

# The place of population mixing in the aetiology of disease: a New Zealand perspective

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It is widely recognised that migration and health are linked. Movements of people to new environments has been noted for having both positive and detrimental impacts on the health of those who move, those they join, and those they leave behind. One emerging area of research in the field of migration and health has been the role of population mixing in influencing population health. Population mixing can be defined as the movement and interaction of people over time and space, and can have a direct influence on local disease rates through the introduction of infections to susceptible populations. As well as increasing the risks of communicable diseases, population mixing has been implicated in the development of childhood leukaemia and type 1 diabetes. This paper reviews the growing body of research which links population mixing to these diseases, and highlights key priorities for future research.

### Introduction

Research in epidemiology, geography and public health has shown that where people live influences their health, independently of individual socio-demographic characteristics.<sup>1</sup> For example, researchers have found associations between health and environmental characteristics of places such as exposure to air pollution and radon gas, features of the built environment including access to shops selling health food or high levels of green space, as well as social features such as levels of crime or social capital.<sup>2</sup> One characteristic of places that has received increased attention has been the study of population movements between places over time. It is widely recognised that migration and health are linked, with movements of people to new environments having both positive and detrimental impacts on the health of those who move, those they join, and those they leave behind.<sup>3,4</sup> One emerging area of health and migration research has been the role of population mixing in influencing population health. Although population mixing has been defined in diverse ways,<sup>5-7</sup> it can be broadly described as the movement and interaction of people over time and space. Population mixing can have a direct influence on local disease rates through the introduction of infections to susceptible populations,<sup>8</sup> and has been implicated in the development of

the childhood diseases of acute lymphoblastic leukaemia<sup>9</sup> and type 1 diabetes.<sup>10</sup> Childhood leukaemia and type 1 diabetes have many epidemiological and potential aetiological factors in common.<sup>11,12</sup>

Although the role of infections in the aetiologies of both diseases has been considered for some time,<sup>13-16</sup> links with population mixing are relatively recent<sup>7,8,17</sup> and remain poorly understood. This paper reviews the growing body of research which links population mixing to the aetiologies of childhood leukaemia and type 1 diabetes and is organised into three sections. The first two sections review current research on the association between population mixing and both childhood leukaemia and type 1 diabetes, while the third summarises this literature and highlights some priorities for future research.

### Population mixing and childhood leukaemia

Leukaemia is a cancer of the bone marrow<sup>18,19</sup> and although overall incidence is rare, it is one of the most common childhood malignancies.<sup>20,21</sup> Since the mid 1960s there has been a significant increase in the incidence of leukaemia among New Zealand children consistent with similar rises reported in other affluent populations.<sup>21,22</sup> Although the aetiology of this disease remains uncertain, both genetic and environmental factors have been associated with its development. The final event that precipitates the onset of leukaemia however, is most likely to be environmental.<sup>23</sup>

Infections were initially implicated as an environmental trigger in the early twentieth century.<sup>24</sup> This followed observations that the age distribution of leukaemia was similar to that of common childhood infectious diseases, and also that many patients had infections before or coincident with diagnosis.<sup>25</sup> Infection as a cause lost favour when it was recognised that leukaemia was not contagious<sup>16</sup> but is now being reconsidered due to the discovery of viruses as causative factors in adult T-cell leukaemia<sup>26</sup> and in leukaemia in domestic cattle, cats and chickens.<sup>25</sup> Work by Greaves<sup>17</sup> has since shown that at least two genetic mutations are required for childhood leukaemia to develop, with the first mutation usually occurring in the uterus. His 'delayed infection' hypothesis postulated that the second mutation could be triggered some years later by infection. A central tenet of this hypothesis is that the immune system is programmed to anticipate infectious exposure neonatally and in infancy. Absence of infections in early life (a feature of affluent hygienic societies),

thus leaves the immune system weak, and subsequent exposure to infection can place undue stress on the body, resulting in the onset of leukaemia.<sup>25</sup>

Research linking childhood leukaemia incidence to population mixing began in the early 1980s in the United Kingdom after apparent clusters of the disease were reported around the nuclear reprocessing plants of Sellafield and Dounreay. Subsequent research showed that the excess of leukaemia cases around the plants could not be explained by levels of radiation in the environment,<sup>27,28</sup> or by paternal occupation at the plants.<sup>29,30</sup> Epidemiologist Leo Kinlen noted that the increases in leukaemia occurred after an influx of migrant professional workers to these previously remote areas.<sup>7</sup> Consequently, he hypothesised that childhood leukaemia is a rare response to a common infection introduced through population mixing to non-immune children. This is consistent with Greaves' delayed infection hypothesis.<sup>17</sup> He tested his theory by examining leukaemia mortality in Glenrothes, a new town in rural Scotland with no nuclear plants and which experienced a doubling of its population in the 1950s and 1960s. A significant excess of leukaemia deaths (7 observed, 1.5 expected) was found in those aged under 5 years for the period of greatest population growth. Following directly on from this study, Kinlen, Clarke and Hudson<sup>31</sup> inspected leukaemia mortality in other new towns in the United Kingdom. These were separated into two categories: overspill new towns, where the majority of new residents came from adjacent urban areas, and rural new towns, with incomers from diverse origins. The density of children was higher in the rural new towns compared with the areas where the incomers originated, with the converse true for the overspill new towns. These two factors were postulated to encourage a greater rise in the appropriate infection in the rural new towns, with the potential to trigger excess cases of leukaemia. The results supported this theory and showed a significant increase in leukaemia deaths at ages 0–4 years in the rural new towns between 1946 and 1965.

Kinlen's subsequent work has investigated the occurrence of childhood leukaemia in the UK and Europe using various population mixing measures, at both the area and individual level. At the area level, for example, significant excesses of childhood leukaemia were found in areas which experienced increased commuting;<sup>32</sup> in rural areas of England and Wales which witnessed an influx of military personnel;<sup>33</sup> in rural areas of Scotland which received a large influx of oil workers;<sup>34</sup> in rural areas of England and Wales with a high proportion of war-time children evacuees from London;<sup>35</sup> near large rural construction sites in Pembrokeshire and in Scottish hydroelectric counties while construction was underway;<sup>36</sup> in countries in Europe with high levels of rural migration;<sup>37</sup> in Orkney and Shetland when troops outnumbered local people during the second world war;<sup>38</sup> and in West Cumbria when the construction and operation of Royal Ordnance factories resulted in influxes of workers to the area.<sup>39</sup> Individual level analyses have shown leukaemia incidence to be higher in children with fathers in very high contact occupations, especially those working in transport and construction, in the UK as a whole,<sup>40</sup> in rural areas of Scotland,<sup>41</sup> and in rural counties of Sweden.<sup>42</sup>

Work by other researchers overwhelmingly supports the general findings of Kinlen and colleagues; that increased levels of population mixing are significantly and positively associated with childhood leukaemia. Almost all of these studies are ecological in design, with most using population growth as a way of measuring population mixing. Of these studies, work conducted in Hong Kong,<sup>43</sup> Canada<sup>44</sup> and the USA<sup>45</sup> support the UK findings. Studies using more complex measures of population mixing, such as the proportion of in-migrants and the diversity of origins of in-migrants to an area, generally support the trends noted for population growth<sup>46–51</sup> with four exceptions. Ecological work concentrated in Yorkshire in the UK between 1986 and 1996 found childhood leukaemia incidence to be significantly lower in areas of high population mixing, and significantly higher in areas of low population mixing.<sup>6</sup> These results are supported by further ecological work carried out in Yorkshire by Feltbower and colleagues<sup>52</sup> and by a case-control study of children with leukaemia in England, Scotland and Wales.<sup>5</sup> The only study conducted in New Zealand found no significant relationship between age-adjusted rate ratios for childhood leukaemia in three population growth areas in the 1950s in the North Island when compared to the rest of New Zealand.<sup>53</sup>

### **Population mixing and childhood type 1 diabetes**

Childhood type 1 diabetes is a chronic autoimmune disease, the incidence of which is rising in many parts of the world,<sup>54–57</sup> including Australia<sup>58,59</sup> and New Zealand.<sup>60</sup> Although the precise aetiology of the disease remains unclear, it is widely recognised that both genetic and environmental factors are important.<sup>61–64</sup> No single environmental agent has been identified but evidence from animal studies<sup>65–67</sup> and serological and epidemiological studies<sup>68–71</sup> suggests an important role for infections.

One theory regarding the protective role of infections, the hygiene hypothesis, postulates that reduced exposure to common microbial infections in early life can increase the risk of type 1 diabetes in childhood.<sup>10,72</sup> The hygiene hypothesis has an essentially similar immunological argument to Greaves' delayed infection hypothesis<sup>17</sup> formulated to explain the development of childhood leukaemia.<sup>25</sup> An ecological study in Northern Ireland found indirect evidence to support the hygiene hypothesis. A significantly lower incidence of childhood diabetes was found in areas of both high population density and high levels of household overcrowding. A possible explanation is that children living in these areas were exposed to common infections in early life conferring protection against the subsequent development of type 1 diabetes.<sup>73</sup> A similar inverse relationship with population density and household overcrowding was noted in Northern England,<sup>74</sup> and with population density alone, in Scotland<sup>75</sup> and Finland.<sup>76</sup>

A case-control study conducted in Southampton, England, into early infection and subsequent onset of type 1 diabetes acted as a more direct test of this hypothesis. The findings showed that infection during the first year of life was associated with a reduction in diabetes risk.<sup>69</sup> Children in a Lithuanian case-control study were also less likely to develop diabetes if they experienced one or more infections in the first six months of life.<sup>77</sup> A further case-control study in Yorkshire investigated the link between childhood type 1 diabetes and early social mixing as measured by attendance at day-care facilities and infections occurring under one year. Attendance at day-care centres for infants below one year of age showed a significant inverse association with childhood diabetes. There was also a reduced, but non-significant, risk of diabetes for children experiencing any episodes of infection before their first birthday.<sup>70</sup> Pre-school day-care attendance was also found to be inversely associated with childhood diabetes in data from seven European population-based registers.<sup>78</sup>

At the area level, population mixing variables have recently been used by researchers as a proxy for measuring exposure to infections, and therefore to test the hygiene hypothesis. Similar measures of population mixing to those used in studies of childhood leukaemia have been employed. For example, work by Parslow and colleagues<sup>8</sup> measured the diversity of origins of incoming migrants to electoral wards in Yorkshire following Stiller and Boyle.<sup>51</sup> Regression models were then used to calculate the effect of any age and child population mixing on the incidence of childhood diabetes whilst controlling for population density, ethnicity and the proportion of migrants. Areas with low levels of child population mixing had significantly higher incidence rates of childhood diabetes (0–14 years). A similar study carried out in the same area but using slightly different methods came to the same conclusion; rates of type 1 diabetes were significantly higher in areas of low population mixing.<sup>52</sup> A recent study in Tayside, Scotland, investigated the association between childhood type 1 diabetes and a number of different measures of population mixing.<sup>79</sup> Variables which have been used previously, and a new categorical variable based on different combinations of in-migration and migrant diversity, were employed. Areas with a higher percentage of child in-migrants had significantly lower rates of type 1 diabetes and areas with both low child in-migration and low child migrant diversity had the highest incidence of type 1 diabetes.

### **An agenda for future research**

In summary, the majority of childhood leukaemia studies show raised rates of the disease in areas with high levels of population mixing. However, three recent studies show an inverse relationship between leukaemia and population mixing,<sup>5,6,52</sup> and another shows no association with any population mixing measure.<sup>53</sup> Although only three studies have been conducted on population mixing and type 1 diabetes, all showed an increase in type 1 diabetes to be related to areas of low population mixing.<sup>8,52,79</sup> In view of these findings, this review highlights three priorities for further research.

Firstly, it is important to examine the health effects of population mixing in a wider range of geographical settings. To date, the majority of studies have been conducted in the UK, with only one study undertaken in New Zealand. This omission is perhaps surprising given the high levels of immigration into New Zealand and the rapid movement of people within the country. For example, 23% of New Zealanders were born overseas,<sup>80</sup> and between 2001 and 2006, 60% of residents changed their address at least once.<sup>81</sup>

Secondly, a number of theoretical and methodological limitations need to be addressed. Population mixing is still poorly defined with the majority of definitions to date being influenced primarily by the data available. Most previous studies have defined, and therefore measured population mixing, as population change.<sup>7,31,43–45,82</sup> This approach is unsatisfactory as it does not directly measure the inflow of new people to an area; it includes data on births and deaths as well as migration. In addition it does not take into account where migrants originate and is thus an inadequate proxy for the range of infections introduced. We therefore recommend that population mixing measures consistently include some gauge of both the volume of people entering an area, and an indication of where they came from. In addition, more frequent and short term movements of people need to be considered including commuting patterns<sup>32,51</sup> and everyday trips such as to shops or schools. Similarly, the influence of tourist flows could usefully be assessed, particularly in countries such as New Zealand which receive increasing numbers of overseas tourists every year,<sup>81</sup> often to previously isolated areas.

Finally, limitations relating to study design offer opportunities for improvement. The timing of exposure to population mixing needs to be captured more accurately whilst routinely accounting for the latency period of the diseases.<sup>44,45</sup> Similarly, the issue of change in levels of population mixing over time needs to be addressed. Moreover, comparable to most studies of the contextual determinants of health, the influence of scale effects not well established. It is feasible that the statistical relationship between population mixing and health is sensitive to the choice of geographical unit of analysis. Further research which tests the effects of population mixing at different geographical scales is warranted.

There is now considerable evidence that population mixing influences childhood health. However many future challenges remain. The theory behind this phenomenon requires further attention, as do current methodologies for investigating its role in disease causation. Population mixing also needs to be examined in other geographical settings, especially those with increasingly mobile populations. New Zealand is one such setting.

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