Final Report—OECD CRP Fellowship

Name: Geoffrey H. Donovan

Title: Exposure to plant diversity and the risk of acute lymphoblastic leukaemia (Theme 1: Managing Natural Capital for the Future)

Host Institution: Centre for Public Health Research, Massey University, Wellington, New Zealand

Host Collaborator: Dr. Jeroen Douwes

Dates of Fellowship: March 1, 2019 to May 23, 2019

I consent to my report being posted on the website of the cooperative research program.

1. **What were the objectives of the research project? Why is the research project important?**

The primary objective of my research project was to test the hypothesis that exposure to plant diversity can protect against childhood acute lymphoblastic leukaemia (ALL). My research also had two secondary objectives. First, identify the best plant-diversity metrics to use in studies of biodiversity and human health. Second, establish working relationships with scientists at the Centre for Public Health Research.

Background

Acute lymphoblastic leukaemia (ALL) is the most common paediatric cancer affecting 1 in 2,000 children. The incidence is highest in wealthy countries and is rising by approximately 1% per year. Although the cure rate is around 90%, the required combination chemotherapy can lead to lifelong health problems. ALL is believed to develop in two discrete steps. First, an in utero genetic change generates a pre-leukemic clone, which predisposes to ALL. Second, an infection induces a secondary genetic change in a small proportion (<1%) of susceptible children resulting in overt leukaemia. Paradoxically, although infection is the proximal cause, microbial exposure in early life, a critical step in immune maturation, may reduce the risk of the dysregulated immune response that triggers the development of ALL. This mechanism is consistent with the hygiene hypothesis, which suggests that modern Western lifestyles, characterized by restricted microbial exposure, may increase susceptibility to a range of chronic conditions, including allergies, asthma and other immune disorders. Although direct evidence that this plays a role in ALL is lacking, epidemiological studies have shown that day care-attendance and older siblings (both associated with increased microbial exposure) may be protective, whereas Caesarean delivery (less microbial exposure) may be a risk factor. Indeed, a recent review of the causal mechanisms of ALL noted that through early-life microbial exposure “most cases of childhood ALL are potentially preventable”.

A necessary condition for diverse microbial exposure is diverse microbial habitat, an important source of which is plants. There are 391,0008 known plant species with a total leaf area of 1,017,260,200 km2 (twice the world’s land area) supporting ~10^{26} bacterial cells, which influence surrounding microbial ecology. Specifically, proximity to plant diversity is associated with increased microbial diversity in the air and on human skin.

Sample

We followed all children born in New Zealand from 1998-2011 (n=898,926) for five years. Data on outcomes and covariates were obtained using Statistics New Zealand’s Integrated Data Infrastructure (IDI), which is a collection of linked individual-level databases for approximately 95% of New Zealand residents. We chose this sample frame, because addresses in the IDI are unreliable before 1998, and, because of a reporting lag, 2011 was the latest year that allowed us to follow children for five years.

2. **Were the objectives of the fellowship achieved?**

Yes, all three objectives were achieved. Specifically, I found that children who have more plant diversity in their residential neighbourhood were at a reduced risk of developing ALL (figure 1). Figure 1 shows that children who were exposed to plant diversity that was one standard deviation higher than the mean were at an up to 15% lower risk of developing ALL depending on when the exposure occurred (exposure during the first three years of life offered the greatest protection).

I also successfully achieved my two secondary objectives. I used data from the Global Biodiversity Information Facility (GBIF) to create plant-diversity metrics at different taxonomic scales. The GBIF contains >1 billion geocoded plant records of which 2,057,987 are in New Zealand. Most of these come from systematic surveys by government agencies, although some were collected by individuals participating in the iNaturalist Program. Using GBIF data, I found that plant diversity at the genus level was most protective of ALL (figure 2).

I was also able to form strong working relationships with several scientists in New Zealand. I have already secured an additional research fellowship to return to New Zealand next year and continue this work. In addition, my New Zealand colleagues and I have written a joint grant proposal to the New Zealand Health Research Council to explore the mechanisms linking the exposure to the plant diversity and a decreased risk of allergic disease.

3. What were the major achievements of the fellowship?

The most important achievement of my fellowship was to show that exposure to plant diversity is protective of ALL.

4. Will there be any follow-up work?

Yes. I will return to New Zealand for four months next year to continue this line of research. Specifically, I'll be focusing on the relationship between exposure to plant diversity and the risk of developing other immune diseases such as type I diabetes, lupus, and multiple sclerosis. In addition, my New Zealand colleagues and I have written a NZ$1.2 million grant proposal to look at the relationship between exposure to the natural environment and the composition of human gut biome. Finally, in the next 2-3 months, I will be submit my research findings to *The Lancet Planetary Health.* I anticipate publication in early 2020.

5. How might the results of your research project be important for helping develop regional, national or international agro-food, fisheries or forestry policies and, or practices, or be beneficial to society?

ALL is the world's most common paediatric cancer, and there are currently no public health interventions to reduce ALL risk. Therefore, my results, showing that exposure to plant diversity is protective of ALL, have clear international significance for the management of natural resources. In addition, my results are a clear empirical link between biodiversity and human health. If my findings are confirmed, they will provide support for policies to compensate farmers and other land owners for the public-health benefits they are providing. In addition, my findings suggest city planners should consider policies that increase exposure to plant diversity.

6. How was the research relevant to the objectives of the CRP and the CRP research theme?

My research falls under theme 1 of the CRP: Managing Natural Capital for the Future. In particular, the biodiversity sub-theme notes the need for research on "subsidies for biodiversity". Demonstrating that plant diversity is protective of ALL will help land managers and policy makers set appropriate subsidies to encourage the retention and enhancement of biodiversity.

7. Satisfaction

My OECD CRP fellowship was a very positive experience. I was able to successfully address my research question, and I made some professional connections that will be invaluable to my continuing work on the public-health benefits of exposure to the natural environment.

8. Advertising the CRP

I heard about CRP from a colleague at the USDA Forest Service (Robert Deal). If it wasn't for this contact, however, I would never have heard of CRP. This is surprising given that CRP fellowships are very desirable. The high success rate of CRP applicants—compared to other fellowship programs—also suggests that many potential CRP applicants don't know about the program. One possible solution to this problem is to try and attract scientists from outside agriculture, fisheries, or forestry. For example, although my research addresses a CRP theme, it does so from a public-health perspective.

Figures

Figure 1: Association between exposure to plant diversity and the incidence of acute lymphoblastic leukaemia for all children born in New Zealand from 1998 to 2011 (n=890,085) controlling for number of older siblings, mother's age, and urban residency. Results are shown for exposure to plant diversity across five different age ranges (age 0-1, 0-2, 0-3, 0-4, and 0-5).

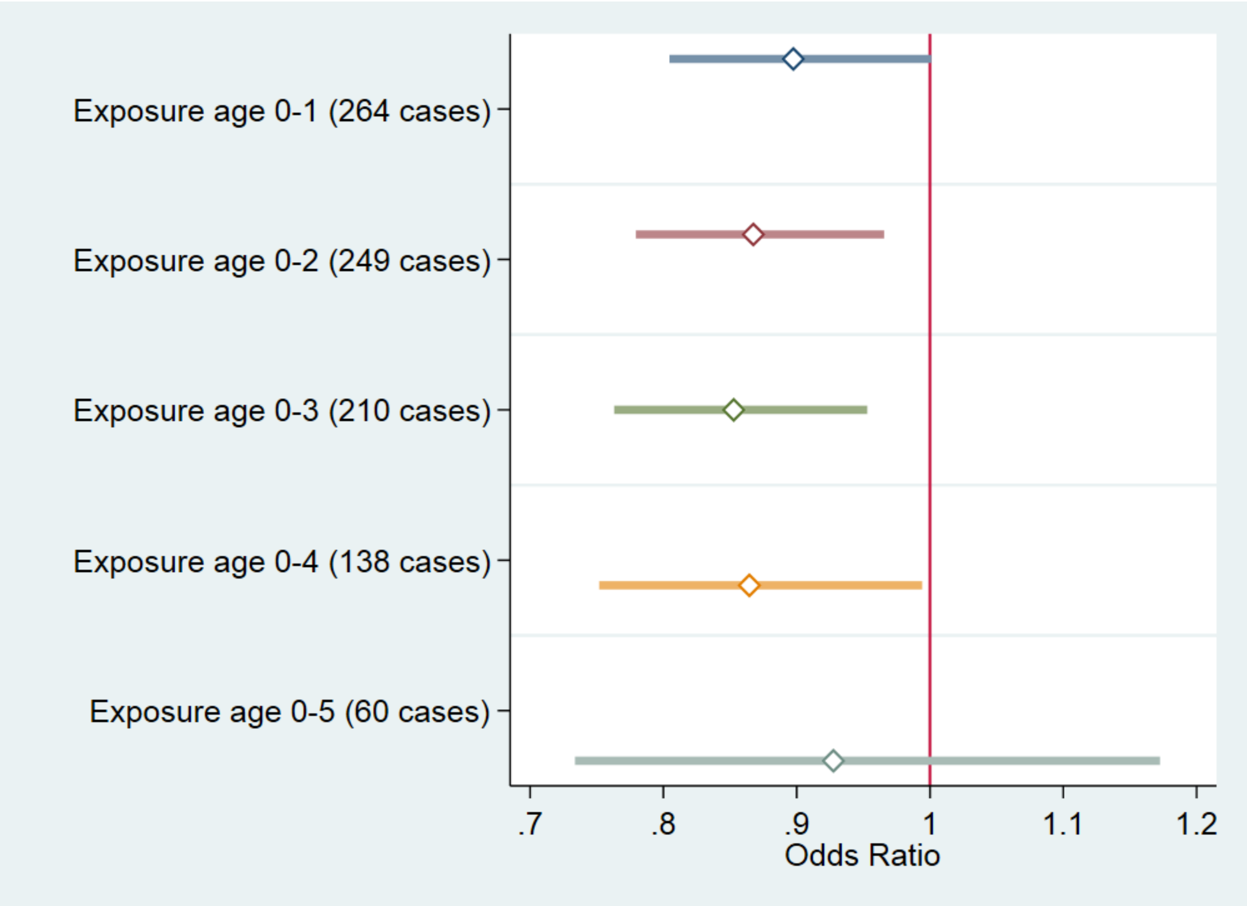
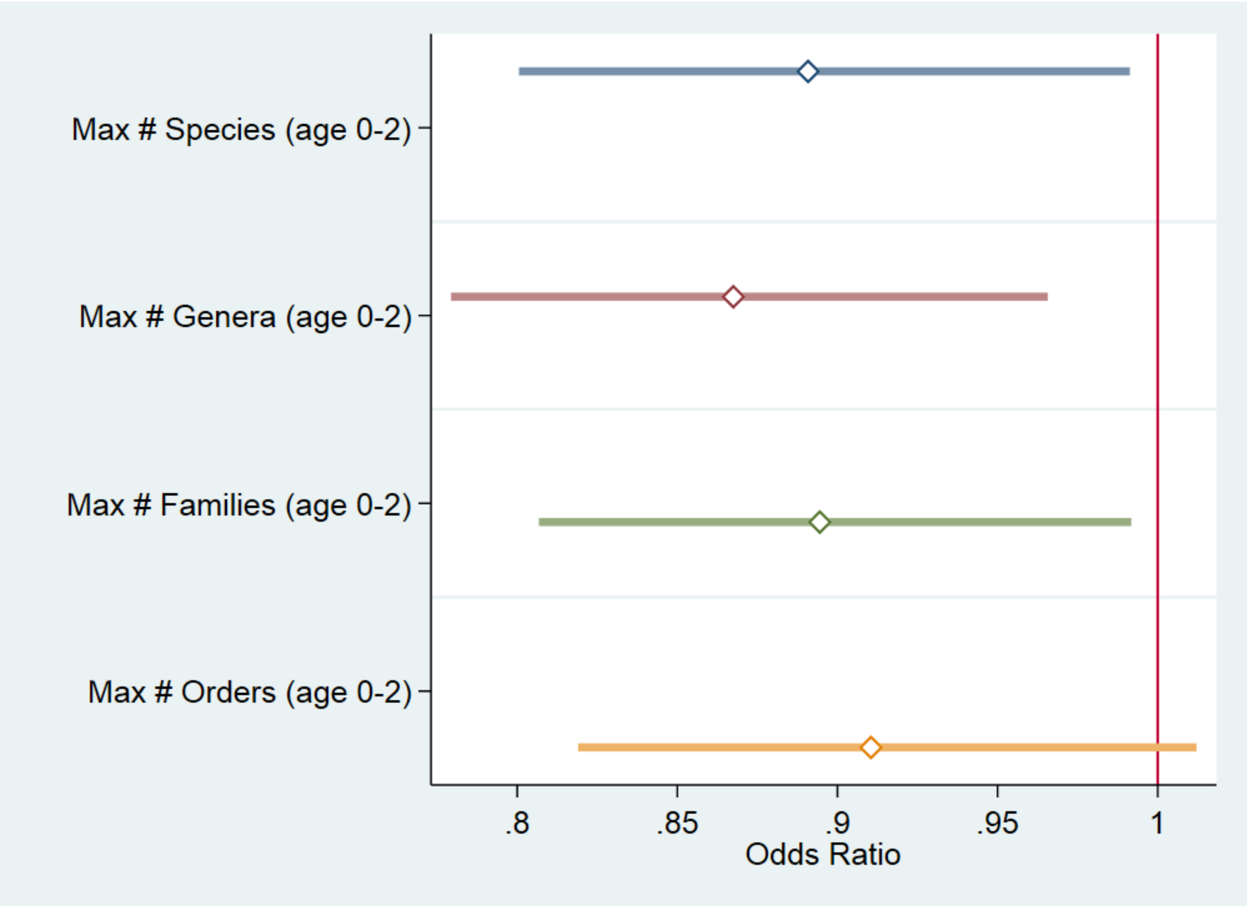


Figure 2: Association between exposure to plant diversity at four different taxonomic scales (species, genus, family, and order) during the first two years of life and the incidence of acute lymphoblastic leukaemia for all children born in New Zealand from 1998 to 2011 (n=890,085) controlling for number of older siblings, mother's age, and urban residency.



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