improvement Network (THIN) database in the UK between 1995 and 2010. Data is prospectively recorded by participating primary care physicians as part of their routine patient care (see 4.2).

Two study cohorts will be identified. The first study cohort will include all women exposed to PPI or H_2RA at any time during pregnancy. The second study cohort will include a random sample (N=10,000) of pregnant women with no recorded use of acid-suppressing drugs at any time during pregnancy. This ”non-exposed” cohort will be frequency-matched to the “exposed” cohort on year and trimester of date of delivery. Only the first pregnancy for each woman during the study period will be included in the study.

These two cohorts will be pooled into one cohort. The rate of first asthma diagnosis will be compared between the exposed and non-exposed cohort. In addition, the cumulative incidence up to six years of age will be compared in the subgroup of these two cohorts that contributed at least 6 years of follow-up.

A graphical presentation of the study design is provided in Figure 1 (end of document). A presentation of the two stage sampling is provided in Figure 2a and 2b.

The rationale of our study design is

1) The cohort design allows estimation of incidence rates and cumulative risks and is more intuitive for the readers. Survival curves can be estimated to describe timing of diagnosis during childhood.

2) Ascertaining the cohort of all “exposed” pregnancies and a random sample of the “unexposed” cohort is cost-efficient as we include all the experience available with prenatal exposure of study drugs and a random sample of the unexposed comparison group of at least four times the size the “exposed” cohort. Given that the outcome is relatively common, this sampling will maintain most of the statistical power while reducing the number of cases we will need to validate. Validation of cases will enhance the validity of risk estimates. Moreover, matching the cohort for calendar time will control for potential confounding effects of trends in both antacids use and asthma incidence, therefore further improving validity of relative risk estimates.

Figure 2 Two stage sampling.

Figure 2.a. Pregnancy-offspring pairs are identified and classified according to exposures to PPIs and H_2RA during pregnancy.

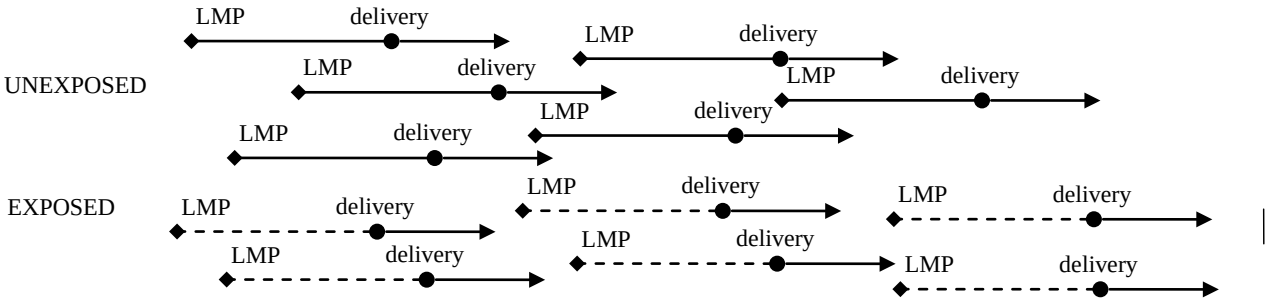
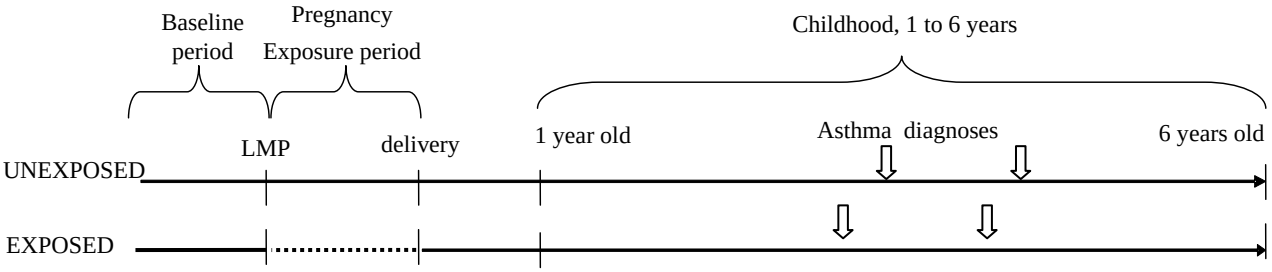


Figure 2b. All exposed and a random sample of unexposed pregnancies matched on delivery (calendar year and trimester) are selected for the study cohorts. Live born infants are followed up starting when they turn one year old until asthma diagnosis, death, or end of study, whichever comes first. Cases are validated for accuracy of diagnosis.



4.2 Source population

THIN is a computerized medical research database that contains systematically recorded data on more than 3 million UK primary care patients. It is representative of this population with regard to age, sex, and geographic distribution, and has been validated for use in pharmacoepidemiological research in multiple studies (Lewis et al 2007). Participating primary care practitioners (PCPs) record data as part of their routine patient care, including demographics and life style factors (e.g. alcohol use, body mass index (BMI) and smoking status), consultation rates, referrals, hospital admissions, laboratory test results, diagnoses, prescriptions ordered by the PCPs, and a free text section, and send their data anonymously to THIN for use in research projects. Prescriptions issued by PCPs are recorded automatically in the database. The Read classification is used to code specific diagnoses (Stuart-Buttle et al 1996), and a drug dictionary based on data from the MULTILEX classification is used to code drug prescriptions (First Data Bank 2010).

The rationale for selection of THIN is the unique attributes of primary care databases in the UK (eg. GPRD, Qresearch) for pharmacoepidemiological research. As GPRD and

THIN are equivalent databases, we chose the one with which our research group has greater experience.

4.3 Study population

THIN will be used to identify all women aged 18–45 years and with at least one pregnancy between 1 January 1995 and 31 December 2007 who have been enrolled with their PCP for at least 1 year and have had a health contact in the year prior to the last menstrual period (LMP) of the respective pregnancy. We will retain as our final study population of mother-child pairs, all pregnancies that we can unequivocally link with live birth(s): based on previous experience, we expect a linkage greater than 90 % among pregnancies with a delivery entry. We will retain only the first pregnancy ascertained during the follow-up for each woman.

Exposed cohort: Acid-suppressing drugs prenatally exposed cohort.

All pregnancies with recorded use of acid-suppressing drugs (PPIs or H_2RAs, table 1) at anytime during pregnancy will be retained.

Non-exposed cohort: not prenatally exposed to acid-suppressing drugs cohort.

Among all remaining pregnancies (free of acid-suppressing drug use at any time during pregnancy), we will randomly sample a cohort of 10,000 pregnancies that will constitute the unexposed comparison cohort. This unexposed cohort will be frequently-matched by year and trimester of delivery to the exposed cohort.

4.3.1 Eligibility criteria

To be included in the pregnancy cohorts, a pregnancy must meet all of the following criteria::

- At least 1 year of enrolment with the PCP at LMP
- At least 1 health visit in the year prior at LMP
- Age 18-45 years at LMP
- Linkage with liveborn children with a permanent or died registration status in last THIN update

Exclusion criteria

- No exclusion criteria will be applied.

4.4 Follow-up

All live-born children linked to an eligible pregnancy will be followed up from one year of age until first recorded entry of asthma, they reach the age of 6 years, die or end of study period (31 December 2010), whatever comes first. The earliest end of follow-up period will be 1 January 2002 (child born on 1 January 1996).

4.5 Outcome definition:

A child over one year of age with a computer entry of asthma diagnosis during follow-up confirmed with review of electronic medical record will be accepted as asthma case.

4.6 Operational definition of case of asthma

The profiles, including free-text comments, of children with asthma diagnoses in their electronic medical records (table 2) identified with the initial computer search will be reviewed manually to ascertain their asthma status. Free text comments will be requested before reviewing patient profiles. Information will include demographic data, all clinical information in children and no information on maternal exposures during pregnancy will be included in the profiles. All patient personal identifiers will be suppressed. Patients will not be retained as asthma cases if the diagnosis is allergic disease without confirmation of asthma or the final diagnosis objectively excludes asthma. Doubtful cases will be reviewed by two epidemiologists with medical background and agreement will be reached. All children not excluded after the manual review will be considered as final cases of asthma. We will consider the date of first recorded diagnosis of asthma as the date of asthma onset in our cohort analyses.

4.6.1 Case validation with PCPs

We will send for a random sample of 200 asthma cases a questionnaire to PCPs requesting them to send copies of all related paper-based medical records in order to validate our operational definition of asthma. If the information from the questionnaire and medical records confirms our asthma cases in 85% of instances or greater, we will not request additional records for the remaining cases.

4.7 Characterization and assessment of risk factors

The following potential confounders and/or effect modifiers will be ascertained:

Demographics: Maternal age, parity, and BMI (<20, <25 (reference), 25–<30, 30–<35 and ≥ 35) at LMP. Socioeconomic status will be computed with the Townsend score. Multiple pregnancy for index kid (singleton, twins, triplets or more). Infant age at index date (for cases only), sex and calendar year at birth (2002-2005, 2006-2008 and 2009-2011).

Life style factors; Smoking status of mothers will be categorized into current smoker, past smoker, never smoker. Missing data will be assessed as a separate category. Smoking status will be ascertained at LMP and at one year after delivery, separately. Smoking status of father/partner will also be ascertained in the time window corresponding to pregnancy. Rural/urban area will be assessed. Alcohol consumption will be categorized into units per week; 0, 1-2, 3-24, 25+ u/w, respectively.

Comorbidity; Maternal diabetes (gestational and non-gestational), asthma, depression, autoimmune disease, allergic rhinitis, hay fever, peptic ulcer/dyspepsia/GERD codes, HP tests the year before or during pregnancy. Health care utilization of mom: number of visits/hospitalizations the year before pregnancy, gestational age at first pregnancy visit, number of different prescriptions the year before and during pregnancy, fertility interventions for the index pregnancy.

Comedication; Maternal use of antibiotics (specifically those for HP), asthma medications, antacids, anticholinergic drugs or analgesics the year before or during pregnancy. In "fathers": use of PPIs and asthma medications. In children: use of PPIs.

Infant status at birth: Low birth weight (less than 2,500g.), preterm birth (birth occurring prior to 37 completed weeks of gestation), small for gestational age (SGA; an infant below the 10th percentile for weight for his/her gestational age).

4.8 Exposure definition

In mothers, we will categorize medication use as follows: *first trimester exposure* when the supply of a prescription overlapped with at least one week of first trimester; *second trimester exposure* when the supply of a prescription overlapped with at least one week of second trimester; *third trimester exposure* when the supply of a prescription overlapped with at least one week of third trimester: Non-use, when there was no use of the relevant medication ever during pregnancy. As a proxy for cumulative dose, total number of prescriptions during pregnancy will be also ascertained.

In fathers/partners, we will use the same time windows related to pregnancy than in mothers.

In children, we will ascertain use during their follow-up experience. For descriptive analyses, ever use will be use of the medication at anytime during follow-up. Non use will be children with no recorded use ever during follow-up.

4.9 Statistical analysis

Primary analysis:

The maternal characteristics at LMP and during pregnancy will be compared between PPI exposed and unexposed pregnancies to assess the degree of imbalance of potential confounders. We will perform Kaplan Meier survival curves for prenatally and non-prenatally exposed children from birth up to six years of life. Cox proportional hazard models will be used to estimate the relative risk and 95% CI of first asthma diagnosis associated with prenatal exposure to acid-suppressing drugs taking into account time to event.

In addition, the cumulative risk of asthma diagnosis up to 6 years of age will be estimated among the subgroup of children with complete follow-up up to that age in the exposed and non exposed cohorts. Unconditional logistic regression will be used to compute multivariate adjusted odds ratios of asthma status at 6 years of age associated with prenatal exposure to acid-suppressing drugs.

We will consider specific PPIs, specific timing of exposure during pregnancy (first, second and third trimester), and total cumulative dose (number of prescriptions) during pregnancy. Models will include sex of the child, maternal asthma and smoking. The final model will also adjust for all potential confounders, described in section 4.7, that change the RR for prenatal PPIs exposure by at least 10%.

Secondary analyses:

Several sensitivity analyses will be performed. One will characterize the use of acid-suppressing drugs between 12 and 3 months prior to the date of conception in mothers and evaluate the association with asthma in children. Another one will analyze the association between exposure in fathers in the time window corresponding to pregnancy and asthma in children. Exploratory analyses of potential effect mediators will adjust for factors in children (eg. perinatal and postnatal).

Other sensitivity analyses: Association between another acid suppressing drug class (H_2RA) and childhood asthma. Association between initiation of PPIs after delivery (no use during or in year before pregnancy) and childhood asthma.

Statistical analyses will be performed using Stata package version 11.0 (StataCorp LP, College Station, TX, USA).

4.9.1 Sample size

We expect to have at least 100,000 pregnancies eligible for these analyses. Assuming that 1% of pregnancies are exposed to PPIs, we are expecting a cohort of 1,000 exposed pregnancies which will be frequency matched with 10,000 unexposed pregnancies. With an assumed cumulative incidence of asthma in the unexposed offspring of 10% before 6 years of life, the power to show a relative risk of 1.35 (which was the lower confidence limit in the Dehlink et al study 2009) with an alpha error of 0.05 will be over 85%.

5. STUDY STRENGTHS AND LIMITATIONS

Strengths:

A major strength of this study is that use of THIN enables analysis of a large population-based sample of pregnancies that is representative of the UK primary-care population, with a similar age and sex distribution to those in the national population supporting a broad external validity of our findings and generalizability. We will conduct multiple sensitivity analyses to assess confounding, selection, and information biases. For example, we will analyze the risks associated with paternal PPI use, and with prenatal exposure to another drug class (H_2RA) that shares similar treatment indication than PPIs.

Outcome misclassification of asthma will be substantially reduced with our two step validation process: first obtaining free text comments for the review of the patient profiles and second the direct validation with the PCP.

The extent of recording of comorbidity, medication use and life style habits in THIN will minimize potential confounding by any these variables.

Limitations:

A potential limitation of the study is that PPI use could be misclassified in some instances. For example, the recording of a PPI prescription in THIN does not necessarily mean that the patient actually took the medication, although it is likely that patients with repeated prescriptions do take their medication. Also, lack of recording of OTC PPI is another source of misclassification. This misclassification of drug exposure will most likely be non-differential and thus will bias the effect estimates towards the null. Therefore, it should be noted that to the extent such misclassification occurs in our study population, our effect estimates will tend to underestimate the true risk.

6. PROJECT FORMALITIES AND TIMELINES

6.1 Privacy and confidentiality

Privacy issues will be addressed and respected at each stage of the study. All analyses and reporting will be done on appropriately de-identified data and only in aggregate form. AstraZeneca will not receive any patient or provider identifiable information from at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices (GPP, 2007). The study protocol is dependent on approval by the ethical review board Multicenter Research Ethics Committee (MREC) for studies performed in THIN.

6.2 Project management

Principal Investigator:

Co-investigator:

6.3 Study reporting

The final analyses and study report is estimated to be delivered within 24 months of external approval from ethic committee assuming 3 months for anonymization of free text comments by the external provider of THIN data (AIS) and 5 months for obtaining questionnaires from PCPs, aiming at high response rate (around 80-90%) with anonymization of all information (Table 3). At least one manuscript based on the findings from this project will be submitted for publication to a peer-reviewed journal.

6.4 Data management

will comply with all applicable data protection, security and privacy laws, rules and regulations with respect to the collection, production, use, processing, storage, transfer, modification, deletion, and/or disclosure of any information related to this study under this Agreement. will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. will ensure that

appropriate technical and organizational measures are taken to protect information against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access and against all other unlawful forms of processing. will store the Database used to perform this study at the premises of .

7. REFERENCES

Algert CS, Bowen JR, Lain SL, Allen HD, Vivian-Taylor JM, Roberts CL. Pregnancy exposures and risk of childhood asthma admission in a population birth cohort. Pediatr Allergy Immunol. 2011 Sep 19. doi: 10.1111/j.1399-3038.2011.01206.x. [Epub ahead of print]

Benn CS, Thorsen P, Jensen JS, Kjaer BB, Bisgaard H, Andersen M, et al. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. J Allergy Clin Immunol 2002 Jul;110(1):72-77.)

Brunner, G., H. Meyer, et al. (1998). "Omeprazole for peptic ulcer disease in pregnancy." Digestion **59**: 651-4.

Dehlink E, Yen E, Leichtner AM, Hait EJ, Fiebiger E. First evidence of a possible association between gastric acid suppression during pregnancy and childhood asthma: a population-based register study. Clin Exp Allergy 2009;39(2):246-253.

Diav-Citrin, O., J. Amon, et al. (2005). "The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study." Alimentary Pharmacolgy and Therapeutics **21**: 269-75.

First Data Bank. MULTILEX for primary care. Available at: http://www.firstdatabank.co.uk/uploads/files/MultilexDDF%20for%20Primary%20C re.pdf. Accessed 25 January, 2010.

Gill, S., L. O'Brien, et al. (2009). "The safety of proton pump inhibitor (PPIs) in pregnancy: a meta-analysis." American Journal of Gastroenterology **104**: 1541-1545.

Guidelines for Good Pharmacoepidemiology Practices (GPP). Revised: August 2007. http://www.pharmacoepi.org/resources/guidelines_08027.cfm International Society for Pharmacoepidemiology, 2007.

Kallen, B. (2001). "Use of omeprazole during pregnancy - no hazard demonstrated in 955 infants exposed during pregnancy." European Journal of Obstetrics and Gynecology **96**: 63-8.

Katz PO, Castell DO. Gastroesophageal reflux disease during pregnancy. Gastroenterology Clinics of North America 1998: 27:153-167,

Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007;16(4):393–401.

Martel MJ, Rey E, Beauchesne MF, Malo JL, Perreault S, Forget A, Blais L.Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. Eur Respir J. 2009 Sep;34(3):579-87.

Mitchell, A., S. Gilboa, et al. (2011). "Medication Use during Pregnancy, with Particular Focus on Prescription Drugs: 1976-2008." American Journal of Obstetrics and Gynecology **205**(51): e1-8.

Nava-Ocampo, A., E. Velazquez-Armenta, et al. (2006). "Use of proton pump inhibitors during pregnancy and breastfeeding." Canadian Family Physician **52**: 853-654.

Nielsen, G., H. Sorensen, et al. (1999). "The safety of proton pump inhibitors in pregnancy." Alimentary Pharmacolgy and Therapeutics: 1085-9.

Olans, L. and J. Wolf (1994). "Gastroesophageal reflux in pregnancy." Gastrointest Endosc Clin N Am **4**: 699-714.

Pasternak, B. and A. Hviid (2010). "Use of protun-pump inhibitors in early pregnancy and the risk of birth defects." New England Journal of Medicine **363**: 2114-23.

Richter J. (2005). "Review article: the management of heartburn in pregnancy." Alimentary Pharmacolgy and Therapeutics **22**: 749-757.

Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. Am J Epidemiol. 2011 Feb 1;173(3):310-8.)

Rothman K. Epidemiology-an introduction. Oxford University Press, 2002.

Ruigómez A, García Rodríguez LA, et al. (1999). "Use of Cimetidine, Omeprazole, and Ranitidine in Pregnant Women and Pregnancy Outcomes." American Journal of Epidemiology **150**(5): 476-481.

Stuart-Buttle CD, Read JD, Sanderson HF, Sutton YM. A language of health in action: Read Codes, classifications and groupings. Proc AMIA Annu Fall Symp. 1996;75-79.

Ane Birgitte Telén Andersen, Rune Erichsen, Dóra Körmendiné Farkas, Frank Mehnert, Vera Ehrenstein, Henrik Toft Sørensen. Use of proton pump inhibitors during pregnancy and the risk of asthma in offspring: a population-based Danish cohort study. Abstract presented 27th ICPE, 2011

Yang Y-X, Metz DC. Safety of proton punp inhibitors. Gastroenterology 2010;139:1115-1127.

Yuan W, Fonager K, Olsen J, Sorensen HT. Prenatal factors and use of anti-asthma medications in early childhood: a population-based Danish birth cohort study. Eur J Epidemiol 2003;18(8):763-768.

Table 1 List of acid-suppressing drugs

PPIs
Lansoprazole
Omeprazole
Rabeprazole
Pantoprazole
Esomeprazole
H_2RAs
Cimetidine
Famotidine
Nizatidine
Ranitidine

Table 2 List of asthma codes

2126200	Asthma resolved
13Y4.00	Asthma society member
14B4.00	H/O: asthma
173A.00	Exercise induced asthma
173c.00	Occupational asthma
173d.00	Work aggravated asthma
178..00	Asthma trigger
1780.00	Aspirin induced asthma
1J70.00	Suspected asthma
1O2..00	Asthma confirmed
212G.00	Asthma resolved
212G.00	Asthma resolved
38DL.00	Asthma control test
38DT.00	Asthma control questionnaire
38DV.00	Mini asthma quality of life questionnaire
663..11	Asthma monitoring
663d.00	Emergency asthma admission since last appointment
663e.00	Asthma restricts exercise
663e000	Asthma sometimes restricts exercise
663e100	Asthma severely restricts exercise
663F.00	Oral steroids started
663f.00	Asthma never restricts exercise
663G.00	Oral steroids stopped
663g.00	Inhaled steroids use
663g000	Not using inhaled steroids
663g100	Using inhaled steroids - normal dose

663g200	Using inhaled steroids - high dose
663g300	Increases inhaled steroids appropriately
663H.00	Inhaler technique - good
663h.00	Asthma - currently dormant
663I.00	Inhaler technique - poor
663J.00	Airways obstruction reversible
663j.00	Asthma - currently active
663K.00	Airways obstructn irreversible
663k.00	Reversibility trial by steroids
663L.00	Bronchodilators used more than once daily
663l.00	Spacer device in use
663M.00	Bronchodilators used a maximum of once daily
663m.00	Asthma accident and emergency attendance since last visit
663N.00	Asthma disturbing sleep
663n.00	Asthma treatment compliance satisfactory
663N000	Asthma causing night waking
663N100	Asthma disturbs sleep weekly
663N200	Asthma disturbs sleep frequently
663O.00	Asthma not disturbing sleep
663O000	Asthma never disturbs sleep
663P.00	Asthma limiting activities
663p.00	Asthma treatment compliance unsatisfactory
663Q.00	Asthma not limiting activities
663q.00	Asthma daytime symptoms
663R.00	Service of nebuliser
663r.00	Asthma causes night symptoms 1 to 2 times per month
663S.00	Peak flow meter at home
663s.00	Asthma never causes daytime symptoms
663T.00	No peak flow meter at home
663t.00	Asthma causes daytime symptoms 1 to 2 times per month
663U.00	Asthma management plan given
663u.00	Asthma causes daytime symptoms 1 to 2 times per week
663V.00	Asthma severity
663v.00	Asthma causes daytime symptoms most days
663V000	Occasional asthma
663V100	Mild asthma
663V200	Moderate asthma
663V300	Severe asthma
663W.00	Asthma prophylactic medication used
663w.00	Asthma limits walking up hills or stairs
663X.00	Irritable airways
663x.00	Asthma limits walking on the flat
663Y.00	Steroid dose inhaled daily
663y.00	Number of asthma exacerbations in past year
66Y5.00	Change in asthma management plan
66Y9.00	Step up change in asthma management plan

66YA.00	Step down change in asthma management plan
66YC.00	Absent from work or school due to asthma
66YE.00	Asthma monitoring due
66YJ.00	Asthma annual review
66YK.00	Asthma follow-up
66YP.00	Asthma night-time symptoms
66YQ.00	Asthma monitoring by nurse
66YR.00	Asthma monitoring by doctor
66YZ.00	Does not have asthma management plan
679J.00	Health education - asthma
679J000	Health education - asthma self management
679J100	Health education - structured asthma discussion
679J200	Health education - structured patient focused asthma discuss
68C3.00	Asthma screening
8791.00	Further asthma - drug prevent.
8793.00	Asthma control step 0
8794.00	Asthma control step 1
8795.00	Asthma control step 2
8796.00	Asthma control step 3
8797.00	Asthma control step 4
8798.00	Asthma control step 5
8B3j.00	Asthma medication review
8CE2.00	Asthma leaflet given
8CMA000	Patient has a written asthma personal action plan
8CR0.00	Asthma clinical management plan
8H2P.00	Emergency admission, asthma
8HTT.00	Referral to asthma clinic
9hA..00	Exception reporting: asthma quality indicators
9hA1.00	Excepted from asthma quality indicators: Patient unsuitable
9hA2.00	Excepted from asthma quality indicators: Informed dissent
9N1d.00	Seen in asthma clinic
9N4Q.00	DNA - Did not attend asthma clinic
9NI8.00	Asthma outreach clinic
9NNX.00	Under care of asthma specialist nurse
9OJ..00	Asthma monitoring admin.
9OJ..11	Asthma clinic administration
9OJ1.00	Attends asthma monitoring
9OJ2.00	Refuses asthma monitoring
9OJ3.00	Asthma monitor offer default
9OJ4.00	Asthma monitor 1st letter
9OJ5.00	Asthma monitor 2nd letter
9OJ6.00	Asthma monitor 3rd letter
9OJ7.00	Asthma monitor verbal invite
9OJ8.00	Asthma monitor phone invite
9OJ9.00	Asthma monitoring deleted
9OJA.00	Asthma monitoring check done

9OJA.11	Asthma monitored
9OJZ.00	Asthma monitoring admin.NOS
9Q21.00	Patient in asthma study
H33..00	Asthma
H33..11	Bronchial asthma
H330.00	Extrinsic (atopic) asthma
H330.11	Allergic asthma
H330.12	Childhood asthma
H330.13	Hay fever with asthma
H330.14	Pollen asthma
H330000	Extrinsic asthma without status asthmaticus
H330011	Hay fever with asthma
H330100	Extrinsic asthma with status asthmaticus
H330111	Extrinsic asthma with asthma attack
H330z00	Extrinsic asthma NOS
H331.00	Intrinsic asthma
H331.11	Late onset asthma
H331000	Intrinsic asthma without status asthmaticus
H331100	Intrinsic asthma with status asthmaticus
H331111	Intrinsic asthma with asthma attack
H331z00	Intrinsic asthma NOS
H332.00	Mixed asthma
H333.00	Acute exacerbation of asthma
H334.00	Brittle asthma
H33z.00	Asthma unspecified
H33z.11	Hyperreactive airways disease
H33z000	Status asthmaticus NOS
H33z011	Severe asthma attack
H33z100	Asthma attack
h33z100	ASTHMA ATTACK
H33z111	Asthma attack NOS
H33z200	Late-onset asthma
H33zz00	Asthma NOS
H33zz11	Exercise induced asthma
H33zz12	Allergic asthma NEC
H33zz13	Allergic bronchitis NEC
TJF7300	Adverse reaction to theophylline (asthma)
U60F615	[X] Adverse reaction to theophylline - asthma

Table 3 Logistical steps of study conduct and estimated time for each step to study completion

Provided estimated timelines for the conduct of the observational study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring are based on the Principal Investigators (PI´s) experience in performing similar pharmacoepidemiology studies with the THIN database.

The timeline of submission of the final report is estimated to be delivered within 24 months after protocol approval and include the following main steps:

Cumulative time period (mths)	Activity	Time AIS * (external provider) of THIN data, mths)	Time PI (mths)
	Final protocol approved by MHRA		
1-2	Ethical approval for studies performed in THIN; MREC (Multicenter Research Ethics Committee)	1-2	
3-4	Quality checking of information in database	1-2	0.5
6-7	Searches in database to identify potential cases and request for free text comments of the identified potential cases		2-3
10	Anonymization of free text comments	3	
12-13	Manual review of computerized records and free text comments (blinded to all exposure information) to identify remaining potential cases for which requests are made to send questionnaires to the general practitioner (GP)		2-3
16-17	AIS to send questionnaire to GP, aiming at a high response rate (around 80-90 %) . Anonymization of data.	4-5	
20-21	PI to review all anonymized information from questionnaires, copies of additional information the GP deemed to be related to the outcome of interest (hospital summaries, consultant referral letters and results of laboratory test) and the computerized profiles to assign case status (blinded for exposure information)		3-4
23	Analyses and draft report provided to AZ		3
24	Final report to be delivered to AZ and AZ to submit to		1

	MHRA		

‘AIS Additional Information Services, Cegedim Strategic Data

Figure 1: Study design