Long term and current medication use and risk of complicated diverticular disease in England and Denmark

Section 1 – Project Details:

Maximum 800 words, using the following headings

Rationale

Complications of diverticular disease such as perforation and abscess account for the majority of the morbidity and mortality associated with diverticular disease[1]. They have recently been highlighted as a top ten research priority by the Association of Coloproctologists of Great Britain and Ireland[2]. Given the age and comorbidity of these patients and the high risks of stoma formation and death following surgery there has been interest in identifying risk factors for their development[3].

Medications notably corticosteroids, opiate analgesics and non-steroidal anti-inflammatory drugs (NSAIDS) have been suggested in previous studies, including some of our own, as potential risk factors for perforation[3-8] while calcium antagonists may be potentially protective against perforation[5]. There are biologically plausible explanations for the development of perforation with exposure to these drugs [4, 5]. Statins have also emerged as potential anti-inflammatory agents and may confer protection against complications[9].

Prior studies have focused on perforated disease neglecting diverticular abscess and have in general been small, principally retrospective, and used self-reported medication use or hospital admission to identify the exposure. In addition to these limitations in population selection and exposure measurement there has been little attempt to measure and adjust for potential confounding factors such as smoking, comorbid illness and body mass index (BMI). Similarly, to take account of confounding by indication a prospective record of symptoms is required to avoid recall bias. We now have linked primary and secondary care data available in the UK and Denmark which gives us a continuous healthcare record with accurate recording of date of diagnosis of complication which is essential to addressing the relationship between prior and current use of medication and the development of complications. It may also be that these associations are due to residual confounding so to account for this we will undertake state-of-the-art within person self-controlled case-series analysis and also investigate the relationship with other medications such as anti-depressants which have no obvious biologically plausible explanations to account for any identified relationship.

Aims and Methodology

The aims of our study are to;

1. Describe prescription medication use in people with complicated diverticular disease, with a focus on NSAIDS, opiates, corticosteroids, calcium channel blockers and statins.
2. Quantify the association between prescription medication use and occurrence of complicated diverticular disease.
3. Identify risk groups for complicated diverticular disease based on age, sex, comorbidity and prescription medication use and develop and validate a risk prediction algorithm.

We have identified 5000 incident cases of diverticular abscess and perforation from linked primary (Clinical Practice Research Datalink(CPRD)) and secondary care data (Hospital Episode Statistics). The cases will be compared to all people with diverticular disease from the CPRD who have not had a complication and a frequency matched general population group. The cases in Danish data will be compared to a frequency matched Danish general population group. Drug exposure will be determined for each drug as current or ever use with reference to the date of complication (for cases) or the corresponding date among controls. We will undertake case control studies using logistic regression accounting for comorbidity, BMI and smoking. We will perform self-controlled within person case series analyses to minimize the risk of residual confounding. For derivation of the risk prediction model, we will initially include all candidate predictors in a multivariable logistic regression model. We will form the risk equation for predicting the log odds of complicated diverticular disease by using the estimated β coefficients multiplied by the corresponding predictors included in the model. The model will be validated in Danish Registry data through our collaboration with Aarhus University.

Benefits and suitability as a PhD project:

The supervisory team and the external partners have, between them, extensive experience of using these data for the studies proposed and, specifically, expertise in the disease and methodology. Big data is an expanding area and a research strength in Nottingham with 3 of the leading primary care database researchers in the world located in Nottingham with Professor West being one of them. The project is clearly defined and will deliver significant outputs which will be returnable by the NIHR BRC. By combining the strengths of the NDDC and EPH the candidate will have access to the epidemiology and statistics training in EPH and the clinical translational training activity in the GI theme of the BRC. This project will allow the candidate to work with UK and international healthcare "big" data and establish a strong collaborative link with a leading international group in this field. This project may well lead to the identification of a group of patients with prior diverticular disease in whom the presecription of particular drugs and their underlying risk factors from comorbidity place them at a high risk of complication. This information could be used to identify patterns of potentially unsafe prescribing in primary care that could be avoided through proven interventions[10].

Key References:

Section 2 – Training Provision:

Maximum of 250 words. Please detail the training provision that will be made available to the student.

This project will train the candidate to become an expert in the use of routinely collected healthcare data with studies in data from the UK and Denmark. Alongside the current taught PhD course requirements the candidate would apply basic and advanced methods of data management along with analysis in undertaking the project. For those with little experience of database research modules on the Masters in Public Health course would be taken to require the basic skills needed to undertake the project. The candidate will also get training in risk prediction modelling via an external course run at Keele University, by a close collaborator of Professor West. The student would work alongside our current team of Post-Doc’s and PhD student and be offered all the supervisory support required to complete the PhD. Given the field and prior track record we anticipate the student to obtain experience in National and International presentations as well as peer reviewed publications. This project which would sit across two Schools in the University would position the candidate well for a future post-doctoral career in pharmaco-epidemiology and health informatics both in the UK and abroad. We will also support the candidate in obtaining a mentor thorough the University of Nottingham Mentor scheme. They will contribute to the GI Epidemiology group meetings and the BRC weekly meetings, and there will be opportunities to spend time working at the Department of Clinical Epidemiology in Denmark.