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Antenatal origins of chronic disease – linking antenatal fetal size to chronic disease outcomes in children and young adults

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ABSTRACT

Incurable chronic conditions in childhood which persist into adulthood and common and lead to considerable morbidity and ultimately mortality. Chronic conditions such as asthma, insulin dependent diabetes mellitus (IDDM), epilepsy and attention deficit hyperactivity disorder (ADHD) can be managed with treatment but prevention, as opposed to cure, offers the best promise of reducing prevalence of these diseases. Better understanding of the early origins of these conditions is required before targeted preventative interventions are introduced, and there is evidence that antenatal factors are important determinants of chronic illness in post natal life. Our group has for the first time related antenatal fetal ultrasound measurements to risk for asthma and also to glycosylated haemoglobin (a biomarker for IDDM). In this project we will extend our findings to a larger and older cohort and also explore associations between fetal measurements and epilepsy and ADHD. The overarching hypothesis is that reduced fetal size is an indicator for many different chronic conditions. The student will (i) link fetal and maternal details held on the Aberdeen Maternity and Neonatal Databank to routinely acquired prescribing of asthma medication and hospital admission data held by the Scottish Government and (ii) describe associations between fetal size and growth to IDDM, ADHD and epilepsy identified from prescribing and admission data. The results will be novel and generate a substantial advance in the understanding of fetal origins of chronic disease.

BACKGROUND

There are several common chronic conditions of childhood which persist into adulthood of which asthma is one example. Asthma affects 5.4 million people in the UK and costs the NHS £1 billion per annum1. Although asthma symptoms can be palliated with inhaled steroids, there is no cure. Prevention is the most promising method for reducing the burden of asthma in Britain but better understanding of asthma pathogenesis (and a method to identify at risk individuals) is required. What is understood is that events in early life are important to asthma outcome in both childhood and adulthood.

A number of observations point to important antenatal/perinatal influences on the development of asthma: (i) Reduced birth weight is associated with adult asthma suggesting that fetal growth is important to asthma aetiology2. (ii) Obstructed lung function, a feature of asthma, is present from one month of age in individuals who later develop asthma3 and (iii) obstructed lung function persists from early infancy to at least 22 years of age4. The “fetal origins” of chronic disease hypothesis was first described in 19855 and suggested that physiological adaptations *in utero* alter risk for future morbidity. Only very recently has fetal ultrasound measurement been used as a surrogate for fetal well-being *in utero* and there is now evidence that small fetal size is associated with increased risk for morbidity in support of the fetal origins hypothesis. What is not known is whether small fetal size is the cause or is merely associated with increased risk for NCD due to a common third factor, but in the first instance any association between fetal measurements and morbidity needs to be thoroughly explored.

Ours was the first group in the world to relate fetal ultrasound measurements to asthma outcomes6-8. We used fetal measurements as a surrogate for fetal well-being in a birth cohort of 2000 individuals designed to relate early life exposures to asthma outcomes. We observed an association between persistently reduced fetal size from ten weeks gestation and increased asthma and reduced lung function in five6 and ten year old children7. We also observed how maternal dietary exposures6 and smoking8 may affect fetal growth at different gestations and these findings may be useful for future interventions. Subsequently our results have been replicated in two cohorts9-10 but not a third11. Although the study which found no association between fetal size and respiratory outcomes may be flawed due to imprecise gestational estimate12, our results require confirmation in a population which is larger and has been followed up beyond childhood.

In addition to asthma, there are other chronic conditions where antenatal growth may be important to causation and these include insulin dependent diabetes mellitus (IDDM), epilepsy and attention deficit hyperactivity disorder (ADHD). In a paper currently in submission we have demonstrated an association between first trimester fetal size and a biomarker for poor IDDM control (glycosylated haemoglobin) and this is proof of concept that fetal size may be an indicator for IDDM Although there are no studies linking fetal size to epilepsy and ADHD, in one cohort fetal head circumference has been linked to language difficulties13 which can be a surrogate for abnormal neurodevelopmental development. Given the increasing prevalence of IDDM, ADHD and the relatively high prevalence of epilepsy (1:1000) we will generalise associations we have seen between fetal growth and asthma to these other conditions.

One method to relate fetal ultrasound measurements to asthma and other non-communicable diseases (NCD) would be to recruit a large birth cohort and follow this up for 25 years. An alternative, and our strategy, is to use routinely acquired fetal ultrasound measurements in Aberdeen, which since 1997 have been collected along with an identifier which allows linkage to routinely acquired prescribing records. Individuals with asthma, IDDM, epilepsy and ADHD are treated with condition-specific medications and thus can be reliably identified. One limitation to this approach is that prescribing data are only available from 2009 and therefore cases with transient asthma, epilepsy, ADHD and potentially IDDM could be missed. A smaller number of individuals with asthma, IDDM and epilepsy can also be identified from hospital admission records. The benefits of this approach, compared to recruiting a new birth cohort in 2016, are (i) results will be available in two-three years and not the 25-30 years it would take to recruit the birth cohort and for the individuals to reach adulthood (ii) the cost is a small fraction of the cost of a birth cohort (iii) drop out of a birth cohort is usually 50% over 10-15 years but our approach will endure that fetal scan measurements can be lined to outcomes individuals still living in Scotland (likely to be 80-90%).

Hypotheses

1. Reduced antenatal fetal size and growth are associated with increased risk for asthma (as evidenced by prescription of medications only prescribed for asthma).
2. Reduced antenatal fetal size and growth are associated with increased risk for type I diabetes (as evidenced by prescription of insulin).
3. Reduced antenatal fetal size and growth are associated with increased risk for epilepsy (as evidenced by prescription of anticonvulsants).
4. Reduced antenatal fetal size and growth are associated with increased risk for ADHD (as evidenced by prescription of dexamphetamine).

Aims

The overall aim of this project is to link fetal size and growth to non-communicable diseases in children and young adults. More specific aims are:

1. To link fetal and maternal characteristics to outcomes in the form of dispensed medications to the specified conditions
2. To identify the key timing of growth changes relating fetal measurements to the specified conditions.
3. To describe the sensitivity and specificity of fetal measurements for predicting asthma, IDDM, epilepsy and ADHD.

Plan of investigation

*Study design.* This will be a whole population cohort study. Fetal measurements held on the Aberdeen Maternity and Neonatal Databank (AMND) will be linked to prescribing data held by the Scottish Government’s Information Services Division (ISD). ISD will also provide hospital admission details (from SMR01) which will allow hospitalisation for asthma, epilepsy and IDDM to be linked to fetal measurements. Every individual in Scotland has a community health index (CHI) number and this unique identifier means that Scotland is one of the few places in the world where the proposed linkage can take place.

*Fetal measurements.* In 1985, fetal ultrasound scans became part of routine antenatal care in Aberdeen. Fetal measurements were entered into maternal case notes and we have already demonstrated that fetal measurements can be retrieved from paper records, entered onto an electronic database and linked to post natal outcomes6-8. The first trimester measurement will be crown rump length, and second trimester measurements will be head circumference, femur length and abdominal girth. Fetal size, i.e. crown rump length, biparietal diameter and femur length, will be expressed as an absolute measurement and also as a z score as previously6. Gestation at scan will be recorded. We have described the strengths and limitations of using fetal measurements as a surrogate for fetal wellbeing14. In one third of pregnancies, where maternal dates of last menstrual period (LMP) are uncertain, fetal gestation is determined by first trimester scan. This is an important potential confounder which we acknowledge and can address by subgroup analysis of those individuals whose maternal LMP is certain but our primary fetal measurements will be from the second trimester since we know that the gestation at these scans are more reliable than for first trimester scan.

*AMND*. The AMND was established in the 1950 and holds details of pregnancy, labour and delivery for each infant born in Aberdeen (http://www.abdn.ac.uk/amnd/). Permission will be sought from the AMND steering committee to access the following data from singleton term pregnancies: infant CHI number, gender, first, second and third trimester fetal measurements, gestation at first, second and third trimester measurement, gestation at birth, and birth measurements (i.e. crown heel length, head circumference and birth weight), maternal age (decimal), maternal deprivation index (Carstairs), maternal smoking status, maternal parity, maternal chronic illness (defined as receipt of medications specific for asthma, IDDM, epilepsy and ADHD), maternal weight and height, and maternal gestation at booking. For pregnancies where more than one scan takes place during an assessment, our standard approach is to use the scan closest to 12, 20 and 32 weeks gestation and the older of two scans in the rare instance that two scans are equally close to these gestations. Individuals with severe congenital anomalies will be excluded, e.g. trachea-oesophageal fistula, tetralogy of Fallot.

*Information Services Division (ISD)*. ISD holds the Prescribing Information Systems (PIS, [http://www.isdscotland.org/Health-Topics/Prescribing-and-medicines/Prescribing-Datamarts/#pis](http://www.isdscotland.org/Health-Topics/Prescribing-and-medicines/Prescribing-Datamarts/" \l "pis)) which contains details of primary care prescriptions issued in Scotland since April 2009. We know that 96% of prescriptions in Scotland have the patient’s CHI number and can therefore be linked to fetal size. Our primary outcome will be prescription of disease-specific medication (*see addendum for specific definitions to be used*). The secondary outcomes will be admission to hospital for asthma, epilepsy and IDDM. Additionally, and to make best use of the data collected, we will determine indices of asthma control (as evidenced by number of reliever medication inhaler/year, also see addendum), asthma exacerbation (as evidenced by prednisolone use/year) and asthma severity (as evidenced by British Thoracic Society treatment step ranging from 1 to 5 where treatment is stepped up and down according to symptoms and also age, http://www.sign.ac.uk/pdf/qrg101.pdf). The combined database containing fetal and maternal details will be merged with the ISD database holding prescribing and admission data (a process called “cross-warehouse analysis”) within the ISD safe haven. To assure confidentiality, the CHI will then be stripped out of the database, rows sorted randomly and the database returned to Aberdeen through nhs.net. The database will be stored in the Grampian Safe Haven.

*Analysis*.  The primary outcome will be receipt of >1 prescription of disease specific medication for each year from 2009 (when ISD started) to 2016 inclusive. Data collected on all participants will be described using number or percentage in each category or mean and standard deviation for normally distributed continuous variables (or median and inter-quartile range if skewed). Computing clustering techniques will be used to find associations (if any) between fetal growth and NCDs (such as asthma, epilepsy, ADHD and type II diabetes). The idea is that by using an unsupervised learning algorithm, a computer might be able to find these associations purely on the data's characteristics, this will remove any statistical assumptions which might bias any results. The software will be written in R, the statistical programming language, it was chosen due to a strong online support community and large repositories that haven been written over the years by other programmers.

*Power*.This calculation is based on asthma since this is where we have robust data to inform a power calculation.  Assuming 5000 deliveries per year and scans available between 1985 and 1996, there will be as many as 60,000 scan results to enter into the database; our experience is that the actual figure will be closer to 55,000 as some mothers do not have ultrasound scans and some scan results will be misplaced.  On a *pro rata* basis we will expect 20,350 (37%) to have persistent high growth, 16,500 (30%) persistent low growth, 11,000 (20%) growth acceleration and 7,700 (14%) growth deceleration between the first and second trimesters8.  We shall assume that the prevalence of asthma (as evidenced by receipt of more than one inhaled corticosteroid prescription in 6 months) is 10% in the persistently low group and 5% in the persistently high group. Using a two group chi-squared test with a 1% two-sided significance level will have greater than 90% power to detect the difference between a Group 1 proportion of 0.100 (persistent low group) and a Group 2 proportion of 0.050 (persistent high group) (odds ratio of 0.474) suggests samples of at least 824 in each group indicating that the sample sizes of 16500 and 20350, respectively will be sufficient.

*Permissions and governance*

Approval for this proposal will sought from the Privacy Panel for Health and Social Care (PBPP), the North of Scotland Research Ethics Committee and the Steering committee of the AMND.

*Time Lines*

01/06/16. Submit applications for approval

01/10/16. Receive all approvals

01/11/16. Linkage commences

01/02/16. Linkage completed. Analysis commences

01/05/16. Analysis complete.

*Funding*

The PhD studentship and costs for linkage have been paid for by the FARR institute

*Dissemination*

The results will be published as part of Mr Chapman’s PhD thesis and also submitted for publication to a journal such as the International Journal of Epidemiology or Journal of the American Medical Association.

*Patient and public engagement*

This study will be specifically discussed with members of the public at the Mayfest (28th May 2016).

**REFERENCES**

1. Asthma UK. <http://www.asthma.org.uk/news-centre/facts-for-journalists/>
2. Shaheen et al. Birth weight, body mass index and asthma and young adults. Thorax 1999;54:396-402
3. Turner SW, et al. The relationship between infant airway function, childhood airway responsiveness and asthma. Am J Respir Crit Care Med 2004;169:921-927
4. Stern DA. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007; 370: 758–764.
5. Barker DJ. Fetal origins of coronary heart disease. Br Med J 1995;311:171–174
6. Turner SW, et al. Associations between fetal size, maternal α-tocopherol and childhood asthma. Thorax 2010;65:391-397
7. Turner S, et al. First and second trimester fetal size and asthma outcomes at age ten years. Am J Respir Crit Care Med 2011; 184:407-413
8. Prabhu N, et al. First trimester maternal smoking habits and fetal growth. Thorax 2010;65:235-40

9. Pike KC, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010;65:1099–1106

10. Hall G, et al. Increased fetal growth protects against early wheeze, airway hyper-responsiveness (AHR) and current asthma in early mid-childhood: Results from the Raine birth cohort (abstract). Eur Respir J 2011;38:S569

11. Sonnenschein-van der Voort AM. Fetal and Infant Growth and Asthma Symptoms in Preschool Children: The Generation R Study Am J Respir Crit Care Med 2012; 185: 731-737

12. Turner S, Devereux G. Fetal Ultrasound: Shedding Light or Casting Shadows on the Fetal Origins of Airway Disease. Am J Respir Crit Care Med 2012 185: 694-695

13. Whitehouse AJ, Zubrick SR, Blair E, et al. Fetal head circumference growth in children with specific language impairment. Arch Dis Child 2012;97:49–51.

14. Turner S. Perinatal Programming of Childhood Asthma: Early Fetal Size, Growth Trajectory during Infancy, and Childhood Asthma Outcomes. Clin Dev Immunol 2012; 2012, Article ID 962923