Route Choice

I will be applying for the 1+3 pathway with a MSc [removed] at [removed]. My undergraduate degree in [removed] provided some taught statistical courses and this Masters programme will provide me with an opportunity to further develop my practical skills and knowledge of statistical methods in preparation for the following research proposal. In the future, this will enable me to contribute to the growing area of big-data analysis with a focus on reproductive and women's health.

Research Proposal

Title

Identification of teratogenic effects of medications through analysis of groups of anomalies.

Background

Several medications are teratogenic when taken in the 1st trimester of pregnancy, however the risk to the fetus of most drugs is undetermined (1). Clinical trials fail to assess possible effects of new medications on a fetus as pregnant women are purposefully excluded; randomised control trials would be unethical; and the effects of medications on animal models are not always comparative to humans due to differences in developmental pathways (2). Identification of teratogenic medications, therefore, requires careful analysis of observational data on congenital anomalies occurring in exposed pregnancies in the clinical setting.

Although around 2-3% of pregnancies are affected by a birth defect, specific birth defects are rare. Therefore, the analysis of very large numbers of exposures is required to identify statistically significant effects for specific birth defects. Previous statistical methods for teratogen identification using EUROmediCAT data has focused on identifying increased occurrence of single defects (3). However, teratogen exposure often results in constellations of defects dependant on timing, dosage and genetic interactions. Analysis of a group of birth defects may produce a statistically significant result when separate analysis of the single defects did not, implicating the medication as associated to the pattern of defects.

Most pregnant women take prescribed or over-the counter medications in the 1st trimester of their pregnancy (4). In many cases the medication is imperative to the health of the woman and cannot be avoided. In some cases, a woman who is taking medication may not know she is pregnant until after organogenesis has begun. In this project I will produce a statistical methodology to increase the ability to identify teratogenic medications through analysis of groups of birth defects. This methodology will be developed on the EUROmediCAT data set currently available but can be repeated for EUROmediCAT as new cases are reported, and can also be applied to other datasets. It will provide information on potential teratogens and will therefore influence targeted evidence gathering for these medications. This evidence can be used to help women and healthcare providers make better decisions when balancing the risk and benefit of medications taken during pregnancy.

Hypothesis and Aims:

Hypothesis**:** Statistical analysis of groups of birth defects allow for identification of new teratogenic effects of medications taken in the 1st trimester of pregnancy.

The project has two key aims:

- Development of a statistical methodology for assessing associations between medications and groups of anomalies.
- Identification of new medication-birth defect associations

Any new associations identified would require further research to confirm a causal link. Literature review assessing if the associations identified makes biological sense would form part of the assessment of the validity of the pipeline, but experiments attempting to confirm causality would be out of scope of this project.

Method

Year 1: The project would use EUROmediCAT data (5) consisting of over 33,000 pregnancies, to develop and assess the validity of the methodology. Development of an initial method for grouping of

anomalies would include testing the effect of groupings on a subset of the dataset and refining until appropriate groupings are produced. This will be done before any statistical analysis to prevent bias towards already known teratogens. I will program a computational algorithm for consistent reproduction of the grouping methodology for the dataset.

Year 2: A statistical analysis approach will be decided before the start of the project, considering methods learnt from the MSc. A random split of the cohort will allow for initial analysis and replication. If results do not replicate, grouping methodology may be re-visited. If results replicate, analysis will be repeated using the whole dataset to increase statistical power.

Year 3: Evaluation of the methodology will include results of replication, identification of new teratogenic effects and a literature review to check that associations make biological sense. Write up of results.

Previous Experience and Future Work

Working for the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) for the past 3 years, I have developed a detailed understanding of congenital abnormalities that will assist in the development of the grouping method and literature review for this project. Also, I already understand the dataset to be used through involvement in reporting cases to EUROCAT. Working for NCARDRS has allowed me to understand the impact that diagnosis of a congenital malformation has on a mother and family. Consequently, I feel strongly about the importance of research into this field.

In my undergraduate degree I have developed programming skills that will assist with the development of the algorithm and statistical analysis. This has included Chi-squared, ANOVA, correlation and regression analysis, analysis of complex genetic datasets, and general Turing-complete programming. Undertaking an MSc in Medical Statistics will build upon this, improving these skills.

This project would allow me to further develop the research skills I will require for future work. Following on from this PhD, I would be looking to continue research in this area, using big-data statistical analysis and modelling to look at gene-medication interactions during pregnancy and their effect on development.

References

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3. Luteijn JM, Morris JK, Garne E, Given J, de Jong-van den Berg L, Addor MC, et al. EUROmediCAT signal detection: a systematic method for identifying potential teratogenic medication. Br J Clin Pharmacol. 2016;82(4):1110-22.

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