Access to diabetes drugs in New Zealand is inadequate

The case for a national service for primary immune deficiency disorders in New Zealand

Sleep of Māori and non-Māori of advanced age
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Access to diabetes drugs in New Zealand is inadequate
Jeremy Krebs, Kirsten Coppell, Pip Cresswell, Michelle Downie, Paul Drury, Ann Gregory, Timothy Kenealy, Catherine McNamara, Steven Miller, Kate Smallman

New Zealand is well behind the rest of the developed world in access to funded drugs for managing type 2 diabetes. Over the last 12 years three new classes of glucose-lowering drugs have come through clinical trials to market. The principal strengths of all three novel classes of medicine are their lack of hypoglycaemia (low blood sugar), their frequent acceptability in patients intolerant of or contraindicated for existing funded drugs, and avoidance of weight gain. International guidelines focus on individualization of treatment and avoidance of hypoglycaemia. This is extremely difficult for New Zealanders with type 2 diabetes when we do not have access to modern drug treatments.

Geography matters: the prevalence of diabetes in the Auckland Region by age, gender and ethnicity
Briar Warin, Daniel J Exeter, Jinfeng Zhao, Timothy Kenealy, Susan Wells

We identified and mapped the proportion of people diagnosed with Type 1 or Type 2 diabetes in the Auckland region in 2011 by General Electoral Districts (GEDs). We found marked geographical variation in the prevalence of diabetes across the region, with the highest rates in the electorates based in South Auckland (eg, Mangere, Manakau East and Manurewa) and lowest rates in electoral districts in central and north Auckland (Auckland Central, Epsom, North Shore, and East Coast Bays). The fact that residents living in the Mangere GED, just 25km away from the North Shore GED, are nearly twice as likely to have diabetes is unacceptable. This research highlights the extensive inequities in diabetes among electorates in the Auckland region. Further research into potential geographic factors such as food affordability and availability is required in addition to a more targeted approach to area-based prevention strategies and the provision of health services for people with diabetes.

Trampoline-associated injuries are more common in children in spring
Michael S Yule, Sanjeev Krishna, Jamie-Lee Rahiri, Andrew G Hill

Trampoline-associated injuries are common among children in New Zealand. This study has shown that many of these injuries occur in the spring, when New Zealand clocks change to daylight savings time. Most of these injuries, at least those that present to hospital, are broken bones of the arm or forearm. Public safety messages to decrease injuries associated with playing on trampolines should be targeted around spring when clocks in New Zealand change to daylight savings time.

The management of Graves’ disease in New Zealand 2014
Stephanie C Cox, Jade AU Tamatea, John V Conaglen, Marianne S Elston

We did an online survey of specialists asking how they usually treat patients with Graves’ disease (A condition where the thyroid gland produces too much thyroid hormone, caused by an over-active immune system). There are several equally good treatments available, so doctors must help their patients choose the right treatment for them. The results were compared with surveys from specialists in Europe and North America to see if New Zealand doctors use the same tests and treatments. We also compared results with a similar survey done in New Zealand in 1991 to see if how we treat Graves’ disease has changed over time. We found that how we treat Graves’ disease has changed over time, and we also manage the disease differently to specialists overseas.
Screening, prevalence and ethnic variation of diabetes mellitus in people with acute stroke and transient ischaemic attack: a cross-sectional study in Northland, New Zealand
Steven WM Wong, Nicole M McGrath
People suffering strokes in Northland have higher rates of diabetes than amongst the general population, yet screening for diabetes and how well it is controlled in this group is not yet occurring universally. We also found that Māori have strokes 12 years younger than non-Māori. Possible reasons for this include higher rates of diabetes and poorer control, as well as higher rates of smoking and atrial fibrillation (irregular heart rhythm).

Sleep of Māori and non-Māori of advanced age
Rosemary Gibson, Philippa Gander, Sarah-Jane Paine, Mere Kepa, Lorna Dyall, Simon Moyes, Ngaire Kerse
This is the first study to estimate the prevalence of reporting sleep problems among Māori and non-Māori of advanced age. Among 251 Māori and 398 non-Māori aged 79–90 years, we found that 25.5% of Māori and of 31.7% non-Māori reported a sleep problem. Reporting a current sleep problem was more likely among non-Māori, and among those who reported a past sleep problem, or poorer self-rated physical or mental health. Results highlight the importance of sleep for the health-related quality of life of our rapidly ageing population.

The case for a national service for primary immune deficiency disorders in New Zealand
Rohan Ameratunga, Richard Steele, Anthony Jordan, Kahn Preece, Russell Barker, Maia Brewerton, Karen Lindsay, Jan Sinclair, Peter Storey, See-Tarn Woon
Primary immune deficient disorders (PIDS) are rare conditions for which effective treatment is available, particularly if recognised early. Treatment of these conditions requires the expertise of adult and paediatric immunologists. Currently not all patients are under the care of immunologists, leading to variability in care. There also inconsistencies in the use of intravenous immunoglobulin, which may have contributed to a shortage necessitating importation of product. A national PID service would result in an improvement in patient care and a substantial reduction in costs.
Access to diabetes drugs in New Zealand is inadequate

Jeremy Krebs, Kirsten Coppell, Pip Cresswell, Michelle Downie, Paul Drury, Ann Gregory, Timothy Kenealy, Catherine McNamara, Steven Miller, Kate Smallman

Type 2 Diabetes (T2DM) is one of the biggest health challenges facing New Zealand and is a stated priority of the Minister and Ministry of Health. The prevalence of diabetes in New Zealand is around 7% of the adult population, with over 250,000 individuals in total at the end of 2014, and consistently rising at 7–10% per annum. T2DM is considerably more common in Māori, Pacific and Indian people. Although the actual attributable cost of diabetes to New Zealand is unknown, it is estimated to be approximately $1.3 Billion. Much of this is related to management of diabetes complications, such as renal failure requiring dialysis, amputations, retinopathy and cardiovascular disease, together with the increased length of stays and excessive number of hospitalisations in people with diabetes.

There is overwhelming evidence that effective management of hyperglycaemia and cardiovascular risk factors dramatically reduces the risk of developing, and the high cost of managing, complications of diabetes. This is particularly supported by early intensive glucose lowering, however, recent evidence shows that very intensive management with aggressive glycaemic targets increases the mortality risk in some individuals who have had T2DM for many years, with suggestive evidence that this is linked with hypoglycaemia. In New Zealand, a HbA1c target of 50–55 mmol/mol is recommended, or as individually agreed taking into account the benefits and harms, in particular hypoglycaemia and weight gain. Despite the evidence and current New Zealand guidance for good glycaemic control, many of those with diabetes have an HbA1c higher than the recommended 50–55 mmol/mol. Access to pharmaceuticals which can effectively control glucose, with minimal risk of hypoglycaemia especially in the elderly and those with established cardiovascular disease, is therefore essential for the improved management of T2DM.

Over the last 12 years, three new classes of glucose-lowering drugs have come through clinical trials to market. These include two classes, which for the first time specifically target fundamental pathological defects present in T2DM, acting through the incretin mechanism, and specifically through the gut-derived hormone glucagon-like peptide-1 (GLP-1). GLP-1 is released from the lower small bowel in response to food, and has multiple actions including stimulating insulin release, suppressing raised glucagon, slowing gastric emptying and inducing satiety. The first of these classes, the dipeptidyl peptidase 4 (DPP-4) inhibitors (the ‘gliptins’), reduce the activity of the enzyme which inactivates GLP-1, increasing endogenous levels and thus allowing improved and more prolonged GLP-1 action. The second class (GLP-1 agonists), are a group of injectable peptides which stimulate the GLP-1 receptor, but are not deactivated by the DPP-4 enzyme, and thus produce a prolonged and pharmacological GLP-1 effect. The third new group of drugs, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors (the ‘flozins’), reduce the reabsorption of glucose from the proximal tubules of the kidney, increasing urinary glucose excretion by up to 80g/day. This effect is independent of insulin or other oral agents.

The principal strengths of all three novel classes of medicine are their lack of hypoglycaemia, unless combined with insulin or an insulin secretagogue such as a sulphonylurea, and their frequent acceptability in
patients intolerant of or contraindicated for metformin and/or sulphonylurea. Additional benefits are also striking. While significant weight gain is often associated with sulphonylureas and peroxisome proliferator-activated receptor (PPAR\(\gamma\)) agonists, the DPP-4 inhibitors are weight neutral, and GLP-1 agonists encourage progressive weight loss sustained over many years of use. SGLT-2 inhibition also leads to modest weight loss, and slight lowering of blood pressure. With cardiovascular safety now shown for one DPP-4 inhibitor\(^9\) and similar trials close to reporting for GLP-1 agonists and SGLT-2 inhibitors, there has been no concerning safety signal and at least one SGLT-2 inhibitor to date showing cardiovascular benefits.\(^{10}\) Furthermore, these agents do not necessitate self-monitoring of blood-glucose to the extent that sulphonylurea and insulin therapy requires which in itself is an expensive process.

Despite this, not a single example of any of these three classes has yet been funded in New Zealand, even where conventional treatment is contraindicated, as in chronic kidney disease, or where funded drugs are not tolerated or not effective. Even the inexpensive extended-release metformin, which is better tolerated than its simple counterpart and widely used internationally, remains unfunded.

### International guidelines and recommendations

In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) combined to produce a position statement on the management of hyperglycaemia in individuals with T2DM.\(^{11}\) In 2015, this has been further updated to reflect the progress made over the last decade in the choice of agents, and large, prospective, randomised controlled clinical trial evidence to help understand the efficacy and safety of existing and new drugs, and their combinations.\(^{12}\) One of the central themes of these guidelines, and those of other international bodies, is the need for and importance of individualising management, taking into account many modifiable and non-modifiable factors, to derive patient-specific targets. This is especially important when gastrointestinal intolerance of metformin, the drug of first choice, affects between 5 and 15% of patients, and when hypoglycaemia is so dangerous for the frail, the elderly, and those with pre-existing cardiovascular disease.

In the UK, the National Institute for Health and Care Excellence (NICE) has been grappling with the issue of optimal management of glycaemia in T2DM and has recently released a draft guideline.\(^{13}\) This has been heavily criticised by a wide range of diabetes experts in the UK as being overly influenced by economics and downplaying the clinical value of new agents and the importance of side effects from old agents.\(^{14}\) From this and the other recommendations, it is clear that there are many perspectives on this controversial issue and there is no easy or single solution. While large, randomised, controlled clinical trials are rightly seen as the ‘holy grail’ of evidence for efficacy and safety of new drugs, these trials inevitably overlook the inter-individual variability in responses to and tolerability of treatments, the very essence of the patient-centred ADA/EASD guidelines.

The Australian Diabetes Society has recently published a revised position statement and blood glucose management algorithm for T2DM.\(^{15}\) This is largely aligned with the principles of the ADA/EASD guideline, and incorporates all three new classes of drugs.

### Availability and funding of agents

DPP-4 Inhibitors have been available and funded in Australia since 2008 (8 years ago). Two SGLT-2 inhibitors were listed in 2013, and two GLP-1 agonists are also funded under the Pharmaceutical Benefits scheme. Similarly in the UK and most of Western Europe, examples of each class are funded, though often under restrictions for selected patients. The same applies to Canada.

### The situation in New Zealand

New Zealand lags behind the rest of the developed world in the availability of funded medication for T2DM. Despite
international evidence-based guidelines, continuing evidence-based advice from local diabetes specialists and New Zealand Society for the Study of Diabetes (NZSSD) over the past 10 years, PHARMAC continues to decline the funding of any of the three new classes of agents, all of which are now extensively used in Australia, the UK, and Western Europe as second- and third-line drugs. Multiple applications for funding, and responses to requests for information, have been submitted to PHARMAC from many pharmaceutical companies, as far back as 2007 for GLP-1 agonists, for DPP-4 inhibitors since 2008, and more recently for SGLT-2 inhibitors (ref PHARMAC website).

These drugs are relatively expensive in comparison with metformin and sulphonylureas, often costing $100–$200 per month retail. Wholesale use for everyone with T2DM is neither justified nor required, but it is clear that there is an important role for these drugs in selected individuals who cannot use, cannot tolerate, or do not respond to the first- or second-choice agent. PHARMAC has a track record of staged introduction of new pharmaceutical classes through special authority criteria to limit access and contain costs. While this is a reasonable approach, repeated delays in the introduction of important new agents is curtailing the recommended individualisation of Type 2 DM management in New Zealand, putting them at risk and ultimately costing the country more in the management of late complications. The Executive Committee of NZSSD urges PHARMAC to review their position and to allow better access to newer diabetes agents in appropriate cases.

Author information:
Jeremy Krebs, Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington; Kirsten J Coppell, Medicine, University of Otago, Dunedin; Pip Cresswell, Endocrine, Diabetes and Research Centre, Capital and Coast Health, Wellington; Michelle Downie, Department of Medicine, Southland Hospital, Invercargill; Paul Drury, Medicine, University of Otago, Dunedin; Ann Gregory, ORA services, Capital and Coast Health, Wellington; Timothy Kenealy, South Auckland Clinical School, University of Auckland, Auckland; Catherine McNamara, Endocrinology, Waitemata DHB, Auckland; Steven CM Miller, Diabetes Centre, North Shore Hospital (WDHB), Auckland; Kate Smallman, Diabetes Projects Trust, Auckland.

Corresponding author:
Jeremy Krebs, Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington, New Zealand.
jeremy.krebs@ccdhb.org.nz

URL:

REFERENCES:
research and clinical practice. 2011;91:164-170
13. NICE. Type 2 diabetes in adults: Management of type 2 diabetes in adults. 2015
The management of Graves’ disease in New Zealand 2014
Stephanie C Cox, Jade AU Tamatea, John V Conaglen, Marianne S Elston

ABSTRACT

BACKGROUND: Treatment options for Graves’ disease (GD), namely anti-thyroid drugs (ATD), surgery or radioiodine (RAI), have not changed over the past two decades. There is no ‘gold-standard’ treatment for GD.

AIMS: To assess whether the management of GD in New Zealand has changed since the previous 1991 New Zealand survey and compare current management with that of contemporary international studies.

METHODS: We conducted an online survey of New Zealand physicians currently practising internal medicine, diabetes and/or endocrinology, using the cases and questions from the original European and 1991 New Zealand studies.

RESULTS: The first-line use of RAI was 5.5%, compared to 41% in the 1991 New Zealand survey. This corresponded to an increase in ATD use, while the rates of surgery as a first-line treatment have remained static over time. New Zealand physicians use technetium scanning for diagnosis, whereas ultrasound and radioiodine uptake were the most commonly selected investigations by European and North American physicians, respectively. The pattern of ATD use in pregnancy was similar to international practice.

CONCLUSION: Treatment of GD in New Zealand has shifted away from the use of RAI as first line treatment. There are significant differences in the investigation and treatment of Grave’s disease between New Zealand, Europe and North America.

Graves’ disease (GD) is the leading cause of thyrotoxicosis in New Zealand, accounting for approximately 64% of cases of thyrotoxicosis. Treatment is with anti-thyroid drugs (ATD), radioiodine (RAI) or thyroidectomy. Despite these treatments being in use for over 50 years, none have been proven to be superior and each has potential risks. There have been developments in our understanding of these risks over the last two decades, in particular with regard to the risks of anti-thyroid drugs in pregnancy. In addition, concerns over the long-term effects of radiation exposure have been reported, and advances in anaesthesia and surgical techniques have resulted in lower surgical morbidity. Multiple surveys were undertaken in North America, Europe and Australasia in the late 1980s and 1990s assessing patterns of clinical practice by physicians treating patients with GD. A New Zealand survey was conducted in 1991, and an Australian study in 2000. More recently, similar surveys have been repeated in Europe and North America, and these international studies continue to show significant differences in practice throughout the world.

The aim of this study was to assess whether the management of GD by New Zealand endocrinology/internal medicine specialists has changed since the 1991 New Zealand survey, and to compare current management of GD with that of contemporary international studies.

Materials and methods

An online survey (Appendix 1) was developed using a freely available web-based service (Google forms). The index case (Box 1) and two variations were the same as those used in the recently reported surveys from North America and Europe. These in turn were based on the original 1987 European survey by Glinoer et al, as was the 1991 New Zealand survey by Ford et al.
ARTICLE

Box 1: Index case.

A 42-year-old woman presents with moderate hyperthyroid symptoms of 2 months duration. She is otherwise healthy, takes no medications, and does not smoke cigarettes. She has two children, the youngest of whom is 10 years old, and does not plan on being pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goiter, approximately two to three times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal, with an undetectable thyrotrophin level (TSH<0.01mIU/L).

Participants were identified from the Medical Council of New Zealand Register of Physicians. Those identified as practicing predominantly in the areas of general medicine, endocrinology/diabetes or obstetric medicine were e-mailed invitations to participate, which included an individual electronic link to the survey. Survey responses were anonymous and stored electronically in a password-protected Google Drive account. Multiple reminder emails were sent to try to improve response rates and ‘Champions’ were recruited at each main centre to promote the survey face-to-face with their colleagues (at departmental meetings, etc.). Those respondents who reported seeing less than two cases of GD per year were excluded from further analysis.

Statistical Analysis

Statistical analysis was performed using Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). A p value of <0.05 was considered significant. Results are reported as number of responses/number of respondents where possible. Some questions allowed more than one option to be selected; these are presented as percentages of the respondents. Chi-square analysis was used to compare key results from the 1991 New Zealand survey to each of the recent North American and European studies, using data as available in their publications.\textsuperscript{11,13,14}

Ethics

The study was conducted in accordance with the National Health Advisory Committee’s Ethical Guidelines for Observational Studies, and with approval from the Waikato District Health Board Research Committee (RD14047).

Results

Responses and demographics

A total of 117 physicians were initially identified. Six were not able to be located, two had retired, and one had permanently emigrated. The remaining 108 were sent the survey and 47 responses were received. Of these, 11 were from physicians who reported seeing <2 patients with GD in the past year, and so were excluded from further analysis. Respondent demographics are shown in Table 1.

Diagnostic evaluation of the index case

Serum free T4 and thyroid-stimulating hormone (TSH) were the most frequently selected tests (requested by 35/36, [97%]), followed by free T3 (30/36 [83%]). The use of thyroid antibody testing and thyroid imaging studies is shown in Figure 2.

Management of the index case

First-line treatment

ATD use, aiming for remission, was the treatment of choice for the index case by 33/36 (92%) respondents. RAI was selected as first-line treatment by 2/36 (5%) and one respondent selected thyroidectomy as first-line treatment. One third (12/36) would definitely use beta-blockers as adjuvant treatment, 19/36 (52%) would consider beta-blockade, whereas 5/36 (14%) would definitely not use beta blockers in the index case. Metoprolol was the most commonly selected beta-blocker (16/31, 52%), followed closely by propranolol (13/31, 42%).

Table 1: Medical practice of respondents.

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ATD treatment
All respondents reported that they would use carbimazole (CBZ) as the ATD of choice (methimazole is not available in New Zealand). Most respondents would use a starting dose of 20–30mg administered daily (29/36, 81%). None of the respondents would use a ‘block and replace’ regimen, with 36/36 opting for dose titration aiming for euthyroidism. To assist dose titration, most respondents would repeat thyroid hormone levels 4–6 weeks after commencing treatment. There was a large spread of opinion on the best interval for monitoring thyroid hormone levels once the patient was euthyroid, with a fairly even spread across 4 weeks, 6 weeks, and 2 months, although a 3-month interval was most commonly selected (22%, 17%, 19%, and 39% respectively). Three quarters of respondents would not request any routine monitoring apart from thyroid hormone levels, whereas routine monitoring of liver enzymes and complete blood count would be requested by 22% and 25% of respondents, respectively. TSH-receptor antibody (TRAb) titers were routinely measured by 11% of respondents in addition to thyroid function. The majority would recommend 12–18 months of ATD treatment aiming for remission, before recommending an alternative form of therapy. Criteria for cessation of ATD treatment were a clinically and biochemically euthyroid patient (89%), duration of treatment (58%), and undetectable TRAb (25%). In the presence of a pruritic macular rash unresponsive to antihistamine treatment, 30/36 respondents would switch to an alternate ATD, while 6/36 would select an alternate mode of therapy.

ATD treatment as an adjunct to radioiodine (RAI) and thyroid surgery
The majority of physicians surveyed would pretreat with ATDs in preparation for RAI (28/35, 80%). A further 14% would pretreat with ATDs prior to the use of RAI only in the presence of additional clinical factors such as severe thyrotoxicosis, underlying heart disease, patients with multiple comorbidities or over the age of 65. ATDs are withdrawn 5–7 days prior to RAI by 70% of respondents. Only 15% would routinely use ATDs after RAI therapy with the majority reserving them for selective use only (73%). When thyroid surgery was proposed, 90% (27/30) of physicians would aim to restore normal thyroid function preoperatively with ATDs.

RAI treatment
All of the physicians surveyed treat patients with RAI, either by directly prescribing and administering it, or by referral to another specialist. The aim of treatment was to restore euthyroidism off medication for 14/36 (39%), whereas an attempt to achieve hypothyroidism followed by thyroid hormone replacement was the goal for 22/36 (61%). A fixed dose was used by 50%, with 7/36 reporting the use of a variable dose. Thirty percent of respondents did not know how the dose was calculated as treatment was administered by another specialist. All of those surveyed would administer a second dose of RAI if the patient was not cured by the initial treatment. The majority (20/32), would wait 6 months prior to the second dose, with 5/32 re-treating at 12 months.

Surgical management
The majority of physicians had previously referred patients with GD for thyroid surgery, although six respondents reported they did not ever refer patients for surgery. Referral to an endocrine surgeon was made by 49% of respondents, 20% to a general surgeon and the remainder to either head and neck, or ear nose and throat surgeons. Thirty-seven percent of the physicians surveyed were unaware of the number of thyroidectomies performed per year by the surgeon to whom they refer. The remainder were fairly evenly distributed between low-volume and high-volume surgeons. The operation of choice was total thyroidectomy (87%). The majority of centres did not discharge patients routinely on prophylactic doses of calcium and vitamin D (19/30, 63%).

Variation 1: moderate active Graves’ ophthalmopathy
The majority of physicians surveyed (94%) would recommend evaluation by an ophthalmologist for patients presenting with ophthalmopathy, and if the patient required corticosteroid therapy this was most likely to be administered and super-
vised by an ophthalmologist (19/36, 53%). The presence of ophthalmopathy would alter the choice of first-line treatment, with only 23/36 (64%) now opting for ATDs, and no respondents selecting RAI, with or without adjuvant corticosteroid treatment. Twenty-five percent would recommend thyroidectomy as first line treatment for the patient with ophthalmopathy, compared with 2.8% for the index case.

Variation 2: planning pregnancy in the next 6–12 months

ATDs remained the first line treatment of choice, but decreased from 91% to 67%. Correspondingly, RAI treatment and thyroid surgery were each selected by 4/36 (11%) of respondents, compared with 2/36 (5.5%) and 1/36 (2.8%), respectively, for the index case. The choice of ATD was now split between CBZ (20/36, 56%) and propylthiouracil (PTU) (16/36, 44%). Eighty-six percent of respondents reported they would change from CBZ to PTU in a euthyroid patient with a positive pregnancy test. If the patient was on PTU in the first trimester, 23/36 (63.9%) reported they would switch to CBZ from the second trimester, assuming the patient still required ATDs. The majority would monitor thyroid function tests 4-weekly during pregnancy (28/36, 78%), and 75% (27/36) routinely measure TRAb during pregnancy. Of those, 31/36 (86%) would monitor TRAb every 12 weeks, or once per trimester. Of those who measure TRAb levels during pregnancy, only 25% would alter treatment based on these results.

Comparison with 1991 New Zealand study

Practice in New Zealand has changed over the last 20 years, with a move away from radioiodine treatment as first line treatment (Figure 1). In comparison to the 1991 New Zealand survey, the first-line use of radioiodine is now only 5.5%, compared with 41%, using the same clinical scenario (p<0.0005). This corresponded with an increase in the use of ATDs (92% vs 55%, p<0.0005), while the rates of surgery as a first-line treatment do not appear to have changed over time (3% vs 4%, p=0.709). An exception was in active ophthalmopathy, where thyroidectomy was a more frequent choice, selected by 25% in our survey.

Comparison with American and European surveys

The responses to this survey were compared with those from the 2011 American survey by Burch et al., and the 2013 European survey reported by Bartalena et al. There were significant differences between the laboratory and radiological investigations selected by New Zealand physicians and those from Europe and North America (Figure 2a & b). New Zealand physicians requested TPOAb and
ARTICLE

Figure 2a: Comparison of thyroid-associated antibody testing rates.

Figure 2b: Comparison of first line thyroid imaging preferences.

TgAb titres more frequently than either of the other two groups (TPOAb 69% vs 42% US [p<0.0005] vs 65% EU [p=0.585]), whereas TRAb titres were requested at similar rates to North American physicians (61% vs 52%, p=0.289), but significantly less than European physicians (61% vs 86%, p=0.001). Technetium scanning was the modality of choice for New Zealand physicians (31%), whereas ultrasound was the most commonly selected investigation by European physicians (71%) and radiiodine uptake scanning (RAIU) by those from North America (47%) (Figure 3).

There were significant differences in the choice of first-line treatment across the continents (Figure 3). New Zealand physicians reported higher rates of ATD use than those in North America (92% vs 54%, p=<0.0005), similar to those reported in the European study (92% vs 84%, p=0.226). US physicians were much more likely to use RAI as first-line treatment, with New Zealand physicians reporting the lowest rate of RAI use as first-line (5.5% vs 45%, p<0.0005). Surgery was infrequently selected as first-line treatment across all groups studied, and no significant differences identified.

Preferred treatment in preparation for and during pregnancy

As preparation for pregnancy, New Zealand physicians appear to use PTU much
the same as North American physicians (56% vs 46%, p=0.156) and the majority would switch to PTU in early pregnancy (31/36, 86%) (Figure 4).

Most New Zealand physicians (63%) and 60% (p=0.391) of European physicians switch back to CBZ from the second trimester, when compared with 46% of US physicians (p=0.035) (Figure 4).

Discussion

There are three effective treatments for Graves' disease: ATD, RAI and thyroidectomy. Despite all of these being used regularly in clinical practice since the 1940s, there have been few head-to-head studies comparing treatment options, and those that have been done have failed to show any significant difference in overall efficacy or safety. With no 'gold standard' of treatment, physicians need to guide patients to select a treatment based on individual clinical circumstances and patient preferences. Therefore, trends in practice can vary depending on the population involved, the ease of access to treatments and patients perceptions and understanding of treatment options.

The impetus behind the shift away from RAI towards ATDs in New Zealand is unknown, but proposed factors include New Zealand’s ‘nuclear-free’ policies and their effects on the practicalities of treatment, as well as public perception of nuclear medicine treatments. The passage of the New Zealand Nuclear Free Zone, Disarmament, and Arms Control Act in 1987 not only prohibited the use of nuclear weapons, but also nuclear-powered ships and nuclear-generated electricity. The status of New Zealand as a nuclear-free nation has become increasingly popular over time, and a source of nationalist feeling. This stance, and widespread media coverage of international nuclear disasters such as Chernobyl and, more recently, Fukushima, have likely increased the level of distrust felt by the public towards ionising radiation and its long-term effects. Studies of public perception of the risks of radiation from medical diagnostic tests and treatments, including RAI, show that their estimation of risk is often greater than reality, and differs significantly from that of health professionals. Two recent papers on thyroidectomy for GD both found that the majority of patients were referred for surgery over RAI due to patient preference and/or patient refusal of RAI. Non-radiologic physicians have also been shown to have major deficiencies in their ability to accurately assess the risk of radiation exposures. This issue has been highlighted in recent times by the concerns over the long-term cancer risk of patients...
Figure 4: Preferred treatment in preparation for and during pregnancy.

A. Choice of ATD in a patient planning pregnancy

- Cox et al (NZ)
- Bartalena et al (EU)
- Burch et al (US)

B. Switch to PTU on confirmation of pregnancy

- Cox et al (NZ)
- Bartalena et al (EU)
- Burch et al (US)

C. Switch to Carbimazole in second trimester

- Cox et al (NZ)
- Bartalena et al (EU)
- Burch et al (US)
exposed to multiple CT scans. This over-estimation of the risks of radiation by doctors and patients alike may be combined with an underestimation of the risks of treatment with ATDs. While these agents are remarkably well tolerated and serious adverse events are rare, when they do occur they can be severe, and even fatal.

On a practical level, the lack of nuclear facilities in New Zealand means that radioisotopes have to be imported from Australia, creating restrictions on supply. This is particularly relevant with regard to I\(^{131}\), used primarily in diagnostic imaging. This isotope has a short half-life, and is therefore not readily available in New Zealand. This is likely to be the reason technetium scanning is used in New Zealand in comparison to RAIU scanning in the US.

Although the majority of physicians surveyed did not report impediments to accessing surgical services, over half of those surveyed did not have access to a high-volume thyroid surgeon. This may contribute to the low rates of surgery as first line treatment. It is worth noting that these numbers reflect only the physician’s knowledge of the practice of their surgical colleagues and may not represent the true picture of surgical practice in New Zealand for thyroid patients.

The use and selection of anti-thyroid drugs in pregnancy is an area where there has been significant debate in response to new research and recent changes in international guidelines. CBZ and methimazole have been associated with an increased risk of congenital abnormalities, in particular choanal atresia and aplasia cutis. Therefore, the recommendations for many years were to use PTU as first-line during pregnancy. However, over the last 20 years there has been increased awareness of the risk of fulminant hepatitis from PTU, leading to the FDA issuing a black box warning in 2010. A recent, large, Danish registry study showed similar rates of malformation after foetal exposure to PTU and CBZ (8.0 and 9.1% respectively) although the types of abnormalities differ. The most recent published guidelines continue to recommend PTU in the first trimester, and CBZ in subsequent trimesters. In this study, New Zealand physicians’ use of ATDs in pregnancy is similar to that of their international colleagues. The only significant finding was that fewer North American physicians would switch to CBZ from the second trimester. This may reflect the fact that this is the oldest of the three studies, and was undertaken prior to the release of the most recent North American guidelines.

This study was limited by the small number of responses received. This is due to both the small number of physicians in New Zealand and a relatively low response rate (41%). Response rates of physicians to surveys are low compared to the general population, and have been shown to be declining over time. Possible explanations include increased time pressure, ‘survey fatigue’, and an increasing number of physicians who have a policy of not replying to surveys. Endocrinologists were more likely to reply than general physicians, with 32/70 responses (44%) compared with 13/38 (34%). Regardless of speciality, 83% of those who responded see >10 new cases per year. This suggests that responses received do represent a sample from the group of physicians for whom the management of GD is part of their core practice.

**Conclusion**

The results of this survey provide an up to date overview of the management of GD by physicians in New Zealand. Treatment of GD in New Zealand over the past 25 years has moved towards ATDs, and away from the use of RAI as a first-line treatment. Outside the setting of pregnancy there are significant differences in the investigations and treatment of GD between New Zealand, Europe and the US. Currently, there is no evidence to say which approach is superior, but if future research alters this perspective this study would provide a useful baseline from which to assess the impact of such information on the practice of New Zealand physicians.
Thyroid Survey 2014
This survey aims to investigate the current patterns of diagnosis and management of Graves’ disease in New Zealand. It takes approximately 15 minutes to complete. Your answers will remain strictly confidential. As you answer the questions please consider the last several Graves’ disease patients you have treated, as the survey would like to assess actual current practices rather than idealized approaches. To decrease ambiguity, assume that the patient wants to defer to your judgement as to the preferred approach.

1. How many new cases of Graves’ disease do you see, on average, per year? * Mark only one oval.
   - <2
   - 2-5
   - 6-10
   - 11-50
   - >50

Demographics
2. What is your main area of practice? * Mark only one oval.
   - Endocrinology
   - Diabetes
   - General Medicine
   - Other:

3. Which of the following best describe your practice location? * Check all that apply.
   - Tertiary Public Hospital
   - Secondary Public Hospital
   - Rural Hospital
   - Private Practice
   - Primary Care
   - University/Academic
   - Other:

4. What year did you attain your FRACP or equivalent qualification? *

5. Which of the following professional associations do you belong to? * Check all that apply.
   - Royal Australasian College of Physicians
   - NZ Society of Endocrinology
   - Endocrinology Society of Australia
   - The Endocrine Society
   - American Thyroid Association

6. Optional identification
   You are welcome to submit this survey anonymously. If you would like to identify yourself please enter your name and email address here. If you choose to identify yourself, you will not receive any future emails reminding participants to complete this survey. Your individual identified responses will not be published or released to any third party.

Index Case
A 42-year-old woman presents with moderate hyperthyroid symptoms of 2 months duration. She is otherwise healthy, takes no medications, and does not smoke cigarettes. She has two children, the youngest of whom is 10 years old, and does not plan on being pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goitre, approximately two to three times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal, with an undetectable thyrotropin level (TSH <0.01 mIU/L).

A. Diagnosis
7. Which of the following tests do you obtain in the majority of patients such as the index case? * Check all that apply.
   - Thyroid Stimulating Hormone (TSH)
   - Free T4
   - Total T4
   - Free T3
   - Total T3
   - Thyroglobulin
   - Anti-Thyroglobulin Antibodies (Anti-Tg)
   - Anti-Thyroid Peroxidase Antibodies (Anti-TPO)
   - Anti-TSH Receptor antibodies (Thyroid Stimulating Immunoglobulins)
   - TRH test
   - Full Blood Count
   - Serum Electrolytes and Creatinine
   - Liver function panel
   - Thyroid Ultrasound Scan
   - Thyroid Scintiscan (Technetium)
   - Radioactive Iodine Uptake (I-131)
   - Radioactive Iodine Uptake (I-123)
   - Urinary Iodide excretion
   - Other:

B. Management - General
8. Would you start this patient on Beta Blockers? * Mark only one oval.
   - Yes
   - No Skip to question 11.
   - Maybe

9. Which beta blocker would you use? Mark only one oval.
   - Metoprolol
   - Atenolol
   - Propranolol
   - Carvedilol
   - Other:
10. If using beta blockers in this patient, what target heart rate would you aim for? Mark only one oval.
   - <110bpm
   - <100bpm
   - <90bpm
   - <80bpm
   - <70bpm
   - <60bpm
   - Don’t titrate to heart rate
   - Other:

11. Assuming the evaluation of the above patient reveals uncomplicated Graves’ disease, which first-line (long term) mode of therapy would you recommend? * Mark only one oval.
   - Beta blockers alone
   - Anti-thyroid drugs aiming for remission
   - Antithyroid drugs as a long term treatment
   - Radioactive iodine
   - Thyroid Surgery
   - No therapy

C. Management - Radioactive Iodine

12. Do you use radioactive iodine to treat patients with Graves’ disease? (Either by prescribing and administering it yourself, or by referral to another specialist) * Mark only one oval.
   - Yes
   - No
   - Skip to question 23.

13. What is your primary aim of therapy with radioactive iodine? Mark only one oval.
   - To restore euthyroidism off medication
   - Ablation of the thyroid followed by thyroid hormone replacement

14. How do you calculate the dose of radioactive iodine used? Mark only one oval.
   - Use a fixed dose
   - Thyroid uptake function
   - Size of thyroid gland
   - Unknown (treatment administered by other specialists)
   - Other:

15. If you use a fixed dose of radioactive iodine, what dose do you use?

16. Do you use a “split dose” for initial treatment? Mark only one oval.
   - Yes
   - No
   - Don’t know what this is

17. If the patient is not cured by the initial dose(s), would you administer a second dose? Mark only one oval.
   - No
   - Yes

18. If you answered “Yes” to the questions above, how long (in months) would you wait before giving the second dose?

19. Do you pretreat patients with antithyroid drugs as a means of preparation for radioiodine therapy? Mark only one oval.
   - Yes
   - No
   - Only in selected cases

20. If you answered “Only in selected cases”, which clinical circumstances would lead you to use pretreatment with anti-thyroid drugs before radioiodine?
   - Check all that apply
   - Age >65
   - Underlying Heart Disease
   - Multiple co-morbidities
   - Severe thyrotoxicosis
   - Other:

21. If you use pretreatment with antithyroid drugs before radioiodine, how many days before giving radioiodine do you recommend stopping the antithyroid drug? Mark only one oval.
   - Don’t stop anti-thyroid drugs
   - 1 day
   - 2 days
   - 3 days
   - 4 days
   - 5 days
   - 7 days
   - 14 days
   - Unsure
   - Other:

22. Do you administer antithyroid drugs to most patients after radioiodine therapy? Mark only one oval.
   - Yes
   - No
   - Selective use only

D. Management - Anti-thyroid drugs

The next questions apply to patients receiving prolonged courses of anti-thyroid drugs in an attempt at achieving a remission.

Index Case

A 42-year-old woman presents with moderate hyperthyroid symptoms of 2 months duration. She is otherwise healthy, takes no medications, and does not smoke cigarettes. She has two children, the youngest of whom is 10 years old, and does not plan on being pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goitre, approximately two to three times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal, with an undetectable thyrotopin level (TSH < 0.01 mIU/L).
23. Which anti-thyroid drug would you generally use first? * Mark only one oval.
   - Carbimazole
   - Propylthiouracil
   - Other:

24. When using carbimazole, what starting dose would you use in the index case? *
   Mark only one oval.
   - 40mg daily
   - 30mg daily
   - 20mg daily
   - 10mg daily
   - 20mg BD
   - 30mg BD
   - Other:

25. When using propylthiouracil, what starting dose would you use in the index case? *
   Mark only one oval.
   - 200mg three times daily
   - 200mg twice daily
   - 200mg daily
   - 150mg three times daily
   - 150mg twice daily
   - 150mg daily
   - 100mg three times daily
   - 100mg twice daily
   - 100mg daily
   - 50mg three times daily
   - 50mg twice daily
   - 50mg daily
   - Other:

26. After starting anti-thyroid drugs, when would you first check thyroid hormone levels? *
   Mark only one oval.
   - 1 week
   - 2 weeks
   - 3 weeks
   - 4 weeks
   - 6 weeks
   - 8 weeks
   - 12 weeks
   - 18 weeks
   - 24 weeks
   - Other:

27. Do you most often titrate the dose of anti-thyroid drug to euthyroidism, or use antithyroid drugs to fully suppress thyroid hormone production and then administer thyroxine replacement (“block and replace”)? * Mark only one oval.
   - Dose titration
   - Block and Replace

28. How often do you adjust the dose of anti-thyroid drug? * Mark only one oval.
   - Never
   - Weekly
   - 2 weeks
   - 4 weeks
   - 6 weeks
   - 8 weeks
   - 12 weeks
   - Other:

29. Which do you use most when deciding on dose adjustments? * Mark only one oval.
   - Clinical findings
   - Thyroid function tests
   - Both of the above equally
   - Other:

30. After achieving euthyroidism on anti-thyroid drugs, how often do you monitor thyroid hormone levels? * Mark only one oval.
   - Monthly
   - Every 2 months
   - Every 3 months
   - Every 6 months
   - Other:

31. When using anti-thyroid drugs, in addition to thyroid hormone levels, which of the following do you routinely monitor? * Check all that apply.
   - Liver Enzymes
   - Full blood count
   - No routine monitoring
   - TSH receptor antibodies / Thyroid stimulating immunoglobulin

32. After two weeks of anti-thyroid drug therapy, your patient develops a pruritic macular rash, which fails to improve with antihistamine. There are no systemic signs or symptoms. Which one of the following most closely describes your usual approach to this circumstance? * Mark only one oval.
   - Continue same antithyroid drug plus an antihistamine
   - Switch to a different anti-thyroid drug
   - Select an alternative mode of therapy (radioactive iodine or surgery)

33. When using anti-thyroid drugs in an attempt to achieve a remission, how long of a course do you recommend before attempting an alternate form of therapy? * Mark only one oval.
   - 3 months
   - 6 months
   - 9 months
   - 12 months
   - 18 months
   - 24 months
   - Other:
34. What criteria do you use to stop treatment? *
Check all that apply.
☐ Clinical and biochemical euthyroidism
☐ Negativisation of TSH receptor antibodies / TSI
☐ Negativisation of Anti-Tg and Anti-TPO antibodies
☐ Thyroglobulin level
☐ TRH test
☐ Normalisation of suppression test
☐ Duration of treatment
☐ Other:

35. Do you ever refer patients with Graves’ disease for surgery? * Mark only one oval.
○ Yes
○ No Skip to question 43.

36. Are Graves’ disease patients at your center routinely given SSKI or Lugol’s solution prior to thyroidectomy, even if euthyroid on anti-thyroid drugs? Mark only one oval.
○ No
○ Yes
○ Not sure

37. Do you generally render patients euthyroid with anti-thyroid drugs prior to thyroidectomy? Mark only one oval.
○ Yes
○ No
○ Not sure

38. Are Graves’ disease patients undergoing thyroidectomy at your center routinely discharged on prophylactic doses of calcium and/or vitamin D therapy, even if the serum calcium is within the normal range? Mark only one oval.
○ No
○ Yes
○ Not sure
○ Other:

39. Which form of thyroid surgery is most often recommended/preferred by the surgeon(s) you refer to? Mark only one oval.
○ Near-total or total thyroidectomy
○ Subtotal thyroidectomy
○ Not sure

40. Who is responsible for the long-term follow-up of patients after thyroid surgery? Mark only one oval.
○ Surgeon
○ Referring Physician
○ General Practitioner

41. Does the location of long term follow-up influence the surgical strategy chosen? e.g. Patients followed by surgeon more likely to have total thyroidectomies vs patients who are followed by physician, or preference for subtotal thyroidectomy for patients with limited access to health care etc.
Mark only one oval.
○ Yes
○ No
○ Don’t know

42. If so, how?

43. In addition to your previous responses, which of the following (if any) would you obtain in this patient with moderate active Graves’ ophthalmopathy? * Check all that apply.
☐ Visual field testing
☐ CT Orbits (non-contrast)
☐ Orbital ultrasound
☐ MRI Orbits
☐ Ophthalmologist evaluation
☐ Other:

44. What is your usual therapeutic approach to hyperthyroidism for a patient with moderate active ophthalmopathy? * Mark only one oval.
○ Anti-thyroid drugs to achieve remission
○ Radioactive iodine alone
○ Radioactive iodine plus corticosteroids
○ Thyroidectomy once euthyroid on anti-thyroid drugs
○ Thyroidectomy plus radioactive iodine ablation
○ Other:

45. If your patient’s ophthalmopathy requires corticosteroid therapy, who is most likely to administer this? * Mark only one oval.
○ Endocrinologist
○ General Physician
○ Ophthalmologist
○ General Practitioner
○ Other:

46. If so, how?

G. Pregnancy
The following questions relate to the management of Graves’ disease in the soon to be pregnant or currently pregnant patient.
Case 2
The patient is a 22 year old woman with newly diagnosed thyrotoxicosis who wishes to become pregnant within the next 6-12 months. She has a diffuse goitre, approximately two to three times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal, with an undetectable thyrotropin level (TSH < 0.01 mIU/L). Assume that the diagnosis of Graves' disease is already confirmed.

46. Which principal mode of therapy would you recommend to this patient who plans to become pregnant in the next 6-12 months? * Mark only one oval.
   o Anti-thyroid drugs
   o Radioactive Iodine
   o Thyroid surgery
   o No treatment
   o Other:

47. If the patient elects to use anti-thyroid drugs as the principal mode of therapy, which anti-thyroid drug would you use in this patient before pregnancy? * Mark only one oval.
   o Carbimazole
   o Propylthiouracil

48. The patient becomes euthyroid, and now has a positive pregnancy test. If you had started carbimazole prior to pregnancy, would you now switch to propylthiouracil? * Mark only one oval.
   o Yes
   o No

49. If you gave the patient propylthiouracil during the first trimester, would you switch to carbimazole as the patient enters the second trimester, assuming she still requires anti-thyroid drugs? * Mark only one oval.
   o No
   o Yes

50. How often do you routinely monitor thyroid function tests in pregnancy in a patient with Graves' disease? * Mark only one oval.
   o 4 weekly
   o 6 weekly
   o 8 weekly
   o 12 weekly
   o Other:

53. If you measure TSH receptor antibodies during pregnancy, do you alter treatment based on antibody levels? * Mark only one oval.
   o Yes
   o No
   o Not sure Skip to question 54.

H. Access to services

54. Do you have difficulties in accessing any of the following for your patients? Check all that apply.
   □ Specialist Endocrinology Services
   □ Nuclear Medicine Imaging
   □ Radioactive Iodine
   □ Surgical Services
   □ Appropriate laboratory investigations
   □ Other:

55. With respect to the Surgeon(s) you refer to, is their main area of practice: Mark only one oval.
   o Endocrine surgery
   o General surgery
   o Head and Neck surgery
   o ENT surgery
   o Other:

56. Approximately how many thyroidectomies are performed per year by the surgeon(s) you refer to? Mark only one oval.
   o 1-5
   o 6-10
   o 11-20
   o 21-50
   o 51-100
   o >100
   o Don't know
   o Other:

Survey Complete
Thank you for taking the time to complete this survey

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Nil

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Author information:
Stephanie C Cox, Endocrinology Registrar, Department of Endocrinology, Waikato Hospital, Hamilton; Jade AU Tamatea, Research Fellow, Waikato Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Auckland; John V Conaglen, Endocrinologist, Waikato Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Auckland; Marianne S Elston, Endocrinologist, Department of Endocrinology, Waikato Hospital, Hamilton, and Waikato Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.

Corresponding author:
Stephanie Cox, Department of Endocrinology, Waikato Hospital, Private Bag 3200 Hamilton, 3420, New Zealand.
stephaniec@adhb.govt.nz

REFERENCES:


Geography matters: the prevalence of diabetes in the Auckland Region by age, gender and ethnicity

Briar Warin, Daniel J Exeter, Jinfeng Zhao, Timothy Kenealy, Susan Wells

ABSTRACT

AIM: To determine whether the prevalence of diagnosed diabetes in the greater Auckland Region varies by General Electoral District (GED).

METHODS: Using encrypted National Health Identifiers and record linkage of routine health datasets, we identified a regional cohort of people with diagnosed diabetes in 2011 from inpatient records and medication dispensing. The geographical unit of a person’s residence (meshblock) was used to determine the GED of residence. We calculated prevalence estimates and 95% confidence intervals and used binary logistic regression to map geographical variations in diabetes.

RESULTS: An estimated 63,014 people had diagnosed diabetes in Auckland in 2011, a prevalence of 8.5% of the adult population ≥30 years of age. We found significant variation in diabetes prevalence by age, gender, ethnicity and GED. There was a more than five-fold difference in the unadjusted prevalence of diabetes by GED, ranging from 3.2% (3.1 to 3.4%) in the North Shore to 17.3% (16.8 to 17.7%) in Mangere. Such variations remained after binary logistic regression adjusting for socio-demographic variables. Compared to New Zealand Europeans, Indian people had the highest odds of having diabetes at 3.85 (3.73 to 3.97), while the odds of people living in the most deprived areas having diabetes was nearly twice that of those living in least deprived areas (OR 1.93, [1.87 to 1.99]). Geographic variations in diabetes remained after adjusting for socio-demographic circumstances: people living in GEDs in south-west Auckland were at least 60% more likely than people living in the North Shore GED to have diabetes.

CONCLUSIONS: There is significant variation in the prevalence of diabetes by GED in Auckland that persists across strata of age group, gender and ethnicity, and persists after controlling for these same variables. These inequities should prompt action by politicians, policymakers, funders, health providers and communities for interventions aimed at reducing such inequities. Geography and its implications on access to and availability of health resources appears to be a key driver of inequity in diabetes rates, supporting an argument for interventions based on geography, especially a public health rather than an individual risk approach.

Diabetes will be one of the defining health problems of the 21st century. The prevalence of diabetes has been steadily increasing in New Zealand over the last 30 years,1–4 with annual health system costs predicted to reach $1 billion in 2016.5 Diabetes prevention and treatment needs to be built not only on a foundation of robust epidemiology, but also evidenced-based interventions.

Two recent sources of diabetes prevalence in New Zealand are the Virtual Diabetes Register and the 2013/14 New Zealand Health Survey. The Virtual Diabetes Register was compiled by the Ministry of Health, using nationwide information on hospital admissions, outpatient clinic attendance, medication prescribing, laboratory tests, and Primary Health Organisation (PHO) enrolments.6 In 2013, the Register estimated that there were 243,125 people with diagnosed diabetes. Data available from the 2013/14 New Zealand Health Survey showed a lower total diabetes prevalence of 5.5% (approximately 198,000 adults) of the adult population (≥15 years old).5 This lower
rate may be due to the data being based on self-identification of diabetes. There was a clear increase in diabetes prevalence with increasing age. Men were substantially more likely than women to have diabetes, and there were also marked ethnic inequities, with Pacific, Māori and Asian people bearing a disproportionate burden. There was also evidence of a socio-economic gradient, with people living in the most deprived quintile of neighbourhoods (as defined by the New Zealand Deprivation Index 2013) having a prevalence of 7.9%, compared with those living in the least deprived quintile having a diabetes prevalence of 4.9%.

The Auckland Region is the largest metropolitan area in New Zealand, with a population of 1.5 million people, which constitutes approximately one-third of the national population. About 90% of its residents live in urban areas. This region is the most ethnically diverse in New Zealand, with the largest population of Māori and Pacific peoples. Diabetes prevalence in the Auckland region is higher than the national estimate (9% vs 5.5%), and higher in the Counties Manukau District Health Board (DHB) catchment than the two other Auckland regional DHBs. In order to focus efforts towards reducing the burden of diabetes for those most in need, a better understanding of the geography of diabetes in Auckland is required. This study aimed to map the prevalence of diabetes in the Auckland region by General Electoral Districts (GEDs) stratified by age, gender and ethnicity. Using InstantAtlas™ mapping software we present variations in the prevalence of diabetes among adults aged ≥30 years, which are freely available from www.fmhs.auckland.ac.nz/view-maps.

**Methods**

Every New Zealand resident has a unique health identifier, the National Health Index (NHI) number, which is used consistently across patient medical records within the health and disability support sectors.

We used encrypted NHIs (eNHIs) to anonymously link nationally held datasets that record a patient’s interaction with New Zealand’s universal health care system including PHOs, hospital discharges and mortality. We developed a regional cohort comprising the residing population aged 30 years and above enrolled in an Auckland regional PHO in the third quarter of 2011. We excluded the population aged below 30 years, consistent with our wider research programme, which focuses on the cardiovascular disease risk. People with diagnosed diabetes were identified from inpatient events in the national hospitalisation database (the National Minimum Data Set, NMDS), with a primary or secondary diagnosis coded under the ICD 10 AM classification system as: E10 to E14 Diabetes mellitus. They were also identified from the following classes of dispensed pharmaceuticals: oral hypoglycaemic agents (eg, Gliclazide, Metformin hydrochloride, Tolbutamide); hyperglycaemic agents (eg, Glucagon hydrochloride); and insulin preparations. Participants were eligible for inclusion in this study if they were: aged ≥30 years at 1 July 2011; were enrolled in any PHO within the Auckland Region between 1 July and 30 September 2011; and had complete information regarding age, gender, ethnicity, residential address, diabetes status (diagnosed/undiagnosed) as at 30 September 2011, and area deprivation. Residential address can be assigned to a meshblock, the smallest level of aggregation available for the analysis of census and other social data, designed to nest neatly within GEDs. The residential address was also used to assign New Zealand Index of Deprivation (NZDep2006) scores to each participant. NZDep2006 is a small-area measure of social conditions derived from nine variables from the 2006 Census. Typically, the deprivation scores assigned to a meshblock are categorised into deciles, with Decile 1 representing the 10% of least deprived meshblocks and Decile 10 depicting the most deprived 10% of meshblocks nationally. In this study, we collapsed the deciles into quintiles, each representing 20% of meshblocks, with quintile 5 representing the most deprived 20% of meshblocks in New Zealand.

We excluded potentially eligible participants who were aged below 30 years, had died during the study period, missing geo-locators, and those who lived in the Northland and Waikato GEDs, whose boundaries overlap with the geographic limits of the Auckland Region.
We used the Ministry of Health's protocol for prioritising ethnicity codes into Māori, Pacific, Indian, and New Zealand European (NZEO) ethnic groups. According to the MOH protocols, the Indian ethnic group is a subset of the broader Asian ethnic category. However, given the CVD risk among South Asians is substantially higher than for other Asian sub-populations such as Chinese, Korean or Japanese, we separated Indian patients from Other Asians. Moreover, the Other Asian ethnic group was combined with the NZEO ethnic group. Statistical analysis was performed using SAS version 9.4. We report prevalence estimates and corresponding 95% confidence intervals. Population age- and gender-specific denominators were available from Statistics New Zealand's mid-year population estimates for 2011 by GED, and we used the World Health Organization's Standard Population to calculate age-sex standardised diabetes prevalence rates for the cohort overall and for gender by GED. Ethnic-specific population estimates were only available for the Māori, Pacific, or Other ethnic groupings, and the Other Ethnic group was used as the standard population. Unadjusted age-specific estimates were also calculated by GED. The GEDs were defined in 2007 and were used for the 2007 and 2011 general elections, and are designed by legislation to be areas of roughly equal population size, with an average of 60,000 residents.

We used the extremal quotients (EQ) to measure variation within each ethnic or age group. The EQ is calculated as the ratio of the highest value to lowest values and its interpretation is similar to the relative risk; the larger the EQ, the larger the inequality. To further investigate trends by GED, we modelled the likelihood of people having diabetes, controlling for their age, gender, ethnicity and neighbourhood deprivation to determine whether geographical variation remained. Given Indian people have a higher risk of CVD and diabetes-related events, the logistic regression models considered four ethnic groups: NZEO, Māori, Pacific and Indian.

This research is part of the Auckland Region Vascular Atlas study and ethical approval was granted by the Northern X Regional Ethics Committee in 2010 (NXT/10/EXP/224).

Results

We obtained data on 798,238 people enrolled in PHOs within the Auckland Region in Quarter 3, 2011 for this study. Figure 1 shows that there were 738,687 people aged 30 years and over living in the Auckland region in 2011, of whom 63,014 (8.5%) had diabetes, giving an age-standardised prevalence of 7.5%.

Table 1 shows the prevalence of people diagnosed with diabetes, stratified by age, gender and ethnicity. The number of cases peaked among people aged 60 to 64 years, with 8,548 people with diagnosed diabetes, however the highest age-specific proportions were seen in those aged 70 to 74 and 75 to 79 years (both 15.6%). There was marked variation in diabetes by ethnicity with age-standardised prevalence rates of 10.3% among Māori, 15.8% among Pacific, and 6.3% among NZEO.

Table 2 presents the age-standardised rates of diabetes overall and by gender with age-specific rates and EQ, for each GED in the Auckland region. A customisable online version of this data with the accompanying maps is available to access from http://view.ac.nz/AKL_Diabetes_Prevalence_SingleMap/.

We found marked geographical variation in the prevalence of diabetes with the highest rates in GEDs in the south (Mangere, Manakau East and Manurewa, Mt Roskill and to a lesser extent Maungakiekie, Botany and Papakura) and lowest rates in GEDs in central and north Auckland (Auckland Central, Epsom, North Shore, and East Coast Bays). The highest diabetes prevalence was 17.3% in Mangere and the lowest was 3.2% on the North Shore, resulting in an EQ of 4.5. The GEDs on the urban/rural fringe also had lower rates, including Rodney, Helensville and Hunua. The west Auckland areas of Waitakere, Te Atatu and New Lynn had intermediate levels of diabetes.

Overall, males had a higher rate of diabetes than females. There was considerable variation in the prevalence of diabetes both within and between ethnic groups. Overall, Pacific participants had the highest rate of diabetes (15.8%), more than two-and-a-half times greater than for the NZEO population (6.3%). Controlling for other socio-demographic variables, we found that the Indian people were nearly
Figure 1: Eligibility flowchart.
Table 1: Number of people aged 30 years and over with diagnosed diabetes in the Auckland region in 2011 by age, gender and ethnicity (unadjusted).

<table>
<thead>
<tr>
<th>Diagnosed Diabetes</th>
<th>Enrolled PHO Study Population (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (N)</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>63,014</td>
</tr>
<tr>
<td>30 to 74 years</td>
<td>54,345</td>
</tr>
</tbody>
</table>

**Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Population (N)</th>
<th>%</th>
<th>PHO Study Population (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31,194</td>
<td>9.0</td>
<td>345,346</td>
</tr>
<tr>
<td>Female</td>
<td>31,820</td>
<td>8.1</td>
<td>393,341</td>
</tr>
</tbody>
</table>

**Age Group**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Diagnosed Diabetes (N)</th>
<th>%</th>
<th>Enrolled PHO Study Population (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 34</td>
<td>2,546</td>
<td>2.8</td>
<td>89,793</td>
</tr>
<tr>
<td>35 to 39</td>
<td>3,502</td>
<td>3.6</td>
<td>97,305</td>
</tr>
<tr>
<td>40 to 44</td>
<td>4,733</td>
<td>4.7</td>
<td>100,405</td>
</tr>
<tr>
<td>45 to 49</td>
<td>6,287</td>
<td>6.4</td>
<td>98,409</td>
</tr>
<tr>
<td>50 to 54</td>
<td>7,423</td>
<td>8.7</td>
<td>84,987</td>
</tr>
<tr>
<td>55 to 59</td>
<td>8,014</td>
<td>11.3</td>
<td>70,887</td>
</tr>
<tr>
<td>60 to 64</td>
<td>8,548</td>
<td>13.6</td>
<td>62,690</td>
</tr>
<tr>
<td>65 to 69</td>
<td>7,204</td>
<td>15.9</td>
<td>45,421</td>
</tr>
<tr>
<td>70 to 74</td>
<td>6,088</td>
<td>17.6</td>
<td>34,541</td>
</tr>
<tr>
<td>75 to 79</td>
<td>4,164</td>
<td>17.6</td>
<td>23,669</td>
</tr>
<tr>
<td>80 to 84</td>
<td>2,753</td>
<td>16.0</td>
<td>17,174</td>
</tr>
<tr>
<td>≥85</td>
<td>1,752</td>
<td>13.1</td>
<td>13,406</td>
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</tbody>
</table>

**Ethnicity**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Diagnosed Diabetes (N)</th>
<th>%</th>
<th>Enrolled PHO Study Population (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>6,048</td>
<td>12.3</td>
<td>49,052</td>
</tr>
<tr>
<td>Pacific</td>
<td>16,171</td>
<td>19.5</td>
<td>82,758</td>
</tr>
<tr>
<td>Indian</td>
<td>7,399</td>
<td>17.4</td>
<td>42,521</td>
</tr>
<tr>
<td>NZEO</td>
<td>33,396</td>
<td>5.9</td>
<td>564,300</td>
</tr>
</tbody>
</table>
Table 2: Prevalence rates (%) of diagnosed diabetes by General Electoral District (GED) in Auckland in 2011.*

<table>
<thead>
<tr>
<th>GED</th>
<th>Total (%) (age &amp; sex standardised)</th>
<th>Male (%) (age-standardised)</th>
<th>Female (%) (age-standardised)</th>
<th>Gender (%) (age-standardised)</th>
<th>Age-specific rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auckland Central</td>
<td>4.4</td>
<td>5.0</td>
<td>3.8</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Botany</td>
<td>8.0</td>
<td>8.4</td>
<td>7.5</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td>East Coast Bays</td>
<td>4.3</td>
<td>4.7</td>
<td>3.9</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Epsom</td>
<td>4.0</td>
<td>4.4</td>
<td>3.7</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Helensville</td>
<td>4.5</td>
<td>5.0</td>
<td>4.1</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Hunua</td>
<td>5.6</td>
<td>5.8</td>
<td>5.3</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Mangere</td>
<td>17.3</td>
<td>16.7</td>
<td>17.7</td>
<td>5.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Manukau East</td>
<td>15.0</td>
<td>14.5</td>
<td>15.4</td>
<td>4.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Manurewa</td>
<td>13.4</td>
<td>13.5</td>
<td>13.3</td>
<td>3.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Maungakiekie</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Mt Albert</td>
<td>7.6</td>
<td>7.6</td>
<td>7.7</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Mt Roskill</td>
<td>9.6</td>
<td>10.0</td>
<td>9.3</td>
<td>2.7</td>
<td>3.9</td>
</tr>
<tr>
<td>New Lynn</td>
<td>7.8</td>
<td>8.2</td>
<td>7.4</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>North Shore</td>
<td>3.2</td>
<td>3.6</td>
<td>2.9</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Northcote</td>
<td>5.3</td>
<td>5.6</td>
<td>5.0</td>
<td>1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Pakuranga</td>
<td>5.2</td>
<td>5.4</td>
<td>5.1</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Papakura</td>
<td>7.9</td>
<td>8.2</td>
<td>7.5</td>
<td>3.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Rodney</td>
<td>3.4</td>
<td>3.8</td>
<td>3.1</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Tamaki</td>
<td>5.6</td>
<td>6.1</td>
<td>5.2</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Te Atatu</td>
<td>8.5</td>
<td>8.7</td>
<td>8.4</td>
<td>2.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Waitakere</td>
<td>8.2</td>
<td>8.0</td>
<td>8.4</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Extremal Quotient</td>
<td>5.3</td>
<td>4.6</td>
<td>6.1</td>
<td>6.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Auckland Region</td>
<td>7.5</td>
<td>7.7</td>
<td>7.3</td>
<td>2.4</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* Note that the World Health Organization’s Standard Population was used to calculate age-sex standardised diabetes prevalence rates for the cohort overall and for gender by GED. Therefore the rates for these groups may differ slightly from the (unadjusted) rates reported in Table 1.
Table 3: Unadjusted and adjusted* odds ratios of the likelihood of people aged 30 years and over having diagnosed diabetes in the Auckland Region, in Quarter 3 2011.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>30–34</td>
<td>0.21</td>
<td>0.20–0.22</td>
</tr>
<tr>
<td>35–44</td>
<td>0.31</td>
<td>0.30–0.32</td>
</tr>
<tr>
<td>45–54</td>
<td>0.57</td>
<td>0.56–0.59</td>
</tr>
<tr>
<td>55–64</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>65–74</td>
<td>1.41</td>
<td>1.37–1.44</td>
</tr>
<tr>
<td>75–84</td>
<td>1.44</td>
<td>1.40–1.49</td>
</tr>
<tr>
<td>85+</td>
<td>1.06</td>
<td>1.01–1.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Male</td>
<td>1.13</td>
<td>1.11–1.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZEO</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Māori</td>
<td>2.24</td>
<td>2.17–2.30</td>
</tr>
<tr>
<td>Pacific</td>
<td>3.86</td>
<td>3.78–3.94</td>
</tr>
<tr>
<td>Indian</td>
<td>3.35</td>
<td>3.26–3.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NZDep06 Quintiles</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (Least deprived)</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Q2</td>
<td>1.25</td>
<td>1.21–1.29</td>
</tr>
<tr>
<td>Q3</td>
<td>1.61</td>
<td>1.56–1.66</td>
</tr>
<tr>
<td>Q4</td>
<td>2.27</td>
<td>2.21–2.34</td>
</tr>
<tr>
<td>Q5 (Most deprived)</td>
<td>3.46</td>
<td>3.37–3.55</td>
</tr>
</tbody>
</table>

* controlling for age, gender, ethnicity, deprivation and GED.
Figure 2: Geography matters. Geographical variation in the odds ratios of patients being diagnosed with diabetes in the Auckland region by GED in Quarter 3 2011, controlling for age, gender, ethnicity, and deprivation (Note: N.P. = No Population).
four times as likely as NZEO people to have diabetes (OR 3.85 [3.73 to 3.97])—significantly higher than both Pacific and Māori. Table 2 suggests that the geography of diabetes by GED shows a remarkably consistent trend, in which residents in the Mangere GED have significantly more diabetes cases than other GEDs in Auckland. To move beyond univariate analyses however, this trend was further confirmed in our adjusted model in Table 3. We also modelled the geographic variation in the prevalence of diabetes using the North Shore GED as the reference, since this GED had the lowest diabetes prevalence for the total population. Figure 2 shows that after controlling for age, gender, ethnicity and deprivation, substantial geographical variations in diabetes remain. While the odds of people in the Rodney (OR: 0.98 [0.91 to 1.05]) and Auckland Central (OR: 1.01 [0.94 to 1.09]) GEDs having diabetes was not significantly different to residents in the North Shore GED, the odds of people living in South Auckland GEDs having diabetes are at least 65–87% higher than the odds of people living in the North Shore GED.

Our findings are broadly consistent with previous research. We estimated an overall prevalence of 8.5% which is very similar to the estimates of Balalla10 (9%, using the same definitions, with people aged ≥30, for territorial authorities in the Auckland Region rather than GEDs) and Thornley19 (9.6%) using capture-recapture methodology in south Auckland in 2007; aged ≥15 and unadjusted. Our estimates were higher than those of Smith et al,11 who reported age- and sex-standardised diabetes prevalence estimates of 7.1% (included all age groups) in Counties Manukau DHB (CMDHB) and 5.2% for the other three northern DHBs (Auckland DHB, Waitemata DHB, Northland DHB) in 2006–7. Similar to previous research, our results show that the prevalence of diabetes increased significantly with age,2,4,10,11 and that women have slightly lower rates than men.10,19

Investigating the ethnic trends of diabetes has been a focus of numerous research projects. A cross-sectional study of people aged 35–74 carried out in 2002–3 by Sundborn20 found significant ethnic inequalities: Pacific people had a prevalence of diabetes more than four times higher than New Zealand Europeans. The overall prevalence for Pacific people with new and previously diagnosed diabetes was 4.0% and 19.5% respectively. The highest rates were found among Samoan men (26.2%) and Tongan women (35.8%). Smith et al11 found high rates among Pacific people in Auckland too, with Pacific women having the highest diabetes prevalence of all the groups measured (15.0%). In agreement with that research, we found that Pacific people had the highest age-standardised prevalence of diabetes (15.8%).

Māori also face a high burden of diabetes. Balalla10 found that Auckland Māori were three times as likely to have diabetes than NZEO people. In CMDHB, Smith et al11 estimated the age-standardised prevalence to be 12.2% for Māori men, compared to 5.0% of NZEO men, and 10.6% for Māori women, compared to 4.0% of NZEO women. Our
findings were similar, finding an age-standardised prevalence of 10.3% for Māori.

The geographical and ethnic inequities in diabetes prevalence in the Auckland region shown in this study are stark reminders that even in one relatively small metropolitan area, there can be huge variation in rates of key health conditions. The reasons behind such variation are complex, and are most likely the result of a multitude of factors. While traditional explanations have focused on the development of unhealthy behaviours, such as excess calorie intake, physical inactivity and smoking in adulthood leading to obesity and diabetes, the social determinants of health that begin even before birth are increasingly being seen as important causal factors. These distal antecedents of diabetes include material deprivation (of the mother when pregnant, as well as material resources as people grow up and age), obesogenic environments (which promote calorie-dense nutrient-poor food, driven by urbanisation and globalisation), psychosocial stress (which relates to both the neuroendocrine mechanisms of stress and the more indirect path of increasing the likelihood of the development of unhealthy behaviours), and access to health care. Addressing these factors presents a number of challenges and requires concerted action across a range of government departments and services.

Looking internationally, Fano et al investigated the link between type 2 diabetes prevalence and deprivation in Rome (n=27,642; aged ≥35), and found a social prevalence and deprivation in Rome mitigated the link between type 2 diabetes government departments and services.

The geographical and ethnic inequities in diabetes prevalence in the Auckland region shown in this study are stark reminders that even in one relatively small metropolitan area, there can be huge variation in rates of key health conditions. The reasons behind such variation are complex, and are most likely the result of a multitude of factors. While traditional explanations have focused on the development of unhealthy behaviours, such as excess calorie intake, physical inactivity and smoking in adulthood leading to obesity and diabetes, the social determinants of health that begin even before birth are increasingly being seen as important causal factors. These distal antecedents of diabetes include material deprivation (of the mother when pregnant, as well as material resources as people grow up and age), obesogenic environments (which promote calorie-dense nutrient-poor food, driven by urbanisation and globalisation), psychosocial stress (which relates to both the neuroendocrine mechanisms of stress and the more indirect path of increasing the likelihood of the development of unhealthy behaviours), and access to health care. Addressing these factors presents a number of challenges and requires concerted action across a range of government departments and services.

Looking internationally, Fano et al investigated the link between type 2 diabetes prevalence and deprivation in Rome (n=27,642; aged ≥35), and found a social gradient, as has been reported in this study. Cox et al analysed type 2 diabetes by area in Tayside, Scotland (n=3,917; aged 45–75+). Interestingly, they found that neighbouring areas made a significant difference to an area’s incidence of diabetes. That is, areas with less deprived areas around them had lower rates of diabetes, and areas with more deprived areas around them had higher rates. They propose this may be due to a variety of factors, in which less deprived areas have better access to healthy food options, outdoor areas (e.g., parks), health care, as well as increased employment opportunities, all of which may also have influenced our results for Auckland.

To our knowledge this is the first study to investigate diabetes prevalence by GED. The GEDs are of particular importance as these are the areas for which elected members of parliament stand. This has the advantage of allowing researchers, and the public, the opportunity to present politicians with data that directly relates to the area they represent. The GEDs allow the inequities in health outcomes to speak for themselves, so that politicians can represent their constituents when seeking to improve the health of their populations. We believe this innovative methodology could be a catalyst for change. Second, the data are robust and based on a large cohort. Using the encrypted NHIs and linking health databases is a reliable method for estimating the prevalence of diabetes, and avoids the drawbacks of relying on self-report.

This study is not without its limitations. First, we did not stratify the data by deprivation level. While it has become customary to provide analysis of differences between socioeconomic groups, we felt it was inappropriate to do so in this study. The GEDs, although of equal size, are heterogeneous in their socioeconomic composition. That is, neighbourhoods within a GED can be substantially different making it difficult to have one value that represents the entire community. In the absence of individual-level indicators of socioeconomic position (SEP), NZDep06 was included as a proxy measure. Nevertheless, as NZDep06 measures the area-level social conditions rather than the circumstances of individuals, caution is required for its interpretation, given the implications of the ecological fallacy. Furthermore, as NZDep06 measures the area-level social conditions rather than the circumstances of individuals, caution is required for its interpretation, given the implications of the ecological fallacy. Furthermore, as NZDep06 measures the area-level social conditions rather than the circumstances of individuals, caution is required for its interpretation, given the implications of the ecological fallacy.

Second, it should be noted that while our GED classification is based on the 2007 boundaries, the configuration of the GEDs changed for the 2014 election resulting in the splitting of some GEDs to create the new Upper Harbour and Kelston GEDs. This could potentially result in reduced political accountability, particularly where those boundary splits affect areas of higher diabetes prevalence. Our ongoing research program will explore geographic variations in diabetes and other factors associated with CVD nationally, mapped to the 2014 GEDs.
Third, we were unable to account for cases of undiagnosed diabetes. It has been noted that rates of undiagnosed diabetes are in themselves inequitable, with research suggesting the highest prevalence of undiagnosed diabetes is found among Pacific people (6.4%), followed by Māori (2.2%), and NZEO (1.5%). Our results will have therefore not only underestimated the overall prevalence of diabetes, but also the extent of the ethnic and GED inequities.

Fourth, our analysis only included people who were enrolled in a PHO. While the vast majority of people are indeed enrolled (an estimated 94% of the population in the Auckland region), there is a chance that we are missing people with diabetes who do not have access to the primary health care system. While likely to be a small number of cases, this could further contribute to the underestimation of the prevalence of diabetes.

Finally, there is some inherent difficulty in distinguishing between cases of pre-diabetes and diabetes. Increasingly, people with prediabetes are prescribed metformin, and by using medication to identify cases, this could have led to an over-estimation of the prevalence.

This research highlights the extensive inequities of diabetes prevalence among the GEDs in the Auckland region. It is beyond the scope of this research to speculate on the local mechanisms that underlie this significant inequity, but further research into potential geographic factors such as food affordability and availability are required. For example, a recent systematic review found that taxing unhealthy foods in combination with subsidising healthy foods at sufficiently high rates has the potential to promote healthier eating and weight loss. Other interventions that have been shown to be cost-effective in reducing obesity include: reducing advertising of unhealthy food and beverages to children; and school-based programmes aiming to reduce viewing of television; improving knowledge about nutrition; increasing physical activity; and reducing consumption of sugar-sweetened beverages.

Researching these topics in the context of Aotearoa New Zealand, and subsequently implementing evidence-based practices could have a substantial impact on the increasing rates and associated inequities of diabetes in this country. It has often been thought that factors that may be of particular importance in explaining neighbourhood variation in health outcomes include population density, food outlet density, average distance to parks, walkability, and alcohol outlet density, however, the idea that more deprived communities have less access to health-promoting resources is being challenged as an explanation.

Community-based action programmes could be especially important, for instance by involving local schools through education and making the physical environment more conducive to healthy lifestyles. In our own backyard, implementation of programmes such as Let’s Beat Diabetes in CMDHB, Project Energize in the Waikato, and Ngati and Healthy on the East Coast have shown that local, community-driven initiatives can have positive impacts on health. Other programmes targeting overall healthy lifestyles in the Pacific community are also areas of promise. Many of the effects of these programmes may not be evident in the short-term however, and creating systems, funding processes, and community engagement that can be sustained in the long-term remain challenging.

Whatever decisions are made about the future of diabetes policy, prevention and management programmes, the fact that residents living 25km away from the North Shore GED are 1.87 times more likely to have diabetes is unacceptable.
Competing interests:
Susan Wells reports grants from the Stevenson Foundation, and the Health Research Council of New Zealand during the conduct of the study, and grants from Roche Diagnostics, and the National Heart Foundation of New Zealand, outside the submitted work.

Funding:
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Author information:
Briar Warin, School of Population Health, University of Auckland, Auckland; Daniel J Exeter, School of Population Health, University of Auckland, Auckland; Jin Feng Zhao, School of Population Health, University of Auckland, Auckland; Timothy Kenealy, School of Population Health, University of Auckland, Auckland; Susan Wells, School of Population Health, University of Auckland, Auckland, New Zealand.

Corresponding author:
Daniel J Exeter, Section of Epidemiology & Biostatistics, School of Population Health, University of Auckland, PB 93019 Auckland Mail Centre, 1142, Auckland, New Zealand.
d.exeter@auckland.ac.nz

URL:

REFERENCES:


20. Sundborn G. Cardiovascular Disease Risk Factors and Diabetes in Pacific Adults: The Diabetes Heart and Health Study (DHAH), Auckland, New Zealand 2002/03. Auckland: University of Auckland; 2009.


Trampoline-associated injuries are more common in children in spring

Michael S Yule, Sanjeev Krishna, Jamie-Lee Rahiri, Andrew G Hill

ABSTRACT

AIMS: Trampoline use is a popular pastime amongst children in New Zealand, and has many advantages for child development. However, recent reports claim that trampoline-associated injuries are still highly prevalent. In order to help prevent these injuries in the future, this study aims to provide more up-to-date epidemiological information in children, with emphasis on the time of year that injuries most commonly occur.

METHODS: A retrospective review was carried out utilising a prospective maintained trauma database. The database was searched electronically for injuries involving trampolines in children aged 0–15 years. Patient demographics and information regarding month of injury, injury type and management were extracted.

RESULTS: There were 344 admissions to hospital for trampoline-related injuries between June 2000 and January 2015. Injuries were uncommon in winter, but rose in spring and summer. Fracture of the radius and/or ulna was the most common injury (34.0%), followed by humeral fracture (32.0%).

CONCLUSION: The peak incidence of trampoline-related injuries occurred around the beginning of spring daylight savings time each year. This could therefore prove an opportune time to remind children and parents about trampoline safety at the same time as daylight savings reminders.

Trampoline use is a popular past time among children. Trampolines provide the opportunity for physical activity, as well as contributing to childhood development through risk taking and play. While an enjoyable activity, the advantages of trampoline use do come at a cost.

Unpublished data by the New Zealand Injury Prevention Research Unit claims that there were 1,537 hospital admissions for trampoline-related injury between 2007 and 2011 among children aged 0–14. Children between the ages of 3–6 years accounted for more than 40% of all the trampoline-related admissions. Comparing these data to an older study that reported 2,098 first admissions into public hospitals between 1979 and 1988, there has been a clear increase in the number of trampoline-related injuries in recent years.

While the importance of trampoline safety has been recognised through child injury prevention initiatives, such as Safekids Aotearoa, there is still a need to decrease the burden of injury from trampolining. One approach to decreasing trampoline-associated injuries may be to target public safety campaigns just before the peak incidence of injuries.

This retrospective study, carried out in the Counties Manukau District Health Board (CMDHB) population, aims to give more up-to-date epidemiological information about trampoline-related injuries in children ages 0–15 in order to identify periods of peak incidence of injury, thus enabling strategically targeted injury prevention public safety campaigns.

Methods

This retrospective review was carried out by identifying patients from a prospectively collected trauma database. The trauma database includes all trauma admissions to the Emergency Department at Middlemore Hospital, and Kidz First Hospitals in South Auckland, New Zealand, from June 2000 to January 2015. The ‘cause of injury’ field
was searched electronically using the key word “tramp”. All those over the age of 15 at the time of admission were excluded. Patients were also excluded if their reason for admission was not trampoline related. Data were extracted from electronically stored patient files and discharge summaries. Paper records of notes were reviewed when necessary information was not available electronically.

The extracted data included: month of injury; injury pattern/type; treatment required; age; gender; ethnicity; and if the patient had a previous trampoline-associated injury. Injury pattern/type was further categorised into: musculoskeletal sprain/strain; fracture managed without operative intervention; fracture requiring operative intervention; minor head injury; major head injury; and other. A diagnosis of intracranial haemorrhage defined major head injury, separating it from minor head injury. Treatment required was classified as: conservative management (eg, pain relief, rest from activities); fracture manipulation and casting; and operative intervention. Operative intervention was defined as treatment that required a skin incision to be made, eg, insertion of a Kirschner wire, a titanium elastic nail or washout and debridement of a wound. For ease of data handling, subject ethnicity was classified according to Level 1 of the Statistic New Zealand (SNZ) Ethnicity Classification, producing five categories: European, Māori, Pacific Island, Asian, and Other ethnic groups.

Using SPSS® (IBM, 2015) descriptive statistics were calculated. The final database was then reformatted into count data for each month of each year of the study (ie, how many injuries occurred in each month of each year). Poisson regression was then performed to give a ratio of incidence and p-values for each month of the year.

Because of the format of the available census data, only years that were observed in whole were included in the calculation of the age standardised incidence rate, using World Health Organization standard populations. This was calculated in Excel® (Microsoft, 2007).

**Results**

Electronic search of the trauma database with the keyword “tramp” produced 378 results. Of these, four were excluded because there was no evidence that these admissions to hospital were related to a trampoline accident. Twenty-nine were excluded because they were outside the age range selected for this project. One was excluded as it was a duplicate. This left 344 subjects in total for analysis.

Of the subjects, 14 (4.1%) had experienced a previous trampoline-related injury. There was a small female dominance (1.06:1) in the number of trampoline-related injuries. Europeans made up the majority of subjects (Figure 1), but this was expected given they are represented similarly in the population. The Māori population was overrepresented (around 15.7% of CMH population), which was in stark contrast to the Asian population which is underrepresented (24.0% of CMH population).

![Figure 1: Pie chart showing ethnicity distribution of trampoline associated injuries n=344.](image)
### Table 1: Classification and incidence of trampoline associated injury types.

<table>
<thead>
<tr>
<th>Injury Classification</th>
<th>Number of subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK strain/sprain</td>
<td>5</td>
<td>1.5%</td>
</tr>
<tr>
<td>Fracture not requiring operative intervention</td>
<td>162</td>
<td>47.1%</td>
</tr>
<tr>
<td>Fracture requiring operative intervention</td>
<td>151</td>
<td>43.9%</td>
</tr>
<tr>
<td>Minor head injury</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>Major head injury</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>7.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>344</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

MSK = musculoskeletal.

### Table 2: Trampoline associated injuries classified by site.

<table>
<thead>
<tr>
<th>Injury Site</th>
<th>Number of subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture of radius and/or ulna</td>
<td>117</td>
<td>34.0%</td>
</tr>
<tr>
<td>Fracture of humerus</td>
<td>110</td>
<td>32.0%</td>
</tr>
<tr>
<td>Fracture of tibia and/or fibula</td>
<td>41</td>
<td>11.9%</td>
</tr>
<tr>
<td>Laceration/degloving injury</td>
<td>14</td>
<td>4.1%</td>
</tr>
<tr>
<td>Fracture of ankle</td>
<td>10</td>
<td>2.9%</td>
</tr>
<tr>
<td>Fracture of femur</td>
<td>13</td>
<td>3.8%</td>
</tr>
<tr>
<td>Fracture of digit</td>
<td>6</td>
<td>1.7%</td>
</tr>
<tr>
<td>Fracture of facial bone including dental trauma</td>
<td>4</td>
<td>1.2%</td>
</tr>
<tr>
<td>Elbow dislocation only</td>
<td>6</td>
<td>1.7%</td>
</tr>
<tr>
<td>MSK strain/sprain/ligament damage</td>
<td>6</td>
<td>1.7%</td>
</tr>
<tr>
<td>Head injury</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>2.9%</td>
</tr>
<tr>
<td>Multiple injuries</td>
<td>5</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>344</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

### Table 3: Number of trampoline associated injuries classified by month.

<table>
<thead>
<tr>
<th>Month</th>
<th>Total no. of injuries</th>
<th>Average no. of injuries per month</th>
<th>Average % of injuries per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>42</td>
<td>2.8</td>
<td>11.9</td>
</tr>
<tr>
<td>February</td>
<td>42</td>
<td>3.0</td>
<td>12.8</td>
</tr>
<tr>
<td>March</td>
<td>28</td>
<td>2.0</td>
<td>8.5</td>
</tr>
<tr>
<td>April</td>
<td>26</td>
<td>1.9</td>
<td>7.9</td>
</tr>
<tr>
<td>May</td>
<td>12</td>
<td>0.9</td>
<td>3.7</td>
</tr>
<tr>
<td>June</td>
<td>7</td>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>July</td>
<td>12</td>
<td>0.8</td>
<td>3.4</td>
</tr>
<tr>
<td>August</td>
<td>11</td>
<td>0.7</td>
<td>3.1</td>
</tr>
<tr>
<td>September</td>
<td>28</td>
<td>1.9</td>
<td>8.0</td>
</tr>
<tr>
<td>October</td>
<td>51</td>
<td>3.4</td>
<td>14.5</td>
</tr>
<tr>
<td>November</td>
<td>48</td>
<td>3.2</td>
<td>13.7</td>
</tr>
<tr>
<td>December</td>
<td>37</td>
<td>2.5</td>
<td>10.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>344</strong></td>
<td><strong>23.5</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

### Table 4: Poisson regression of trampoline associated injury data by months. December is used as the reference month.

<table>
<thead>
<tr>
<th>Month</th>
<th>Monthly ratio of incidence</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>1.135</td>
<td>0.730–1.766</td>
<td>0.574</td>
</tr>
<tr>
<td>February</td>
<td>1.129</td>
<td>0.720–1.771</td>
<td>0.596</td>
</tr>
<tr>
<td>March</td>
<td>0.782</td>
<td>0.476–1.284</td>
<td>0.331</td>
</tr>
<tr>
<td>April</td>
<td>0.724</td>
<td>0.436–1.202</td>
<td>0.212</td>
</tr>
<tr>
<td>May</td>
<td>0.347</td>
<td>0.181–0.666</td>
<td>0.001</td>
</tr>
<tr>
<td>June</td>
<td>0.189</td>
<td>0.084–0.424</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>July</td>
<td>0.324</td>
<td>0.169–0.622</td>
<td>0.001</td>
</tr>
<tr>
<td>August</td>
<td>0.270</td>
<td>0.134–0.543</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>September</td>
<td>0.757</td>
<td>0.463–1.236</td>
<td>0.266</td>
</tr>
<tr>
<td>October</td>
<td>1.378</td>
<td>0.903–2.105</td>
<td>0.137</td>
</tr>
<tr>
<td>November</td>
<td>1.270</td>
<td>0.826–1.954</td>
<td>1.270</td>
</tr>
<tr>
<td>December</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>344</strong></td>
<td><strong>23.5</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>
The majority of injuries sustained were fractures (Tables 1 and 2). Laceration or degloving injuries and musculoskeletal sprains, strains or ligament damage totalled only 5.8%.

Injuries were lowest during the month of June, and remained low during winter. Injury rates rose at the start of spring (September), peaking in October, and were sustained over summer. Injury levels then fell as autumn approached (March) (Tables 3, 4 and 5).

Table 6 shows the breakdown of ages involved in trampoline related accidents. The 5–9 age group were responsible for the greatest number of trampoline-related injuries.

Figure 2 shows the age standardised incidence rate/100,000 per annum across years 2001–2014 was 5.60. An increase in incidence was noted between 2002 and 2006. From 2010 till 2014 there was decrease in the incidence of injuries.

**Discussion**

The principal aim of this study was to determine the time of year that trampoline injuries most commonly occurred. The highest incidence of injuries tended to occur during the spring and summer months, with the peak incidence occurring in October. The vast majority of injuries were fractures, with the most common site affected being the upper limb.

The time of peak incidence coincides with the beginning of spring and daylight saving time. Since 2009, the clocks in New Zealand have changed on the last Sunday of September. Unsurprisingly, June and July, on average, were found to have the lowest
number of trampoline-related injuries. Outside temperature and favourable weather conditions clearly play a key role here.

The pattern of injuries suggests most trampoline-related injuries that resulted in hospital admission are the result of a fall onto the outstretched hand. This is a mechanism of injury that one would not expect to occur during safe trampoline use. Unsafe trampoline use, such as multiple users and the performance of ‘stunts’ without appropriate supervision, are therefore likely to be the cause of these injuries.

The Māori population were over represented in trampoline-related injuries. This could simply be due to the small sample size of this study, or reflect the dynamic nature of changing demographics in the CMDHB area. If studied over a longer period of time and confirmed, then further targeting of injury prevention strategies may be appropriate.

The incidence of head injuries in this study was much lower than previously reported in other studies. This may be because the neurosurgical unit for the greater Auckland area is based at Auckland City Hospital (ACH), and there is no neurosurgical service in South Auckland. It may be that emergency services sent children with severe head injuries to ACH without the patients being admitted. A search of all admissions to the neurosurgical unit at ACH between June 2006 and January 2015 would need to be conducted to determine if this was the case. However, improved padding and safety enclosure nets have been introduced since previous studies were conducted. These interventions may account for the lower number of head injuries witnessed in this study.

A significant limitation of the database is underreporting of injuries. Hume et al. found that for every one admission to hospital, there were 12 emergency department presentations with trampoline-related injuries. This is reflected by the very small percentage of MSK strain/sprain reported among subjects in this study. There would have also been a significant number of minor injuries which may have presented to general practice, or did not present at all to a healthcare professional. This underreporting could be seen in the database. Of the 14 subjects who had a previous trampoline-related injury, only one patient appeared in the database twice. The others patients had sustained injuries which were not significant enough to warrant inclusion on the trauma database.

**Conclusion**

In summary, the demographics reported in this study compare well to larger ones carried out previously. The peak incidence of trampoline-related injuries occur in spring around the time that New Zealand clocks change to daylight savings time. We therefore recommend that at the same time or closely before the public are reminded about the change of clocks to daylight savings time, that public safety campaigns concerning safe use of trampolines are issued. This would hopefully reduce the incidence of trampoline-related injuries and remind children and their families about safer recreational environments.
REFERENCES:


ARTICLE

Use of full strength fluoride toothpaste among preschoolers in New Zealand, and factors determining toothpaste choice

Judy Li, Sarah Dallas, Karen McBride-Henry

ABSTRACT

AIM: International researchers have highlighted an inconsistent knowledge-base for parents and caregivers regarding the use of toothpaste among preschoolers. The New Zealand Government has published recommendations on the use of toothpaste in this age group. This study aimed to explore parents and caregivers’ knowledge about toothpaste, with the aim of improving health literacy and overall oral health of New Zealand preschoolers.

METHOD: The study was conducted via an online sample of parents and caregivers of preschoolers (n=1,056).

RESULTS: Only 19% of the preschoolers in the sample used full-strength fluoride toothpaste. Preschoolers were significantly more likely to use full-strength toothpaste if they were not the first child in the family (OR=1.77, 1.28–2.47) or have previously visited a dental professional (OR=1.84, 1.18–2.85). In addition, parents and caregivers made decisions around purchasing of toothpaste based on the level of trust they had in the brand (59%) and also matching age-specific toothpaste to their child (49%).

CONCLUSION: The findings of this research highlight the need for timely advice for parents and caregivers on toothpaste choices for preschool children. The New Zealand Government has published recommendations on the use of full-strength fluoride toothpaste for all ages, including pre-schoolers.

Oral health has been identified as an important public health issue by the World Health Organization (WHO). One of the focuses of the WHO oral health preventative strategies is to prevent dental caries among all population and social groups. Apart from reducing sugar intake, tooth brushing is another effective self-care strategy.

The New Zealand Ministry of Health’s advice on tooth brushing is to brush at least twice daily. The expert advisory group of the New Zealand Guidelines Group provides further advice around the use of fluoride toothpaste; specifically, toothpaste of at least 1,000 parts per million (ppm) of fluoride is recommended for all ages. This amount of fluoride is equivalent to 0.76% sodium monofluorophosphate, or 0.221% sodium fluoride. It is also recommended that toothpastes labelled as ‘child strength’ should be avoided for all ages because of their low level of fluoride. In terms of amount, for children up to the age of 5 years old, a smear of toothpaste should be used.

Findings from the 2009 Oral Health Survey indicated that, despite the Ministry of Health’s recommendation on tooth brushing, only two-thirds of preschoolers aged 2–4 years (66%) brushed their teeth at least twice daily. The proportion of those who brushed twice daily with fluoride toothpaste was only at 15%.

Similar to other countries, in New Zealand a wide range of toothpastes are available for purchase. This includes full-strength toothpastes that are not age-specific, as well as those that are labelled for babies or children,
or as ‘natural’ or ‘herbal’ toothpastes. The strength of fluoride varies hugely, with those labelled for babies/children or as natural/herbal typically containing less fluoride (or no fluoride at all).

While the Ministry of Health\(^5\) endorses the New Zealand Guidelines Group’s recommendation of all people using full-strength toothpaste,\(^6\) there is no published data on the use of different types of toothpastes among New Zealanders.\(^8\) This study fills this information gap by collecting data on the use of different types of toothpastes by preschoolers in New Zealand, and the factors determining toothpaste choice as reported by their parents or caregivers. This information can then be used to inform public health initiatives to enhance the parents and caregivers’ health literacy in relation to toothpaste usage and improve the oral health of young New Zealanders.

Methods

Participants

The research population for the study was parents and caregivers of preschoolers, operationally defined as those aged between 4 months and 4 years 11 months old. To be eligible to take part, participants must be 18 years old and over, and responsible for providing regular care and/or guardianship for the preschoolers. Using an identical methodology as the main study, the questionnaire was piloted with 56 respondents. Prior to the commencement of the study, there was an expected sample size of 1,000 for the main survey. No change was made to the recruitment protocol or the questionnaire after the pilot, and therefore responses from the pilot were included in the analysis. This decision resulted in a total of 1,056 participants in the final sample. Ethics approval for this study was obtained from the New Zealand Ethics Committee (Ref: NZEC 15 #23).

Sampling procedure

A convenience sample of parents and caregivers were recruited from an online research panel called Consumer Link. Potential participants received an email invite and received points on completion of the online survey. The points are accumulated and can be redeemed for products or services. Prior to participation, potential respondents were informed that their participation was voluntary. Informed consent was indicated by respondents selecting a tick box to represent their willingness to participate. The response rate was 78%.

Analysis

The analysis was undertaken using STATA IC 13.1. A total of 50 respondents indicated that the preschoolers under their care did not have any teeth, and a further 22 reported that their preschoolers did not use toothpaste. The questions on toothpaste were irrelevant to this group of respondents, and therefore they were not asked in the survey. This reduced the number of cases for the analysis to 984.

The dependent variables were: a) the type of toothpaste used by the preschoolers; and b) the factors parents/caregivers considered when they chose toothpastes for their preschoolers. For both variables, descriptive statistics were calculated. In-depth analysis was also carried out with the first variable, to help with the understanding of factors that were associated with an increased likelihood of using full-strength fluoride toothpastes.

This was undertaken using univariate and multivariate logistic regression models.

Results

Sample characteristics

Socio-demographic characteristics of the total sample and the sub-sample are described in Table 1. A large majority of the adult respondents were females (87%) and the biological parent of the preschoolers (95%). Only 7% and 2% of adult respondents self-identified as Māori or Pacific (when prioritised in the order of Māori, Pacific, and European/other). In terms of the preschoolers’ characteristics, there was an even representation of both boys and girls, and the first and subsequent child of their parents.

Type of toothpaste currently used by the child

Two respondents did not know the type of toothpastes that was used by the preschool child, and their responses were excluded from the analysis on this specific measure.
Table 1: Socio-demographic characteristics of the adult respondents and the child under their care.

<table>
<thead>
<tr>
<th>Adult characteristics</th>
<th>Total Sample n=1,056</th>
<th>Sub-sample (children with 1+ teeth and used toothpaste) n=984</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>138</td>
<td>13.1</td>
</tr>
<tr>
<td>Female</td>
<td>918</td>
<td>86.9</td>
</tr>
<tr>
<td>Ethnicity (prioritised)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>76</td>
<td>7.2</td>
</tr>
<tr>
<td>Pacific</td>
<td>16</td>
<td>1.5</td>
</tr>
<tr>
<td>New Zealand European/ Other</td>
<td></td>
<td>964</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–24 years</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>25–34 years</td>
<td>474</td>
<td>44.9</td>
</tr>
<tr>
<td>35–44 years</td>
<td>518</td>
<td>49.1</td>
</tr>
<tr>
<td>45–54 years</td>
<td>40</td>
<td>3.8</td>
</tr>
<tr>
<td>55+ years</td>
<td>13</td>
<td>1.2</td>
</tr>
<tr>
<td>Relationship to the child</td>
<td></td>
<td></td>
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<tr>
<td>Biological parent</td>
<td>1,003</td>
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<tr>
<td>Mother's/father's partner</td>
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<td>26</td>
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<tr>
<td>Grandparent</td>
<td>14</td>
<td>1.3</td>
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<tr>
<td>Foster parent</td>
<td>7</td>
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<tr>
<td>Legal guardian</td>
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<tr>
<td>Aunt</td>
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<tr>
<td>Household equivalised income</td>
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<td></td>
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<tr>
<td>&lt;$40,000</td>
<td>63</td>
<td>6.0</td>
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<td>$40,001–$70,000</td>
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<td>26.1</td>
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<td>$100,001+</td>
<td>360</td>
<td>34.1</td>
</tr>
<tr>
<td>Don't know</td>
<td>103</td>
<td>9.8</td>
</tr>
<tr>
<td>Child characteristics</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>527</td>
<td>49.9</td>
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<tr>
<td>Female</td>
<td>529</td>
<td>50.1</td>
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<td>Ethnicity (prioritised)</td>
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<tr>
<td>Māori</td>
<td>138</td>
<td>13.1</td>
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<td>Pacific</td>
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<td>2.9</td>
</tr>
<tr>
<td>New Zealand European/ Other</td>
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<td>887</td>
</tr>
<tr>
<td>Age group</td>
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</tr>
<tr>
<td>4–6 months</td>
<td>46</td>
<td>4.4</td>
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<tr>
<td>7–11 months</td>
<td>47</td>
<td>4.5</td>
</tr>
<tr>
<td>1 year</td>
<td>227</td>
<td>21.5</td>
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<tr>
<td>2 years</td>
<td>262</td>
<td>24.8</td>
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<tr>
<td>3 years</td>
<td>278</td>
<td>26.3</td>
</tr>
<tr>
<td>4 years</td>
<td>196</td>
<td>18.6</td>
</tr>
<tr>
<td>First child of the adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>532</td>
<td>52.9</td>
</tr>
<tr>
<td>No</td>
<td>474</td>
<td>47.1</td>
</tr>
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Table 2: Type of toothpaste currently used by the child, reported by the parents/caregivers (n=982).

<table>
<thead>
<tr>
<th></th>
<th>Toothpaste for babies (n=222)</th>
<th>Toothpaste for children (n=535)</th>
<th>Non-fluoridated/natural toothpaste (n=40)</th>
<th>Full-strength fluoride toothpaste (n=185)</th>
<th>Odds ratio (using full-strength fluoride toothpaste)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>22.6</td>
<td>54.5</td>
<td>4.1</td>
<td>18.8</td>
<td>-</td>
</tr>
<tr>
<td><strong>Child's gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=488)</td>
<td>23.0</td>
<td>57.0</td>
<td>3.7</td>
<td>16.4</td>
<td>1</td>
</tr>
<tr>
<td>Female (n=494)</td>
<td>22.3</td>
<td>52.0</td>
<td>4.5</td>
<td>21.3</td>
<td>1.38 (1.00–1.90)</td>
</tr>
<tr>
<td><strong>Child's ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori (n=128)</td>
<td>25.8</td>
<td>50.0</td>
<td>5.5</td>
<td>18.8</td>
<td>1</td>
</tr>
<tr>
<td>Non-Māori (n=854)</td>
<td>22.1</td>
<td>55.2</td>
<td>3.9</td>
<td>18.9</td>
<td>1.01 (.63–1.62)</td>
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<tr>
<td><strong>Adult's ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori (n=72)</td>
<td>25.0</td>
<td>48.6</td>
<td>5.6</td>
<td>20.8</td>
<td>1</td>
</tr>
<tr>
<td>Non-Māori (n=910)</td>
<td>22.4</td>
<td>54.9</td>
<td>4.0</td>
<td>18.7</td>
<td>.87 (.48–1.59)</td>
</tr>
<tr>
<td><strong>Child's age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–6 months (n=6)</td>
<td>16.7</td>
<td>66.7</td>
<td>0.0</td>
<td>16.7</td>
<td>1</td>
</tr>
<tr>
<td>7–11 months (n=23)</td>
<td>43.4</td>
<td>43.5</td>
<td>0.0</td>
<td>13.0</td>
<td>.75 (.06–8.83)</td>
</tr>
<tr>
<td>1 year (n=220)</td>
<td>40.5</td>
<td>39.1</td>
<td>3.6</td>
<td>16.8</td>
<td>1.01 (.11–8.91)</td>
</tr>
<tr>
<td>2 years (n=259)</td>
<td>25.5</td>
<td>50.6</td>
<td>3.1</td>
<td>20.8</td>
<td>1.32 (.15–11.51)</td>
</tr>
<tr>
<td>3–4 years (n=474)</td>
<td>11.8</td>
<td>64.1</td>
<td>5.1</td>
<td>19.0</td>
<td>1.17 (.14–10.15)</td>
</tr>
<tr>
<td><strong>First child of the adult (n=959)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=507)</td>
<td>25.4</td>
<td>55.4</td>
<td>4.1</td>
<td>15.0</td>
<td>1</td>
</tr>
<tr>
<td>No (n=428)</td>
<td>19.4</td>
<td>52.9</td>
<td>4.0</td>
<td>23.8</td>
<td>1.77 (1.28–2.47)</td>
</tr>
<tr>
<td><strong>Perceived oral health status (n=982)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/very good (n=879)</td>
<td>23.1</td>
<td>54.2</td>
<td>4.0</td>
<td>18.8</td>
<td>1</td>
</tr>
<tr>
<td>Good/fair/poor (n=101)</td>
<td>17.8</td>
<td>58.4</td>
<td>5.0</td>
<td>18.8</td>
<td>1.00 (.59–1.70)</td>
</tr>
<tr>
<td><strong>Child had visited a dental professional (n=971)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=755)</td>
<td>38.4</td>
<td>44.9</td>
<td>4.2</td>
<td>12.5</td>
<td>1</td>
</tr>
<tr>
<td>Yes (n=216)</td>
<td>18.1</td>
<td>57.0</td>
<td>4.1</td>
<td>20.8</td>
<td>1.84 (1.18–2.85)</td>
</tr>
<tr>
<td><strong>Agreed that it is important to use age-appropriate toothpaste (n=946)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=362)</td>
<td>9.1</td>
<td>43.1</td>
<td>5.0</td>
<td>42.8</td>
<td>19.13 (11.91–30.71)</td>
</tr>
<tr>
<td>Yes (n=584)</td>
<td>31.0</td>
<td>61.6</td>
<td>3.6</td>
<td>3.8</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Statistically significant difference at p<0.05 are denoted in bold.
(n=982). Overall, only 19% of the preschoolers in our sample used full-strength fluoride toothpaste. Half of them used toothpastes labelled as suitable for children.

The odds ratios generated from the univariate logistic regression models suggested that the likelihood of preschoolers using full-strength fluoride toothpastes did not differ by the preschooler’s demographic characteristics, adult's ethnicity, or perceived oral health of the child, as reported by the adult. However, preschoolers had increased likelihood of using full-strength fluoride toothpastes if they were not the first child of their parents (OR=1.77, 95% CI=1.28–2.47) or if they had ever visited a dental professional (OR=1.84, 95% CI=1.18–2.85). Because of the potential association between dental visit and the child's age, a multivariate logistic regression model was also computed. After controlling for age, having visited a dental professional still predicted the use of full-strength toothpaste (AOR=1.95, 95% CI=1.21–3.16).

Other than birth order and dental visit, the use of full-strength fluoride toothpastes was also associated with agreement with the statement, “it is important for children to use age-appropriate toothpaste”. Preschoolers whose parents or caregivers did not agree with this statement had 19-fold increased odds (95% CI=11.91–30.71) of using full-strength fluoride toothpaste (see Table 2).

Factors determining toothpaste choice
Ten respondents indicated that they were not responsible for choosing toothpastes for their preschoolers, and were not asked the question on what factors they considered when choosing toothpaste for their preschoolers. The remaining respondents (n=974) were asked to select from a list of nine factors, and multiple responses were allowed.

The number of factors selected by respondents ranged from one to seven; 38% of respondents selected only one factor and 31% selected two (see Table 3). The most commonly cited factor was a brand that they trust (59%), followed by choosing a toothpaste that matches the child’s age (49%). One-quarter of respondents commented on taste (25%), while one-fifth commented on price (18%). Having one toothpaste for the entire family was only mentioned by 12% of the respondents, and 11% mentioned there were other reasons affecting their choice. However, the questionnaire did not require respondents to indicate what the ‘other’ reasons were.

Discussion
Despite the Ministry of Health’s recommendation on the use of full-strength fluoride toothpaste for all ages, our data indicated that only 19% of the preschoolers in the sample used this type of toothpaste. Our data suggested that the low uptake of full-strength fluoride toothpaste could be attributed to parents and caregivers’ lack of knowledge around toothpaste use among preschoolers.

Direct evidence could be drawn from the strong inverted relationship between parents and caregivers’ belief that children should use age-appropriate toothpaste.
and the use of full-strength fluoride toothpaste. Less direct evidence came from the differences found among first and subsequent children, with subsequent children being more likely to use full-strength fluoride toothpaste. Differential level of parental knowledge and behaviours associated with preschool oral health has been well documented in a previous New Zealand study and international literature. For example, a study conducted with 104 pregnant women in Dunedin found that overall, there was a low level of knowledge on preschool oral health care. The researchers in this study showed that there was a lack of knowledge of when tooth brushing should begin, or when preschoolers should have their first dental visit. This was particularly true among women who were first-time mothers, young, or with a low socio-economic status.

The other factor that was associated with the use of full-strength fluoride toothpaste was dental visits, with preschoolers who had ever visited a dental professional having increased odds of using full-strength toothpaste. This finding might suggest that dental professionals are an important information source for parents and caregivers on toothpaste choice; however, the first dental visit might happen too late to provide timely oral health advice to parents and caregivers. There is currently no population-based data on the proportion of preschoolers in New Zealand who have ever visited a dental professional. The 2009 Oral Health Survey had collected data on dental visit in the past 12 months, and found that only 60% of two-to-four year olds had done so.

The results from the current study also demonstrated the lack of awareness amongst the participants of the Ministry of Health's recommendation around toothpaste. From a list of nine reasons, the Ministry's recommendation on having one toothpaste for the whole family ranked seventh. In contrast, choosing an age-appropriate toothpaste was the second most commonly-selected reason, at 49%. To put our findings into context, three previous studies were conducted in Asia where parents selected from a list of factors that affected their toothpaste choice for their children. The actual proportion of parents who chose toothpaste for their children based on the fluoride concentration varied hugely across studies: 12% in India, 61% in China, and 85% in Malaysia. Importantly, fluoride concentration was not the most commonly cited reason in any of these studies. Factors that were more commonly reported were brand, taste, and advice and recommendations from friends, family and dental professionals. The consistency across studies around the relatively low priority given on fluoride concentration suggest this might be a universal issue.

In New Zealand, part of the confusion on toothpaste choice could arise from manufacturers' instructions on toothpaste packaging being inconsistent with the Ministry of Health's recommendations. Future studies may investigate the extent to which parents and caregivers read and adopt the tooth brushing information printed on toothpaste packaging. In terms of health promotion strategies, it is important to recognise the different messaging parents and caregivers are exposed to around toothpaste types.

Explicit information that would allow parents and caregivers to distinguish messaging from different sources, and to comply with the Ministry of Health's recommendations might be required.

The responses to the type of toothpaste currently used by the sampled preschoolers and the parents’ or caregivers’ criteria for choosing toothpaste were consistent. It appeared that there is a need to improve parents and caregivers knowledge level to ensure they adopt the Ministry of Health's recommendations. While dental professionals could be an important channel to provide oral health information to parents and caregivers, advices delivered by a range of other health professionals who engage with parents and caregivers at an earlier stage—such as lead maternal carers, Well Child providers, or public health nurses—could also be beneficial. The study conducted in Dunedin has found that pregnant women were receptive to the idea of receiving oral health information from Plunket nurses, general medical practitioners, dentists and midwives. A number of overseas studies have found oral health interventions delivered during pregnancy effective. These interventions also had a
focus on improving the oral health of the women.\textsuperscript{10,14,15}

**Strengths and limitations**

This study provided novel information around the type of toothpastes used by preschoolers in New Zealand, and the findings had important implications on both oral health literacy and promotion. A lot of the literature in preschool oral health has focused on mothers, as they have been identified as playing a key role in the general health and wellbeing of their children. However, understanding the involvement of the whānau would help to address the wider household-related barriers for having good oral health practice. By giving the opportunity for both of the parents and caregivers to participate in this survey, we hope to fill in some of the existing knowledge gaps. This is particularly important in the New Zealand context as grandparents, aunts and uncles often play an important role as a main caregiver in Māori and Pacific families.

It is also important to acknowledge the limitations of the dataset. This includes the small Pacific and Māori sample size. According to the 2013 New Zealand Census of Population and Dwelling, 7\% of the New Zealand population are affiliated with at least one Pacific ethnicity (based on total ethnicity).\textsuperscript{16} The ethnicity composition of the parent and caregiver population in New Zealand is not known, however, the proportion of Pacific people within this sub-population is likely to be smaller than 7\% due to the youthful nature of the Pacific population in New Zealand, when compared with other groups such as New Zealand European and Asian.\textsuperscript{17} In the current study, only 2\% of the adult respondents were Pacific people (using prioritised ethnicity). It is also likely that Māori were underrepresented in the sample (7\%), as Māori make up 14.6\% of the overall New Zealand population.\textsuperscript{16}

Due to the nature of recruiting participants through an established online database, the findings from this study is subject to selection bias. While the prevalence estimates presented in this paper will need to be interpreted with caution, they provide us with solid New Zealand evidence that assists with the understanding of the factors associated with the low use of fluoride toothpaste among children.

**Conclusion**

In summary, data from the current study emphasised the importance of providing timely advice to parents and caregivers on toothpaste choice for preschoolers. The association between dental visits and use of appropriate toothpaste choice for children suggested that dental professionals are a crucial oral health information source for parents and caregivers.

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**Competing interests:**
Nil

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**Author information:**

**Corresponding author:**
k.mcbride-henry@hpa.org.nz

**URL:**
REFERENCES:


17. Goodyear RK. The differences within, diversity in age structure between and within ethnic groups. Wellington: Statistics New Zealand; 2009.
ARTICLE

Sleep of Māori and non-Māori of Advanced Age
Rosemary Gibson, Philippa Gander, Sarah-Jane Paine, Mere Kepa, Lorna Dyall, Simon Moyes, Ngaire Kerse

ABSTRACT

AIM: To estimate prevalence and identify predictors and outcomes of reporting sleep problems in Māori and non-Māori of advanced age.

METHOD: Participants were 251 Māori, and 398 non-Māori adults (79–90 years) from Te Puāwaitanga o Ngā Tapuwae Kia Ora Tonu. Life and Living in Advanced Age: A Cohort Study in New Zealand. Multiple logistic regression identified predictors of reporting a current sleep problem and investigated relationships between current sleep problems and physical and mental health.

RESULTS: 26.3% of Māori and 31.7% of non-Māori reported a current sleep problem. Reporting a current sleep problem was associated with ethnicity (non-Māori, adjusted OR=0.52, 95% CI=0.30–0.90), and reporting a past sleep problem (adjusted OR=2.67, 95% CI=1.25–5.72). Sleep problems were related to poorer physical and mental health, and falling.

CONCLUSION: Sleep problems are commonly reported and associated with poorer health. Early recognition and management of sleep problems could improve physical and mental health.

Getting older is generally associated with more sleep disturbances, with 20%–70% of 50–80 year olds reporting a sleep problem.1-4 Older women (aged ≥50 years) are more likely to report disturbed sleep with insomnia-type symptoms, whereas older men typically report more sleep-disordered breathing and daytime sleepiness.2,3,5 Studies that have measured sleep objectively corroborate these reports, showing that sleep quality and duration generally decrease with age.6 However, limited research has focused on the prevalence of sleep problems among people of advanced age (>80 years). A recent US-based study found that successful ageing (ie, living with good quality physical and mental health status despite physiological ageing) might be associated with a reduction in reporting sleep problems.7

Self-reported sleep problems and disorders are common in New Zealand.8 In a 2001 representative national survey of 4,000 adults aged 20–59 years (72.5% response rate), the estimated population prevalence of chronic sleep problems (lasting at least 6 months) was 28.6% for Māori and 24.6% for non-Māori (p=0.033).9 There are also consistent relationships between poorer sleep health and greater socioeconomic deprivation as measured by the New Zealand Deprivation Index 2006 (NZDep 06, an area-based measure of socioeconomic deprivation).8,10

Sleep problems are negatively associated with self-rated physical and mental wellbeing, mood, and quality of life.1,4,9 Poor sleep degrades daytime alertness and performance, thereby increasing the risk of incidents such as road traffic accidents and falls.11,12 The likelihood of sleep disturbances related to health problems increases with age.13 These include depression, pain, respiratory and cardio-vascular diseases, cognitive impairment and dementia.2,5 When older people are also required to care for someone with an illness, sleep problems are likely to be exacerbated.14,15 The proportion of older people in the population is increasing, and it is becoming more common for people to provide care to their family members at home,16 making the sleep of older carers of interest. People of advanced age are likely to have had
exceptionally good health, therefore the predictors and consequences of sleep problems may not be the same as for younger populations.

The current study used data from the inception interviews (Wave 1) of Te Puāwaitanga o Ngā Tapuwae Kia Ora Tonu. Life and Living in Advanced Age: A Cohort Study in New Zealand (“LiLACS NZ”). This is the first study of its kind, using face-to-face surveys to collect information on factors that contribute to successful ageing by Māori and non-Māori of advanced age. Sleep was not the primary focus of LiLACS NZ, but some general questions on sleep were included. These provide the first insights into sleep health during advanced age, which could contribute to better health services to recognise and manage geriatric sleep problems.

The aims of these analyses were to estimate the prevalence of self-reported sleep problems among Māori and non-Māori of advanced age; to investigate the independent associations between demographic and health-related factors, and self-reported sleep problems; and to determine whether self-reported current sleep problems increased the likelihood of reporting other adverse health-related outcomes.

**Methods**

This project was approved by the Northern X Regional Ethics Committee (NXT 09/09/088). The LiLACS NZ Wave 1 survey was completed with 421 Māori (aged 79–90 years) and 516 non-Māori (aged 84–86 years). The Māori cohort included participants who identified themselves as Māori, either alone or as one of multiple ethnicities. They had a broader age range than the non-Māori cohort to account for known differences in longevity between the two populations. The participants were living in the Bay of Plenty and Lakes District Health Board areas in 2010. All Māori born between 1 January 1 1920 and 31 December 31 1930, and all non-Māori born between 1 January and 31 December 1925, were identified from the electoral roll, primary care databases, word-of-mouth, Māori tribal networks, and through local publicity. The extensive use of local organisations meant that more difficult to reach populations (eg, those who had disabilities) were able to be contacted and invited to participate by someone known to them. Those who gave informed consent completed the face-to-face survey in their own home with a trained interviewer using standardised techniques. An overall response rate of 57% was achieved. The populations recruited approximated the age and sex distribution of the underlying population, except that women were over-represented.

The sample used for the present analyses included all participants who completed the question, “Do you have trouble with your sleeping (on at least 3 nights per week) such that it interferes with your activities the following day (eg, unrefreshed in the morning, fatigue, poor concentration, or irritability)?” This question gave an indication of current sleeping problems. Participants who answered “yes” to this question were asked to indicate the types of problems they were experiencing from a list of eight symptoms (waking up in the early hours of the morning; taking a long time to get to sleep; lying awake for most of the night; getting up at night to go to the toilet; worry keeping you awake at night; snoring; sleep walking/sleep talking; or other sleeping problems). Participants were also asked, “How much trouble did you have with sleeping when you were young?” Answers were dichotomised into “yes” (“a little”, “some”, or “a lot”) vs “no” (“none at all”) to give an indication of past sleeping problems.

Study procedures allowed for participants to complete a shortened core survey that did not include the sleep questions if, for example, they were considered by members of a whānau (extended family) to not be able to manage answering the interview questions for themselves or they were very disabled in residential care. Of the 937 participants in Wave 1, 261 completed the core survey only, and 5 did not complete either version of the survey. There were also 22 instances of participants who completed the full survey, but did not answer the sleep questions, giving a total of 288 participants who did not answer the sleep questions. The analyses presented here focus on the remaining 251 Māori and 398 non-Māori (the ‘sleep sample’). Demographic variables included the following variables provided in the LiLACS NZ database: ethnicity (Māori vs
non-Māori); sex (male vs female), age (year increments); and socioeconomic deprivation, as measured using the NZDep 06 (decile 1 = least deprived to decile10 = most deprived). Caregiving was defined by the question, “How often do you currently provide care or assistance for other people?” For this study, carers included those responding “occasionally”, “less than once a week”, “once a week”, “two to five times weekly”, or “daily” (six to seven times weekly). Non-carers were defined by answering “never”. Residential status (defined as “living alone”, “living with a spouse only”, “living with family including or not including spouse”, or “living in residential care”) was also described.

The physical and mental health variables considered for multivariate analyses included scores from the following standardised scales which were provided in the LiLACS NZ database: the Short-Form Health Survey (SF-12), as a measure of physical and mental quality of life, as well as pain that interferes with daytime functioning; the Mini Mental Status Exam (MMSE), as a measure of cognitive functioning; the Geriatric Depression Scale (GDS-15), as a measure of self-reported depression symptoms; the Pearlin Mastery Scale (PMS), as a measure of perceived control; and the Physical Activity Scale for the Elderly (PASE). Additional measures included: doctors records confirming a diagnosis of depression; a global score from a five-point Likert scale rating coping in different situations (“times of loss”, “financial hardship”, “on-going health problems”, “times of trouble for family and friends”, and “overall”); a five-point Likert scale rating the experience of ageing (“On the whole has growing older been a positive or negative experience for you?”); and single-item questions to define those who had fallen and how often, those who were a current or past smoker, and those who drank alcohol (four or more times a week versus monthly or less).

Analysis

The sleep sample and the participants who did not answer the sleep questions were compared by ethnicity, sex, age, and NZDep 06 using sequential logistic regression modelling with 98.3% of the total observations (n=922).

Differences in the proportion of Māori and non-Māori who reported each type of sleep problem were investigated using chi-square tests. A multivariable logistic regression model was used to investigate the independent associations between self-reported current sleep problems and a range of demographic, physical and mental health factors, and reporting a past sleep problem. The demographic variables of ethnicity, sex, age and NZDep 06 were included in the models, based on a priori evidence. This model included 89.7% of all observations. Due to limited available power, only those health-related factors that were significantly associated with the outcome at the univariate level (p<0.1) were included. A version of the model was run with the interaction term “sex X ethnicity”, but the interaction was non-significant.

A series of multivariate logistic regression models were used to determine whether reporting a current sleeping problem was associated with reporting poorer physical or mental health, after controlling for ethnicity, age, sex, and NZDep 06. In these models, the outcome variables were dichotomised using validated cut-off scores (eg, <25 on the MMSE, and >8 on the GDS) or, in instances when validated cut-offs were unavailable, by scoring within the 25th percentile of the particular scale. Models included between 93.7% and 98.8% of all observations, due to missing values for some variables. Adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) were estimated for groups of interest. Analyses were undertaken in SAS® (2011, Version 9.3, Cary NC).

Results

Demographics

Of the 649 participants who responded to the question concerning a current sleep problem, 38.7% were Māori and 61.3% were non-Māori. Their demographic characteristics are summarised in Table 1. Sequential logistic regression analyses revealed that, after controlling for sex and NZDep 06, Māori were more likely to be within the group who did not answer the sleep question compared to non-Māori (OR=3.00, 95% CI=2.16–4.16, p=<0.0001). The likelihood of not answering the sleep question also increased with age (OR=1.18, 95% CI=1.10–1.27, p=<0.0001).
Table 1: Demographic characteristics of Māori and non-Māori participants in the sleep sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Māori (n=251)</th>
<th>Non-Māori (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Females</td>
<td>153 (61.0%)</td>
<td>211 (53.0%)</td>
</tr>
<tr>
<td>Carers†</td>
<td>84 (33.5%)</td>
<td>107 (26.9%)</td>
</tr>
<tr>
<td>NZDep 06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decile 1 (Least deprived)</td>
<td>4 (1.6%)</td>
<td>12 (3.0%)</td>
</tr>
<tr>
<td>Decile 2</td>
<td>2 (0.8%)</td>
<td>13 (3.3%)</td>
</tr>
<tr>
<td>Decile 3</td>
<td>6 (2.4%)</td>
<td>28 (7.0%)</td>
</tr>
<tr>
<td>Decile 4</td>
<td>24 (9.6%)</td>
<td>47 (11.8%)</td>
</tr>
<tr>
<td>Decile 5</td>
<td>11 (4.4%)</td>
<td>16 (4.0%)</td>
</tr>
<tr>
<td>Decile 6</td>
<td>31 (12.4%)</td>
<td>85 (21.4%)</td>
</tr>
<tr>
<td>Decile 7</td>
<td>20 (8.0%)</td>
<td>67 (16.9%)</td>
</tr>
<tr>
<td>Decile 8</td>
<td>34 (13.6%)</td>
<td>59 (14.8%)</td>
</tr>
<tr>
<td>Decile 9</td>
<td>34 (13.6%)</td>
<td>37 (9.3%)</td>
</tr>
<tr>
<td>Decile 10 (Most deprived)</td>
<td>85 (33.9%)</td>
<td>34 (8.5%)</td>
</tr>
</tbody>
</table>

Residential status:

<table>
<thead>
<tr>
<th></th>
<th>Māori (n=251)</th>
<th>Non-Māori (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>104 (41.4%)</td>
<td>193 (48.5%)</td>
</tr>
<tr>
<td>Lives with spouse only</td>
<td>66 (26.3%)</td>
<td>153 (38.4%)</td>
</tr>
<tr>
<td>Lives with family (+/- spouse)</td>
<td>81 (32.3%)</td>
<td>52 (13.1%)</td>
</tr>
<tr>
<td>Lives in residential care</td>
<td>2 (0.8%)</td>
<td>19 (4.8%)</td>
</tr>
</tbody>
</table>

† n=249 for Māori carers, and 386 for non-Māori.

Figure 1: The proportion of sleep symptoms endorsed by Māori (n=66) and non-Māori (n=126) participants who reported having a current sleep problem.

Type of sleep problem

* = p (chi-square) <0.05, ** = p (chi-square) <0.01.
ARTICLE

Reporting sleep problems
In the sleep sample, 26.3% of Māori and 31.7% of non-Māori reported having a current sleep problem (χ²=2.13, p=0.145). Women were more likely to report a current sleep problem than men (33.0% vs 25.3%, χ²=4.55, p=0.033). Both Māori and non-Māori problem sleepers endorsed a median of three sleep symptoms. Of those who were Māori, 50.0% endorsed more than three symptoms compared to 34.9% of non-Māori (χ²=4.10, p=0.043). All of the participants reporting a current sleep problem endorsed at least one symptom of insomnia (waking up too early, taking a long time to get to sleep, and/or lying awake for most of the night). Figure 1 shows the proportions of Māori and non-Māori reporting a sleep problem who endorsed each sleep symptom. “Other sleeping problems” included physical aches and pains, symptoms of restless legs, sleep disordered breathing, hallucinations, taking medicines, and providing care for others. Of the full sleep sample, 5.2% of Māori and 6.8% of non-Māori reported having a past sleep problem.

Table 2 shows the results of the multiple logistic regression analyses investigating factors associated with reporting a current sleep problem. This shows reduced likelihood for participants who were Māori vs non-Māori (OR=0.52, 95% CI=0.30–0.90). Those who also reported a past sleep

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Categories/range</th>
<th>Adjusted OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>0.52*</td>
<td>0.30–0.90</td>
<td></td>
</tr>
<tr>
<td>Non Māori (Ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.48</td>
<td>0.98–2.24</td>
<td></td>
</tr>
<tr>
<td>Males (Ref)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>79–90</td>
<td>0.94</td>
<td>0.82–1.07</td>
<td></td>
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<tr>
<td>Deprivation (NZDep 06)</td>
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<td></td>
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<tr>
<td>1–10</td>
<td>1.05</td>
<td>0.96–1.14</td>
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<tr>
<td>Caregiving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carer</td>
<td>1.52</td>
<td>0.99–2.32</td>
<td></td>
</tr>
<tr>
<td>Non Carer (Ref)</td>
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<tr>
<td>Past sleep problem</td>
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<tr>
<td>Yes</td>
<td>2.67*</td>
<td>1.25–5.72</td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health (SF-12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.9–79.3</td>
<td>0.95***</td>
<td>0.92–0.98</td>
<td></td>
</tr>
<tr>
<td>Cognition (MMSE)</td>
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<td></td>
</tr>
<tr>
<td>2–30</td>
<td>0.96</td>
<td>0.89–1.03</td>
<td></td>
</tr>
<tr>
<td>Depression rating (GDS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>1.09</td>
<td>0.96–1.24</td>
<td></td>
</tr>
<tr>
<td>Depression diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.37</td>
<td>0.73–2.54</td>
<td></td>
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<tr>
<td>No (Ref)</td>
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<tr>
<td>Perceived coping (PMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–25</td>
<td>1.04</td>
<td>0.96–1.14</td>
<td></td>
</tr>
<tr>
<td>Perceived control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–35</td>
<td>0.98</td>
<td>0.92–1.05</td>
<td></td>
</tr>
<tr>
<td>Physical health (SF-12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0–65.8</td>
<td>0.97*</td>
<td>0.94–1.00</td>
<td></td>
</tr>
<tr>
<td>Pain interference (SF-12)</td>
<td></td>
<td></td>
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<tr>
<td>0–100</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td></td>
</tr>
<tr>
<td>Number of Falls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>1.14</td>
<td>0.92–1.42</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinker</td>
<td>0.81</td>
<td>0.53–1.24</td>
<td></td>
</tr>
<tr>
<td>Non drinker (Ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p <0.05, **p <0.01, *** p <0.001
Covariates: ethnicity, age, sex, and NZDep 06.
Abbreviations: SF-12 (Short Form 12 Item Survey), MMSE (Mini Mental State Exam), GDS (Geriatric Depression Scale), PMS (Pearlin Mastery Scale), OR (Odds Ratio), CI (confidence Interval), Ref (reference group).
problem were more likely to also report a current sleep problem than those who did not (OR=2.67 95% CI=1.25–5.72). With each point of increase on the SF-12 mental health scale, there was a 6% reduction in the likelihood of reporting a sleep problem. With each point increase on the SF-12 physical health scale, there was a 3% reduction in the likelihood of reporting a sleep problem.

Table 3 summarises the findings from the logistic regression models investigating whether current sleep problems are independent risk factors for poorer health outcomes. These show significant associations between sleep problems and health outcomes. For example, those reporting a current sleep problem were more likely to score highly for symptoms of depression on the GDS than those who did not report a current sleep problem (OR=4.42, 95% CI=2.40–8.14).

### Discussion
This is the first study to estimate the prevalence of reporting sleep problems among Māori and non-Māori of advanced age. Among 251 Māori and 398 non-Māori aged 79–90 years, we found that 25.5% of Māori and of 31.7% non-Māori reported a sleep problem. Reporting a current sleep problem was more likely among non-Māori and among those who reported a past sleep problem, or poorer self-rated physical or mental health, after adjusting for demographic variables. The associations between sleep problems and health are likely to be bi-directional, highlighting the importance of sleep for the health-related quality of life of our rapidly ageing population.

In contrast to previous research involving 20–59 year olds, the present study found that Māori were less likely to report a current sleep problem than non-Māori. The reasons for this difference are unknown. However, it should be noted that, of those reporting a sleep problem, non-Maori were more likely to volunteer other sleep symptoms not specifically asked for in the study compared to Māori. This suggests that how sleep problems are understood and reported might differ between the two samples. Response biases may have also been a factor, since Māori were three times more likely than non-Māori to be amongst those who did not respond to the sleep questions, and people with poorer health were less likely to complete the full questionnaire with the sleep questions.

The lower prevalence of reporting sleep problems among Māori could also reflect the fact that the LiLACS NZ sample includes exceptionally long-lived Māori, the majority of whom strongly identify with their culture (eg, many being fluent in speaking te reo Māori [Māori language], and frequently visiting a marae [sacred meeting place of a tribe]) compared to younger generations. Previous LiLACS NZ research has identified cultural engagement (but not socioeconomic status) as an independent predictor of better physical health-related quality of life. Further research is required to clarify whether or not lifestyle and cultural factors play a role in the higher prevalence of sleep problems among non-Māori.

<table>
<thead>
<tr>
<th>Model</th>
<th>Health outcome variable</th>
<th>n (%) with condition</th>
<th>Observations</th>
<th>Adjusted OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Depression, (GDS)</td>
<td>49 (7.6%)</td>
<td>641</td>
<td>4.42***</td>
<td>2.40–8.14</td>
</tr>
<tr>
<td>3</td>
<td>Depression diagnosis</td>
<td>62 (9.8%)</td>
<td>631</td>
<td>1.96*</td>
<td>1.15–3.37</td>
</tr>
<tr>
<td>5</td>
<td>Cognitive impairment</td>
<td>76 (12.1%)</td>
<td>629</td>
<td>1.49</td>
<td>0.89–2.61</td>
</tr>
<tr>
<td>7</td>
<td>Poor mental health</td>
<td>155 (25.5%)</td>
<td>608</td>
<td>2.45***</td>
<td>1.65–3.63</td>
</tr>
<tr>
<td>8</td>
<td>Poor coping</td>
<td>144 (23.5%)</td>
<td>612</td>
<td>1.80**</td>
<td>1.20–2.71</td>
</tr>
<tr>
<td>9</td>
<td>Poor control</td>
<td>167 (27.4%)</td>
<td>610</td>
<td>1.82**</td>
<td>1.23–2.68</td>
</tr>
<tr>
<td>10</td>
<td>Poor physical health</td>
<td>148 (24.3%)</td>
<td>608</td>
<td>1.64*</td>
<td>1.10–2.46</td>
</tr>
<tr>
<td>11</td>
<td>Fallen in last year</td>
<td>215 (34.5%)</td>
<td>624</td>
<td>1.64**</td>
<td>1.14–2.36</td>
</tr>
<tr>
<td>12</td>
<td>Reduced physical activity</td>
<td>147 (23.7%)</td>
<td>624</td>
<td>1.36</td>
<td>0.89–2.06</td>
</tr>
<tr>
<td>13</td>
<td>Increased pain interference</td>
<td>181 (29.2%)</td>
<td>619</td>
<td>1.89**</td>
<td>1.30–2.76</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001, ***p<0.0001
Covariates: ethnicity, age, sex, and NZDep 06, caregiving status.

21 Previous LiLACS NZ research has identified cultural engagement (but not socioeconomic status) as an independent predictor of better physical health-related quality of life. Further research is required to clarify whether or not lifestyle and cultural factors play a role in the higher prevalence of sleep problems among non-Māori.

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engagement are associated with reporting sleep problems.

In further contrast to previous research, in the current study NZDep 06 was not associated with reporting sleep problems in the fully-adjusted models. The Māori participants in the present study were over-represented in the most deprived NZDep 06 deciles, whereas the non-Māori sample had a more normally distributed NZDep 06 profile. These distributions are similar in the general population of Māori and non-Māori aged over 50 years. However, they differ from previous studies of 20–59 year olds, where non-Māori were over-represented in the least deprived deciles. It is also possible that NZDep 06 alone is not the most reliable way to measure socioeconomic position in people of advanced age, who are more likely to live with family members or in rest homes or institutions that may not reflect their true socioeconomic position. Alternatively, socioeconomic position may be less closely related to health-related quality of life in advanced age. Additional research using different methods of defining socioeconomic position is needed to clarify this.

The prevalence of reported sleep problems is lower in the LiLACS NZ sample than in previous studies of adults aged 60–80 years. Grandner et al. propose that this pattern could be related to the exceptional health that leads to living longer, or a reduction in the effects of life or societal stressors on sleep in advanced age. Expectations and perceptions of good or acceptable health are also thought to change with age, and older people as well as their family members may downplay, or be less likely to complain of sleep disruptions. It is therefore important for health-care professionals to actively ask their older patients about sleep.

More symptoms were endorsed by those reporting sleep problems (a median of three for Māori and non-Māori) compared to previous studies. However, the list included trips to the toilet and waking early, which alone may not be considered problematic. All of the participants reporting a current sleep problem reported at least one insomnia symptom. Insomnia is common with ageing and reflects physiological and psychological changes that increase the likelihood of sleeplessness.

Carers are considered likely to have disturbed sleep. However in the present study, caregiving (including carers providing any type or amount of care) was not associated with reporting a current sleep problem. Future research should consider gathering more detailed information on the type of care being provided and the time spent caregiving.

Those who reported having a past sleep problem were more likely to report a current sleep problem, although the definition of “younger” used in the survey is unclear. This relationship has been reported throughout the lifespan and highlights the importance of early diagnosis and treatment of sleep problems as a way of preventing any negative impact in later life.

The first set of regression analyses (presented in Table 2) sought to identify those health factors that increased the likelihood of reporting a current sleep problem. Findings indicate that poorer self-rated physical or mental health was associated with increased likelihood of reporting a sleep problem.

The second set of analyses (presented in Table 3) considered whether reporting a current sleep problem was an independent predictor for poorer health outcomes. Findings indicate that those who reported a current sleep problem had significantly poorer mental health status compared to those who did not. These participants were more likely to score within the lowest quartile for mental health-related quality of life, were also more likely to have depression, and have poorer perceived control than participants reporting no sleep problems. Reporting current sleep problems was also related to poorer physical health outcomes. This is indicated by these participants being more likely to score within the poorest quartiles for physical health-related quality of life, pain that interferes with daytime functioning, as well as being more likely to have fallen in the last year.

Together these analyses highlight that sleeping problems can have current and long-term effects on mental and physical health outcomes. Cognitive functioning and mood have consistently been related to sleep problems, and these relationships have been attributed to physiological
processes as well as to the effects of sleep deprivation. Reporting sleep problems and cognitive impairment (considered as either a continuous or a dichotomous variable) were not significantly associated in the present study, possibly due to those with more severe impairment being less likely to have completed the long form of the survey which included the sleep questions.

The relationship between sleep and pain is likely to be multifactorial, as pain is common with ageing, and is also related to poorer physical and mental health, mobility problems, and quality of life. Participants reporting a current sleep problem were more likely to have fallen in the past year than those who did not. Previous research indicates that this could be due to increased daytime sleepiness causing issues with balance and reaction times, getting out of bed while drowsy, or the residual effects of sleeping medications.

A limitation of this study is that the LiLACS NZ survey was not designed with sleep as a primary focus and therefore the data are difficult to compare to previous studies using different questions. Future studies would be strengthened by the use of validated and standardised sleep questions and scales. Objective sleep monitoring would help identify any potential discrepancies with self-reported sleep problems, but such an intensive protocol may dissuade people of advanced age from participation.

The present analyses did not address the use of sleeping medications, physical exercise, light exposure, doctor’s visits, or co-morbidities. These factors have been highlighted as significantly associated with sleep problems in previous studies. Risk factors for, and symptoms of, sleep disordered breathing were also not examined in detail, although the proportion of snorers was small.

The current study is limited by a selection bias. Although the initial response rate was 57%, the rate of those then completing the full questionnaire including the sleep-related question was only 48.6%. Therefore, the results cannot be generalised to the New Zealand population. Those of poorer health and cognitive capacity are under-represented. The logistic regression models are limited by an information bias due to missing observations, furthermore residual confounds are likely to remain. Lastly, due to the cross-sectional nature of these analyses, causality cannot be imputed. Further analyses of the future waves of LiLACS NZ would be of interest to clarify the relationships found here.

Despite these limitations and the potential biases, LiLACS NZ provides a large sample to investigate the factors related to reporting sleep problems in Māori and non-Māori of advanced age. The unique design and the researchers’ commitment to engaging and recruiting this specific group has provided an outstanding opportunity for the first investigation of sleep of this age group in New Zealand.

Conclusions

These analyses show that 26.3% of Māori and 31.7% of non-Māori of advanced age report current sleep problems. All of these participants reported at least one symptom of insomnia (waking up too early, taking a long time to get to sleep, and/or lying awake for most of the night), whereas symptoms such as snoring or other sleeping problems were reported by 10–30% of the ‘problem sleepers’. The presence of a past sleeping problem (reported by 5.2% of the Māori and 31.7% of the non-Māori participants) was a significant predictor for a current problem. Sleep problems are a significant marker for poorer mental and physical health status in advanced age, thus having the potential to jeopardise successful healthy ageing. It is important to raise public and clinical awareness with regards to the predictors and implications of sleep problems. It is recommended that clinicians as well as family members explore whether the elders in their care have sleep problems. The treatment of sleeping problems may reduce the likelihood of physical and mental health problems as well as the risk of falling.
ARTICLE

Competing interests:
Nil

Acknowledgements:
We would like to acknowledge the participants of LiLACS NZ. We are very grateful to the LiLACS NZ research team and Leadership Group for their willingness to share their data with us and for their advice and support. Funders of LiLACS NZ include the Health Research Council of New Zealand programme grant, and Ngā Pae o te Māramatanga (New Zealand’s Māori Centre of Research Excellence) project grant.

Author information:
Rosemary Gibson, PhD, Research Officer, Sleep/Wake Research Centre, Massey University, Wellington; Philippa Gander, PhD, Professor and Director, Sleep/Wake Research Centre, Massey University, Wellington; Sarah-Jane Paine, PhD, Co-Associate Director, Sleep/Wake Research Centre, Massey University, Wellington; Mere Kepa, PhD, Research Officer, School of Population Health, University of Auckland, Auckland; Lorna Dyall, PhD, alumni, School of Population Health, University of Auckland, Auckland; Simon Moyes, Data Manager / Analyst, School of Population Health, University of Auckland, Auckland; Ngaire Kerse, PhD, Research Professor, Head of School of Population Health, University of Auckland, Auckland, New Zealand.

Corresponding author:
Rosemary Gibson, Sleep/Wake Research Centre, Massey University, Wellington Campus, Private Bag 756, New Zealand.
r.gibson@massey.ac.nz

URL:

REFERENCES:
13. House JS, Lepkowski JM,
ARTICLE


Screening, prevalence and ethnic variation of diabetes mellitus in people with acute stroke and transient ischaemic attack: a cross-sectional study in Northland, New Zealand

Steven WM Wong, Nicole M McGrath

ABSTRACT

AIM: To assess our prevalence and screening rate for diabetes and pre-diabetes in people presenting with acute stroke and transient ischaemic attack (TIA) in Northland, New Zealand, as well as identifying discrepancies between Māori and non-Māori, rates of atrial fibrillation (AF) and effect of metformin on stroke.

METHOD: Data was collected retrospectively on people diagnosed with stroke or TIA in Northland, between 1 January 2014 and 31 December 2014.

RESULTS: 345 people presented with acute stroke/TIA. 49.5% had dysglycaemia: 24.3% diabetes, 25.2% pre-diabetes. An HbA1c was performed on 70.4%. Māori had more diabetes (41.6%) than non-Māori (19.4%), with an HbA1c 12 mmol/mol (3.2%) higher, and were 12 years younger on average. There was no difference in AF prevalence between people with and without diabetes, and in the proportion of severe stroke (total anterior circulation infarction) between people with diabetes on metformin and those not.

CONCLUSIONS: The prevalence of dysglycaemia in acute stroke/TIA in Northland is high. The goal of universal HbA1c screening in stroke is not being met. Māori have stroke younger, and a higher prevalence of diabetes may partially explain this. No association between diabetes and AF was found, nor evidence that metformin may be protective against larger strokes.
diabetes and AF in our acute stroke/transient ischaemic attack (TIA) population. Finally, there is evidence that metformin use reduces the risk of stroke, so our last objective was to assess whether metformin use is associated with reduced stroke severity as illustrated by stroke subtype.

**Methods**

This was a retrospective study of all people diagnosed with acute stroke or TIA in Northland between 1 January 2014 and 31 December 2014. All eligible participants were identified by the stroke nurse specialist. Relevant data was collected from electronic records. The data collected included gender, age, smoking status, ethnicity, stroke type, evidence of diabetes or pre-diabetes (based on HbA1c or history) prior to and following hospitalisation, whether HbA1c was checked during hospitalisation, glycaemic control by HbA1c, diabetic treatment and diagnosis of AF. When data were missing or unavailable, the participant was excluded from that outcome of interest. Statistical analysis was performed using Student’s t-test to compare means and a chi-squared test when comparing percentages.

Ethnicity was obtained by self-report. Where multiple self-identified ethnicities were recorded and included Māori, these people were designated as Māori alone. Diabetes and pre-diabetes were defined according to the New Zealand guidelines: HbA1c greater than or equal to 50 mmol/mol (6.7%) for diabetes and HbA1c 41–49 mmol/mol (5.9–6.6%) for pre-diabetes. Screening for diabetes or assessing control was deemed to have occurred if an HbA1c was checked during admission or in the 1 month prior to admission. The stroke nurse specialist determined stroke type according to the Oxford Community Stroke Project classification, based on clinical symptoms and radiological findings, and where there was uncertainty, the clinical data was reviewed by the author and allocated accordingly.

**Results**

Three hundred and forty-five people were diagnosed with an acute stroke or TIA during the studied timeframe; 193 were men and 152 were women. The mean age was 72.5 years old. Māori comprised 22.3% (77/345), New Zealand Europeans 67.8% (234/345), and all other ethnicities 9.9% (34/345). Of the 304 people where data was available, 16.8% were current smokers, 37.5% were ex-smokers and 45.7% had never smoked.

The overall prevalence of dysglycaemia was 49.5%; 24.3% had diabetes (84/345) and 25.2% had pre-diabetes (87/345). An HbA1c was performed during hospitalisation or in the preceding month on 243 out of 345 people (70.4%). The mean HbA1c overall was 44.3 mmol/mol (6.2%) and 62.1 mmol/mol (7.8%) in the group with diabetes. Only 180 (69%) of the 261 people without a previously known diagnosis of diabetes were screened with an HbA1c, and no new cases of diabetes were detected. Out of 191 people with no prior evidence of diabetes or pre-diabetes, 127 (66.5%) were screened and this yielded 17 new diagnoses of pre-diabetes.

The differences between Māori and non-Māori are outlined in Table 1. Māori

<table>
<thead>
<tr>
<th></th>
<th>Māori</th>
<th>Non-Māori</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>63.4</td>
<td>75.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>41.6</td>
<td>19.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pre-diabetes (%)</td>
<td>20.8</td>
<td>26.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HbA1c (mmol/mol)</td>
<td>69.8</td>
<td>57.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>32.5</td>
<td>9.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>29.9</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>42.9</td>
<td>26.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total anterior circulation infarct (%)</td>
<td>18.2</td>
<td>8.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
were significantly younger, twice as likely to have diabetes, have worse glycaemic control, three times more likely to be a current smoker, one and a half times more likely to have AF, and more than twice as likely to have a total anterior circulation infarct (TACI).

AF was present in 105 out of the 342 people (30.7%) where data was available. There was no significant difference in AF prevalence between people with diabetes (31% [26/84]) and those without diabetes or pre-diabetes (33.9% [59/174]).

Twenty-three percent (23.2%) of events were TIs, 16.5% lacunar infarcts, 28.7% partial anterior circulation infarcts, 10.4% TACI, 10.7% posterior circulation infarcts, 9% intracerebral haemorrhages, and 1.4% were unable to be classified. No significant difference was found in stroke subtype between people with diabetes and those without diabetes or pre-diabetes. There was also no significant difference in the proportion of TACI between those with diabetes on metformin (5.1%) and those not (15.6%).

Discussion

We identified that approximately 50% of Northland people with acute stroke or TIA have dysglycaemia: 24.3% had known diabetes, 20.3% known pre-diabetes, and we diagnosed an additional 4.9% with pre-diabetes through screening with HbA1c alone, although only around 70% of people were screened. This is in comparison to approximately 7% of the general Northland population with known diabetes.9 Those who were not screened had similar demographics to those who were screened, apart from eight people who were palliated from the time of admission and in whom checking an HbA1c would have been inappropriate. It would still be desirable to improve our screening rate given the high prevalence of dysglycaemia in this population. It has been observed that people with diabetes have one-and-a-half to three times the risk of stroke,10,11 and pre-diabetes also carries an increased risk.12 Screening for dysglycaemia provides an avenue for opportunistic intervention in this high-risk group. The identification of diabetes should alert the clinicians to ensure diabetes knowledge and microvascular screening is up to date. For those people with pre-diabetes, targeted healthy lifestyle information can be provided, and advice given on future HbA1c screening. This is in addition to standard stroke/TIA secondary prevention treatment.

While Māori are not over-represented in terms of stroke/TIA incidence, they present almost 12 years younger than non-Māori, and this could be partially explained by the higher rates of diabetes mellitus, with a 22.6% higher prevalence of diabetes. Glycaemic control was worse in Māori, with the mean HbA1c 12 mmol/mol (3.2%) higher. However, there are clearly other factors as well, including higher rates of smoking and AF amongst Māori.

We were unable to identify a clear association between diabetes and AF. Others have previously found a 1.1% increase in the prevalence of atrial fibrillation among people with diabetes.5 Forty-six percent of people with diabetes were on metformin, and while those on metformin had a lower proportion of the most severe stroke subtype (TACI) at 5.1%, compared with those not on metformin at 15.6%, this was not statistically significant. We therefore did not show statistically any protective effect from metformin on stroke severity.

There were some limitations in our study. As an observational study, we are unable to prove causality, and there are likely to be confounders. We did not assess pre-stroke/TIA cardiovascular risk status, or the use of aspirin, statins and angiotensin converting enzyme inhibitors prior to admission. The results are predominantly of relevance to our local geographic area, although the data on Māori may be of interest and generalisable to other Māori populations in New Zealand and abroad.

In summary, the prevalence of dysglycaemia in the acute stroke/TIA Northland population is almost 50%. Only around 70% of people presenting with stroke or TIA are having an HbA1c performed. New Zealand Māori with stroke/TIA are more likely to have diabetes and to present at a younger age. HbA1c screening is an important but under-utilised part of acute stroke triage, and improving this could conceivably assist in improving health
outcomes, particularly in New Zealand Māori, as well as raise awareness of the association between dysglycaemia and stroke. Following the completion of this study, the results were presented to the Whangarei Hospital medical department staff as a reminder to perform an HbA1c on all people presenting to hospital with stroke or TIA. The addition of a ‘vascular event’ panel on the lab request form, containing tests such as HbA1c and lipids, is also under consideration.

Competing interests:
Nil

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Author information:
Steven WM Wong, Medical Registrar, Department of Medicine, Northland District Health Board, Whangarei; Nicole M McGrath, Medical Consultant, Department of Medicine, Northland District Health Board, Whangarei, New Zealand.

Corresponding author:
Steven Wong, Department of Medicine, Northland District Health Board, Whangarei Hospital, Maunu Road, Maunu, Whangarei 0110, New Zealand. stelewong.nz@gmail.com

URL:

REFERENCES:
Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial

Amber Parry Strong, Sylvan Haeusler, Mark Weatherall, Jeremy Krebs

ABSTRACT

AIM: To compare a single 1mg intramuscular hydroxocobalamin injection with a 3-month course of 1mg/day sublingual methylcobalamin supplements on serum vitamin B12 concentrations in participants with type 2 diabetes treated with metformin.

METHOD: Participants on metformin treatment with vitamin B12 concentrations below 220pmol/L were recruited through hospital diabetes clinics and primary care practices. They were randomised to receive either the injection or sublingual treatment. The primary outcome was serum vitamin B12 level after 3 months adjusted for baseline assessed by analysis of covariance (ANCOVA). The trial was registered on the Australia New Zealand Clinical Trial registry (ACTRN12612001108808).

RESULTS: A total of 34 participants were randomised; 19 to the tablet, and 15 to the injection. The mean (SD) age, duration of diabetes, and duration of metformin use were, 64.2 (7.3) years, 13.7 (6.4) years, and 11.6 (5.0) years, respectively. After 3 months, the mean (SD) vitamin B12 was 372.1 (103.3) pmol/L in the tablet group (n=19) compared to 251.7 (106.8) pmol/L in the injection group (n=15), ANCOVA estimated difference -119.4 (95% CI -191.2 to -47.6), p=0.002. After 6 months, the mean (SD) serum B12 was 258.8 (58.7) pmol/L in the tablet group (n=17) and 241.9 (40.1) pmol/L in the injection group (n=15); ANCOVA estimated difference -15.2 (95% CI -50.3 to 19.8), p=0.38. Higher metformin dose was associated with lower serum B12 at 3 months, but not at baseline or 6 months.

CONCLUSION: Decreased serum vitamin B12 level in patients with type 2 diabetes who are treated with metformin can be corrected through treatment with either hydroxocobalamin injections or methylcobalamin sublingual supplements.

Metformin, the most common first-line treatment for type 2 diabetes mellitus (DM), reduces serum B12 concentrations in between 10 and 20% of patients using this medication.1-4 The prevalence of low B12 concentration (<220 pmol/L) in those taking metformin in New Zealand is 18.6%.5 Metformin impairs calcium-dependent membrane activity in the ileum, which leads to malabsorption of vitamin B12 bound to intrinsic factors.6,7 Measurable reductions in vitamin B12 levels occur as quickly as 3 months after starting metformin, although symptomatic deficiency may take between 5 and 10 years to develop.8 Vitamin B12 plays a crucial role in the nervous system. It is a coenzyme for methyl malonyl-CoA mutase, the action of which is required for myelin synthesis. Impaired myelin formation can lead to neuropathy, neuropsychiatric abnormalities, myelopathy, and optic nerve atrophy. Clinical evidence of vitamin B12 deficiency-related neuropathy includes loss of vibratory sensation, diminished proprioception, and loss of cutaneous sensation in the lower limbs.9 Cognitive impairment and
depression are neuropsychiatric syndromes associated with vitamin B12 deficiency. In patients with DM, these clinical manifestations are particularly important because neuropathy is also a complication of DM, and depression is a common comorbidity associated with a chronic health condition.

Internationally, the most common method for treatment of vitamin B12 deficiency is intramuscular hydroxocobalamin injections, initially using a loading regimen, followed by a maintenance administration for long-term treatment. In New Zealand, recommendations are for 1,000 mcg every 2 or 3 months for prophylaxis of macrocytic anaemia associated with vitamin B12 deficiency resulting from gastrectomy, malabsorption syndromes, and strict vegetarianism. However, there are no specific recommendations for metformin induced vitamin B12 deficiency. Intramuscular injections generally require visits to a health clinic for administration. This is costly, both for the clinic and the patient. Intramuscular injections can also be painful and lead to reduced adherence.

Oral vitamin B12 supplementation is possible, but the efficacy is questionable, likely due the compromised route of absorption in the gut. The National Health and Nutrition Examination Survey (NHANES) data reported that oral B12 supplementation reduced the rate of B12 deficiency by two-thirds in those without diabetes, but there was no association seen in those taking metformin. Sublingual vitamin B12 bypasses the mechanism of interaction of metformin on absorption of vitamin B12, and is a feasible alternative to injections. Sublingual treatment is as effective as oral doses in patients who are not treated with metformin, as assessed by serum vitamin B12 and biomarkers of vitamin B12 functionality.

The aim of the study reported here is to evaluate the effectiveness of sublingual vitamin B12 supplementation compared with intramuscular injection for patients using metformin who have low serum vitamin B12 in a randomised trial.

Methods
This was a randomised study of 3 months sublingual treatment with methylcobalamin 1mg/day, compared to a single intramuscular injection of hydroxocobalamin 1mg. Definitions of low serum B12 and B12 deficiency vary. For this study we chose that used by de Jager and colleagues, with vitamin B12 deficiency defined as serum B12 <150 pmol/L, and low B12 as concentrations between 150 and 220 pmol/L. Participants were patients with type 2 DM who were being treated with metformin. The particular intramuscular dose was chosen to replicate the effect of a general practitioner following the New Zealand guidelines in primary care. As there was little guidance in the literature as to what dose would be effective, it was decided the sublingual B12 dose should be 1mg/day, based on the study by Yazaki et al. Both randomised groups were reviewed after 3 months and a second round of treatment started if serum vitamin B12 had not risen above 220 pmol/L. The primary outcome variable was serum vitamin B12 level after 3 months adjusted for baseline vitamin B12. The secondary outcomes were the vitamin B12 after 6 months and the Michigan Neuropathy Screening Instrument (MNSI) score after 6 months.

Recruitment and study visits
Participants were recruited through hospital and primary care clinics by invitation, and randomised based on the results of vitamin B12 screening. Inclusion criteria were a diagnosis of type 2 DM, treatment with metformin for 12 months or longer, and a screening serum vitamin B12 of < 220 pmol/L. Participants were excluded if they were already on treatment for vitamin B12 deficiency (including over-the-counter vitamin supplementation containing vitamin B12), were anaemic for another reason, had prior gastric surgery (eg, gastric bypass), pregnant or breastfeeding, reported past cobalamin allergy, or other reason in the judgement of the investigators as to why vitamin B12 could not be administered. Written informed consent was obtained at the baseline visit. Clinical variables that could affect serum vitamin B12 concentrations, including smoking and alcohol use, and medications known to effect serum B12, in particular omeprazole,
were recorded. The screening serum vitamin B12 level was considered baseline, as all participants were invited to take part in the study immediately after receipt of screening bloods.

After collection of baseline data, participants were randomised on a 1:1 allocation to receive either a single 1mg intramuscular injection of hydroxocobalamin or a 3-month course of sublingual methylcobalamin supplements of a 1,000 mcg/day dosage. The injection was hydroxocobalamin ABM, 1 mL ampoules containing 1 mg hydroxocobalamin acetate per mL equivalent to 0.96 mg of hydroxocobalamin per mL. Other ingredients were sodium chloride, sodium acetate, acetic acid and water for injections. The injections were prescribed by the study doctor, obtained through the hospital pharmacy and administered by a research nurse during the study visit. Prescription records were kept accordingly.

The sublingual tablet used was ‘Bronson’ sublingual B12 1,000mcg—methylcobalamin (Bronson Laboratories, Utah, US). Other ingredients were microcrystalline cellulose, mannitol, fructose, sorbitol, magnesium stearate, lecithin, croscarmellose sodium and artificial cherry flavor. The sublingual tablets were purchased without a prescription online and were all manufactured in the same batch. The sublingual tablets were signed out of a log each time, and given out in 3-month batches by one investigator who undertook all baseline visits to ensure consistency.

Randomisation was carried out using an internet based randomisation tool, located at www.randomizer.org (accessed 29/1/2013), to generate a random order sequence for participant allocation to treatment. Participants were randomised in order of recruitment, blinded to the results of their B12 screening status. Randomisation was not blocked. Due to the nature of the interventions, the participants were unable to be blinded as to their treatment, but the statistician and primary investigator remained blinded throughout the study. After randomisation, participants completed a Food Frequency Questionnaire, and the Michigan Neuropathy Screening Instrument. The food frequency questionnaire is validated for micronutrient intake, and used to assess background dietary B12 intake at baseline (University of Otago Food Frequency Questionnaire, Dunedin, New Zealand). The Michigan Neuropathy Screening Instrument (MNSI) was used to assess neuropathy at baseline and after 6 months. This includes a physical examination (foot inspection, assessment of vibration sensation and muscle stretch reflexes, and monofilament testing) and a questionnaire to elicit indicators of neuropathy. The MNSI was used to detect neuropathic symptoms as a score of ≥7 on the patient questionnaire and a score of ≥2 on the physical examination for neuropathy.

Participants were retested for serum B12 after 3 months. These tests were processed through routine laboratory runs at a central laboratory in order for results to be returned in time for the visit. If the B12 level was below 220 pmol/L, they received a further 3-month treatment course of the same treatment to which they were originally allocated. If the B12 level was above 220 pmol/L, the participant was not provided additional treatment and observed for another 3 months. Participants returned tablet containers for a tablet count after 3 and 6 months as applicable. A compliance percentage figure was then able to be calculated by subtracting the number of remaining tablets from the number of days since the last visit. As the injections were administered during the study visit, compliance was witnessed by the investigator conducting the visit, and checked by an investigator review of the prescription charts. After 6 months, participants returned for a follow-up serum B12 and folate, and a repeat of the MNSI questionnaire, and then were discharged to the care of their general practitioner.

**Statistical analysis and ethical review**

This was a randomised parallel group superiority study. The primary analysis was analysis of covariance (ANCOVA) to estimate the mean difference in serum vitamin B12 between tablet and injection, with baseline Vitamin B12 as a covariate. As an intention-to-treat analysis, all available data was included. Secondary analysis used ANCOVA.
Figure 1: CONSORT diagram of recruitment and retention.

942 Participants with type 2 DM identified through hospital clinic and primary care providers, not on vitamin B12 and taking metformin for >12 months

595 Participants excluded as they did not respond to invitation of the study

347 Participants provided serum vitamin B12 level

282 Participants had normal serum vitamin B12 level (≥220 pmol/L)

65 Participants had suboptimal serum vitamin B12 level (<220 pmol/L) and invited to participate

34 participants randomised

15 participants randomised to injection

19 participants randomised to sublingual tablet

6 participants required a second treatment

Lost to follow-up (n=0)
Discontinued intervention (n=0)

Analysed (n=15)

2 participants required a second treatment

Lost to follow-up (unable to be contacted) (n=1)
Discontinued intervention (unrelated health reasons) (n=1)

Analysed (n=19)
with the addition of duration of metformin use as a continuous covariate. The MNSI scores were compared between randomised groups by independent t-tests and within randomised groups (change from baseline) with paired t-tests. SAS version 9.3 was used for the analysis.

Sample Size
The standard deviation of serum vitamin B12 after 2 months treatment with sublingual B12 was 75 pmol/L in a study of participants with known vitamin B12 deficiency (serum vitamin B12 <138 pmol/L). We were uncertain of the clinically significant difference between two treatments for vitamin B12 in the setting of metformin use, so based the sample size calculation on detecting an effect size of one standard deviation. This required recruitment of 17 participants in each arm, for 80% power with a type I error rate of 5%. Use of ANCOVA with baseline vitamin B12 is likely to improve the statistical power to detect differences. We did not factor in drop-outs. If the standard deviation was the same as in the previous research, this study had sufficient power to detect a 75 pmol/L difference in vitamin B12.

Ethical approval for the study was obtained from the New Zealand Central Health and Disability Ethics Committee (12/CEN/65/AM02). The trial was registered on the Australia New Zealand Clinical Trial registry (ACTRN12612001108808). The study was funded by a University of Otago Research Grant.

Results
Figure 1 shows the process of recruitment and randomisation in the CONSORT Diagram. A summary of demographic information for the 34 participants is shown in Table 1. Most participants were male Europeans with a mean (SD) age of 64.2 (7.3) years. The mean (SD) duration of Type 2 DM was 13.7 (6.4) years, with mean (SD)
duration of Metformin treatment of 11.6 (5.0) years of Metformin treatment. Two participants were identified through the food frequency questionnaire as being vegetarian (no meat or fish), both randomised to the injection group. Thirty two participants completed the study; two participants withdrew from the tablet group (one due to unrelated health reasons, the other lost to follow up). Compliance in the tablet group was 89.2%.

Mean serum B12 concentration increased from baseline after 3 and 6 months in both treatment groups (Table 2). For the primary outcome variable, and when adjusted for baseline B12 concentration, serum B12 concentration was greater in the sublingual treatment than intramuscular injection after 3 months. There was no evidence of a difference between treatments after 6 months. In the secondary analysis of vitamin B12 after 3 months additionally adjusting for metformin dose, we found that metformin dose was associated with lower vitamin B12 concentrations; -75.3 units per 1,000 mg higher metformin dose (95% CI -125.0 to -25.5), p=0.004.

The treatment was repeated at 3 months for six individuals in the injection group, and two individuals in the tablet group. These eight individuals were older than the average participant, had longer duration of both diabetes and metformin use and a higher metformin dose. Seven of these were vitamin B12 deficient (150 pmol/L or less) at baseline, and two were vegetarian.

No patients had neuropathy at baseline according to the MNSI, but one participant in the tablet group registered a neuropathic score after 6 months (Table 3). There was no difference in mean score between the two treatment groups at baseline or after 6 months for the questionnaire or physical examination. There was also no difference in the injection group between baseline and 6 months for either the questionnaire or physical examination. In the tablet group, there was no difference from baseline to 6 months for the questionnaire, but there was a significant deterioration in the physical examination score.

### Discussion

This study provides evidence that the treatment of patients with decreased serum vitamin B12 concentration with methylcobalamin sublingual supplementation is as effective as hydroxocobalamin injection in correcting a low vitamin B12 status over 6 months. Both treatments resulted in improvements in serum vitamin B12 concentration. After

<table>
<thead>
<tr>
<th>Time</th>
<th>Injection Mean (SD)</th>
<th>Sublingual Mean (SD)</th>
<th>Injection minus tablet (95% CI)</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>166.7 (36.5) (n=15)</td>
<td>170.2 (39.0) (n=19)</td>
<td>-119.4 (-191.2 to -47.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>3 months</td>
<td>251.7 (106.8) n=15</td>
<td>372.1 (103.3) n=18</td>
<td>-15.2 (-50.3 to 19.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>6 months</td>
<td>241.9 (40.1) n=15</td>
<td>258.8 (58.7) n=17</td>
<td>-15.9 (-50.3 to 19.8)</td>
<td></td>
</tr>
</tbody>
</table>

SD Standard deviation, CI Confidence Interval
treatment, concentrations in both groups remained in the reference range, and over-correction was not seen.

Currently, the most common treatment for vitamin B12 deficiency is intramuscular hydroxocobalamin injections. These have been shown to improve both biochemical markers for B12 deficiency and also improve physiological functions of vitamin B12 deficiency. The administration of a single dose of 1mg hydroxocobalamin was seen to correct serum vitamin B12 status in 60% of the patients treated in this study at 3 months. There was an association between B12 at 3 months and metformin dose, with a higher metformin dose predicting a lower B12 level, but this was not apparent at baseline or 6 months. Closer inspection of the individuals receiving a second dose indicated several possible risk factors; lower initial vitamin B12 level, greater age, longer diabetes and metformin duration and higher metformin dose.

Some current treatment protocols for vitamin B12 deficiency dictate that a loading period of hydroxocobalamin should be used in order to raise baseline concentrations before a periodic maintenance regimen should be initialised. One study suggests a daily 1 mg administration of hydroxocobalamin daily for 1 week, followed by 1 mg once weekly for 4 weeks, subsequent maintenance of B12 is achieved through 1 mg administration every 2 to 3 months. While we did not compare the New Zealand recommendation with a loading regimen, it is likely from our study that at least two intramuscular injections are required to correct serum B12 concentrations, with on-going monitoring. Further research is required to assess whether on going sublingual supplementation will be required and the optimal injection frequency for maintenance of B12 concentrations in patients taking long-term metformin.

The use of sublingual delivery is a growing trend in vitamin supplementation. This route of administration avoids the issues of interference with absorption in the lower GI tract, and of the first pass metabolism in the liver. This is particularly relevant for metformin induced vitamin B12 malabsorption, where metformin interferes with absorption of intrinsic factor bound vitamin B12. While studies have shown the absorption of sublingual and oral B12 to be similar when treating B12 deficiency from pernicious anaemia, it would be very useful to see whether the same is true in metformin-induced B12 deficiency. The dosage regimen for the sublingual treatment was higher than that of the single 1 mg injection, and although the bioavailability of sublingual administration is less than intramuscular injection, this probably explains the greater concentration of B12 observed with the sublingual treatment after the initial 3 months. The difference in the pattern of response to the two treatment groups may also be attributed to the different clearance and excretion properties of the two cobalamin vitamers. Almost a third of a 1 mg intramuscular dose of hydroxocobalamin is excreted in the urine in the first 72 hours. The excretion rate of the sublingual dose is unknown. In addition, metformin increases preferential hepatic storage of vitamin B12. This, coupled with the higher affinity of hydroxocobalamin to bind to hepatic parenchymal cells via preferential trafficking, may also explain the lower serum B12 concentration after hydroxocobalamin injection compared with methylcobalamin. Total body vitamin B12 stores however may be similar, due to increased hepatic storage.

This study was not specifically designed to assess the effects of treatment on clinical consequences of B12 deficiency, which is perhaps the most important question. No significant symptoms of vitamin B12 deficiency were observed in our study using the MNSI. Only one patient met the criteria for neuropathy, and they had previously documented treatment of diabetic neuropathy. The MNSI score for this participant deteriorated markedly over the 6 months despite replacement of B12, and explained the significant score increase for the sublingual treatment at 6 months. Therefore, there is no evidence from this study that using the sublingual route of administration is less effective than the intramuscular route with regard to preventing neuropathy. Clearly, much bigger and longer studies are required to fully address this question. Similarly, a longer observation period post treatment and use of MMA and tHcy...
concentrations would allow more investigation into sustainability of an initial treatment and whether on-going maintenance treatment is required for either of the cobalamin forms. Although the sample size was similar to previous studies,\textsuperscript{12,13} it would have been preferable to have a larger sample size, and factor in an arm for an oral supplement. The screening for serum B12 concentrations in this study occurred across primary health organisations and a regional hospital. Due to laboratory contracts, this resulted in two different laboratories conducting these initial screening tests. However, every effort was made to ensure inter-laboratory standardisation. A strength of this study was the randomised design. While a full double-dummy double-blinded randomised controlled trial would have provided stronger evidence, such rigour was not possible within the funding constraints of this study, and may have resulted in false positives due to a placebo effect.

In conclusion, this study has shown that decreased serum vitamin B12 level in patients with type 2 diabetes on long-term metformin treatment can be corrected through treatment with either hydroxocobalamin injections or methylcobalamin sublingual supplements. Further study is required to determine the optimal long-term dosing regimen and monitoring duration for both treatments, and clinical significance of metformin related B12 deficiency.

\textbf{Competing interests:}
Amber Parry-Strong reports grants from Otago University and 'other' from Victoria University during the conduct of the study.

\textbf{Acknowledgements:}
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\textbf{Author information:}
Amber Parry-Strong, Research Fellow, Centre for Endocrine, Diabetes and Obesity Research, Capital and Coast District Health Board, Wellington; Sylvan Haeusler, MSc Student, Centre for Endocrine, Diabetes and Obesity Research, Capital and Coast District Health Board, Wellington; Mark Weatherall, Department of Medicine, University of Otago Wellington, Wellington; Jeremy Krebs, Associate Professor, Department of Medicine, University of Otago Wellington, Wellington, New Zealand

\textbf{Corresponding author:}
Amber Parry-Strong, Centre for Endocrine, Diabetes and Obesity Research, Capital and Coast Health, Private Bag 7902, Wellington, New Zealand.

amber.parry-strong@ccdhb.org.nz

\textbf{URL:}

\textbf{REFERENCES:}


The case for a national service for primary immune deficiency disorders in New Zealand

Rohan Ameratunga, Richard Steele, Anthony Jordan, Kahn Preece, Russell Barker, Maia Brewerton, Karen Lindsay, Jan Sinclair, Peter Storey, See-Tarn Woon

ABSTRACT

Primary immune deficiency disorders (PIDs) are rare conditions for which effective treatment is available. It is critical these patients are identified at an early stage to prevent unnecessary morbidity and mortality. Treatment of these disorders is expensive and expert evaluation and ongoing management by a clinical immunologist is essential. Until recently there has been a major shortage of clinical immunologists in New Zealand. While the numbers of trained immunologists have increased in recent years, most are located in Auckland. The majority of symptomatic PID patients require life-long immunoglobulin replacement. Currently there is a shortage of subcutaneous and intravenous immunoglobulin (SCIG/IVIG) in New Zealand. A recent audit by the New Zealand Blood Service (NZBS) showed that compliance with indications for SCIG/IVIG treatment was poor in District Health Boards (DHBs) without an immunology service. The NZBS audit has shown that approximately 20% of annual prescriptions for SCIG/IVIG, costing $6M, do not comply with UK or Australian guidelines. Inappropriate use may have contributed to the present shortage of SCIG/IVIG necessitating importation of the product. This is likely to have resulted in a major unnecessary financial burden to each DHB. Here we present the case for a national service responsible for the tertiary care of PID patients and oversight for immunoglobulin use for primary and non-haematological secondary immunodeficiencies. We propose that other PIDs, including hereditary angioedema, are integrated into a national PID service. Ancillary services, including the customised genetic testing service, and research are also an essential component of an integrated national PID service and are described in this review. As we show here, a hub-and-spoke model for a national service for PIDs would result in major cost savings, as well as improved patient care. It would also allow seamless transition from paediatric to adult services.

Primary immune deficiency disorders (PIDs) are rare genetic defects resulting in compromised host defences. Consequently, affected patients are susceptible to recurrent and severe infections, as well as autoimmunity and malignancy as a result of immune dysregulation. The severity of PIDs range from asymptomatic IgA deficiency, to life-threatening infections from severe combined immune deficiency (SCID). The prevalence of these disorders vary, from being relatively common (1:300) for IgA deficiency, to extremely rare conditions, some of which have not been identified in New Zealand (population: 4.4M).

It is imperative PID patients are identified in a timely manner. Early identification of these conditions, and establishing appropriate treatment, may prevent or mitigate disabling complications such as bronchiectasis. If identified and treated promptly, the majority of patients can lead a full and active life with minimum morbidity.

Severe PIDs, such as SCID are a paediatric emergency and require immediate referral to Paediatric Immunology at Starship Children’s Hospital, Auckland (Starship) for evaluation and treatment. In other cases, there is less urgency, such as patients with IgA deficiency suffering from upper respiratory tract infections. The potential severity of a disorder may not be apparent in the early stages, but there may be rapid deterioration if not identified and referred promptly. This occurs in patients with SCID, who may initially be well until they contract...
CMV or Parainfluenza 3 viral infections, making subsequent management very difficult. Similarly, patients with X-linked lymphoproliferative disease can remain well until they suffer a catastrophic EBV infection. In this example, early identification of males carrying the genetic defect, and pre-emptive bone marrow transplantation, is potentially curative with a much improved prognosis. These examples underscore the need for timely evaluation by specialists in clinical immunology.

Once diagnosed, PID patients should be under the long-term care of an immunology service. This is essential, as there are many aspects of ongoing patient care which require regular input from an immunologist. Some patients may have persistent infections, while others may develop autoimmune and inflammatory sequelae. Furthermore, an immunologist is in the best position to undertake genetic studies, which can have profound benefits to the patient and the family.

Currently, there is a serious maldistribution of clinical immunologists, and particularly immunopathologists, in New Zealand. Most immunologists work in Auckland. The Immunology Department at Auckland District Health Board (ADHB) employs seven part-time consultants, and one fellow. There are three part-time paediatric immunologists at Starship. Two clinical immunologists, and three allergy specialists, are exclusively in private practice in Auckland. The only public paediatric immunology service is based at Starship. also in Auckland.

Christchurch and Wellington have two adult immunologists. A part-time paediatric allergist works in Wellington. The adult Immunology Department at ADHB offers a monthly outreach clinic in Whangarei. One part-time immunologist conducts monthly clinics at Waikato Hospital. The Immunology Department at ADHB has contracts to review a modest number of patients from other hospitals within the Auckland area, and other DHBs in the upper North Island. Other cities, as well as other hospitals in Auckland, do not have a visiting adult immunology service. Visiting paediatric immunology outreach clinics are conducted in Hamilton, Rotorua, Tauranga and Invercargill.

As a consequence of the maldistribution of public hospital immunologists, some adult PID patients, and many with non-haematological secondary immunodeficiencies, have not had the opportunity to undergo a thorough immunology review, and regular follow-up. Current contractual arrangements between DHBs may result in financial disincentives for patient referrals for subspecialty reviews. For example, patients referred from DHBs without a contract with ADHB may be seen, but no funding follows these consultations, which may disadvantage local patients within the ADHB catchment area. By default, some adult patients remain under the care of general physicians or haematologists. In some cases, long-term subcutaneous or intravenous immunoglobulin (SCIG/IVIG) replacement has been initiated and continued without immunology consultation. The cost of SCIG/IVIG over a lifetime is more than $1M and is funded by the local DHB. As shown below, in many cases the inappropriate use of SCIG/IVIG has resulted in a major unnecessary financial burden to individual DHBs.

In this Viewpoint, we present the case for a national service for patients with PIDs. A national PID service would significantly reduce healthcare costs, and more importantly improve patient care. This is similar to HIV medicine, where patients under the care of physicians with appropriate training and experience have significantly better outcomes. We describe some areas where input from an immunologist would make a significant difference to patient management, and would also substantially reduce healthcare expenditure.

Hypogammaglobulinemia/ Common Variable Immunodeficiency Disorder and SCIG/IVIG treatment

Patients presenting with hypogammaglobulinemia are a common clinical scenario. Within the spectrum of hypogammaglobulinemia, it is very important that patients with Common Variable Immunodeficiency...
### Table 1: Ameratunga et al (2013) diagnostic and treatment criteria for CVID.\textsuperscript{14,15}

<table>
<thead>
<tr>
<th>Category A: Must meet all major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogammaglobulinemia IgG &lt;5 g/l\textsuperscript{4}</td>
</tr>
<tr>
<td>No other cause identified for immune defect\textsuperscript{17}</td>
</tr>
<tr>
<td>Age &gt;4 years\textsuperscript{2}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B: Sequelae directly attributable to immune system failure (ISF) (1 or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent, severe or unusual infections</td>
</tr>
<tr>
<td>Poor response to antibiotics</td>
</tr>
<tr>
<td>Breakthrough infections in spite of prophylactic antibiotics</td>
</tr>
<tr>
<td>Infections in spite of appropriate vaccination eg HPV disease</td>
</tr>
<tr>
<td>Bronchiectasis and/or chronic sinus disease</td>
</tr>
<tr>
<td>Inflammatory disorders or autoimmunity\textsuperscript{18}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category C: Supportive laboratory evidence (3 or more criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant reduction or deficiency of IgA (&lt;0.8 g/l) and/or IgM (&lt;0.4 g/l)\textsuperscript{3,21}</td>
</tr>
<tr>
<td>Presence of B cells but reduced memory B cell subsets and/or increased CD21 low subsets by flow cytometry\textsuperscript{20,21}</td>
</tr>
<tr>
<td>IgG3 deficiency (&lt;0.2 g/l)\textsuperscript{22,23}</td>
</tr>
<tr>
<td>Impaired vaccine responses compared to age-matched controls\textsuperscript{24}</td>
</tr>
<tr>
<td>Transient vaccine responses compared with age-matched controls\textsuperscript{25}</td>
</tr>
<tr>
<td>Absent isohemagglutinins (if not blood group AB)\textsuperscript{26}</td>
</tr>
<tr>
<td>Serological evidence of significant autoimmunity eg, Coombs test</td>
</tr>
<tr>
<td>Sequence variations of genes predisposing to CVID eg, TACI, BAFFR, MSH5 etc\textsuperscript{27,28}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category D: Presence of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty, in the context of Category A and B criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid interstitial pneumonitis\textsuperscript{29}</td>
</tr>
<tr>
<td>Granulomatous disorder\textsuperscript{20,21}</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia of the liver\textsuperscript{32,33}</td>
</tr>
<tr>
<td>Nodular lymphoid hyperplasia of the gut\textsuperscript{34}</td>
</tr>
<tr>
<td>Absence of plasma cells on gut biopsy\textsuperscript{35,36}</td>
</tr>
</tbody>
</table>

Patients must meet all major criteria in Category A for consideration of CVID. Category B confirms the presence of symptoms indicating immune system failure (ISF). Patients must be symptomatic to have CVID. To qualify as having possible CVID, patients must have supportive laboratory evidence of immune system dysfunction (Category C) or characteristic histological lesions of CVID (Category D). Patients with mild hypogammaglobulinemia (IgG >5 g/l) are termed hypogammaglobulinemia of uncertain significance (HGUS). Patients meeting Category A criteria but not other criteria are deemed to have possible CVID. Most patients with probable CVID are likely to require IVG/SCIG. Some patients with possible CVID will require SCIG/IVIG but most patients with HGUS are unlikely to need IVG/SCIG replacement. We have suggested HGUS patients are categorised based on their symptomatic state ie sHGUS or aHGUS. Some patients with bronchiectasis with HGUS will need to be treated with SCIG/IVIG irrespective of vaccine responses.\textsuperscript{16}
Disorder (CVID) are identified at an early stage. CVID is the most common symptomatic PID in adults, with a prevalence of approximately 1:25 000. Symptoms can begin in adulthood in many patients. Failure to identify and treat CVID patients may place them at risk of bronchiectasis and/or life-threatening infections, including meningitis and sepsicaemia. Once identified, patients with CVID should receive long-term subcutaneous or intravenous immunoglobulin (SCIG/IVIG) replacement. Our recently published diagnostic criteria for CVID will allow a diagnosis of probable CVID to be made with more precision (Table 1).

CVID is no longer a diagnosis of exclusion. Treatment guidelines are closely linked to diagnostic categories (Figure 1).

As part of the clinical evaluation, predisposing factors for infections should be thoroughly assessed. It is possible the hypogammaglobulinemia is not the dominant cause for infections. In our experience, treatment of conditions such as chronic tonsillitis or chronic sinus disease may result in major improvement in the frequency of infections in some patients with hypogammaglobulinemia, without the need for SCIG/IVIG replacement.

Given the very high cost of SCIG/IVIG, all PID patients should have an immunology evaluation prior to commencing treatment. We also strongly recommend that patients already placed on long-term SCIG/IVIG for PID should be regularly reviewed by an immunologist. We have recently identified an adult patient who had been on long-term IVI,G but was subsequently able to discontinue treatment as he had recovered from “transient hypogammaglobulinemia of infancy” as an adult. As a result, we were able to successfully discontinue his IVIG. He remains well, with no increase in infections with an IgG of 6.5 g/l (7-14 g/l).

Our diagnostic criteria may allow CVID to be confirmed, without the need to stop SCIG/IVIG in some patients, particularly if they have characteristic histological features (Table 1, category D). This could reduce the need to stop SCIG/IVIG treatment to undertake vaccine challenge responses, which can take several months. The patient may be vulnerable to sepsis during this time. Equally, these criteria may identify individuals who can safely discontinue SCIG/IVIG treatment permanently, if they have minimal symptoms, with normal memory B cells and normal plasma cells on gut biopsy (Table 1).

It may not be initially clear if a patient presenting with hypogammaglobulinemia has a primary or a secondary immune deficiency. We have shown that our diagnostic criteria can also be useful in identifying patients with secondary immunodeficiencies. These criteria may also help in...

Figure 1: Treatment algorithm for CVID (Ameratunga et al 2013).
complex situations where an underlying primary immunodeficiency is aggravated by a secondary immunodeficiency, such as an anticonvulsant drug.34 Several other patients with secondary hypogammaglobulinemia have also been able to discontinue IVIG replacement uneventfully and remain well. These patients were commenced on IVIG by other services and successful discontinuation has resulted in significant cost savings.

Once patients are placed on long-term SCIG/IVIG treatment, they need regular immunology review. Patients residing outside centres with immunology units would share their care with local paediatricians and physicians, in the case of adult patients. The frequency of the follow-up visits to immunologists will depend on the individual patient and their disorder. SCIG/IVIG treatment usually results in significant improvement of the frequency and severity of infections, but may not alter the risk of inflammatory disorders or malignancy. IVIG, and to lesser extent SCIG, can cause adverse effects,40 and having an immunologist involved in the patient’s care can facilitate timely review and management of any complication from treatment. Other options, including an alternative immunoglobulin product, may need to be considered. These decisions are best made by immunologists, who are thoroughly familiar with alternative SCIG/IVIG preparations, which may need to be imported for a specific patient.

Some patients with CVID have severe antibiotic allergies because of immune dysregulation. Managing these patients can be challenging and requires the expertise of an allergy/immunology specialist. Diagnostic evaluation may include skin testing and drug challenges to confirm remission. Acute antibiotic desensitisation may be needed for management of severe bacterial infections. Again, this service is available in specialist immunology units.

Patients with CVID are at risk of chronic upper and lower respiratory tract suppuration. We routinely share their care with the respiratory and ORL services. Many patients require functional endoscopic sinus surgery for chronic sinus disease. Having access to respiratory and ORL specialists with experience in PIDs is likely to improve outcomes in these medically complex patients. These are strong clinical arguments for placing patients with PIDs under the care of immunologists, which may be best done through a national service for PIDs. This would ensure uniformity of clinical care.

The New Zealand Blood Service (NZBS) audit of SCIG/IVIG use

Perhaps the strongest economic argument for a national PID service comes from a recent SCIG/IVIG audit conducted by the New Zealand Blood Service (NZBS, Blood Issues 28, October 2015, http://www.nzblood.co.nz/assets/Transfusion-Medicine/Blood-Issues-Newsletter-No-28-October-2015.pdf). The case notes of patients receiving SCIG/IVIG in 2012/2013 from 10 DHBS were reviewed. Access to old notes was sometimes difficult, given that some patients have been on IVIG for decades. Where notes were not available, the prescribing doctor was contacted for further information. This audit was undertaken by nursing staff in each NZBS area. NZBS has indicated there are limitations to the audit. It is likely there was some observer inconsistency. The audit did not determine if the patient was reviewed by an immunologist. Furthermore, the case notes were not critically reviewed by an immunologist and subtle nuances, such as responses to alternative treatments, were not recorded.

The cost of SCIG/IVIG is $88 per gram, and the total cost to the New Zealand taxpayer is $29M per year. The NZBS determined compliance of SCIG/IVIG use against criteria published in the UK and Australia. The audit uncovered inconsistencies in the use of IVIG within the ten DHBs it audited (Tables 2–5). It can be seen there was a high compliance rate in Auckland for PID patients, but relatively poor rates in some of the smaller DHBs without access to immunology services.

It is also clear that compliance for treating secondary immunodeficiencies with SCIG/IVIG is poor in most DHBs (Table 5). The poor compliance for secondary immunodeficiencies may simply reflect a lack of referral to immunology
services, including ADHB. Most patients with non-haematological secondary immunodeficiencies are likely to benefit from an immunology review. Patients with drug induced immunodeficiencies for example may improve if the causative drug is identified and discontinued.41 As noted above, the immunology service at ADHB has been able to discontinue IVIG in several patients with secondary immunodeficiencies. The audit also uncovered patients who had been treated with IVIG for conditions such as autism and chronic fatigue syndrome, which are not supported by either the Australian or UK guidelines.

From these tables we have calculated that $6M of immunoglobulin prescriptions per year do not comply with UK or Australian guidelines.

### The current approval process for SCIG/IVIG treatment

We are very concerned about the current approval process for IVIG/SCIG treatment. At present, the NZBS has to vet SCIG/IVIG requests for immunodeficiencies. Each requesting clinician contacts the regional blood service for approval for IVIG/SCIG. Guidelines for IVIG/SCIG are not strictly enforced by the NZBS. It is currently not a requirement for patients with primary or non-haematological secondary immunodeficiencies to have been reviewed by a clinical immunologist. Each blood service may not be in a position to determine the appropriateness of the request, and it is likely there are inconsistencies in the approval process. This may explain use of IVIG/SCIG for disorders such as autism and chronic fatigue syndrome. We feel decisions on IVIG/SCIG usage in primary and non-haematological secondary immunodeficiencies should be made by clinical immunologists after thorough clinical evaluation of these patients. The NZBS strongly supports the creation of a national service for PIDs with oversight for the prescription of SCIG/IVIG for PIDs and non-haematological immunodeficient patients (Dr Peter Flanagan, Director NZBS, personal communication, October 2015). Patients with secondary immunodeficiencies from haematological disorders should be reviewed by a haematologist. A national PID service is likely to result in a fairer and more transparent process for IVIG/SCIG prescriptions.

We accept that there may be potential inaccuracies with retrospective review of patient notes. However, we are confident there will be substantial financial benefits to each DHB if a national PID service was established with oversight for immunoglobulin prescriptions for
**Table 3:** NZBS audit showing use of SCIG/IVIG by various District Health Boards in New Zealand.

<table>
<thead>
<tr>
<th>DHB</th>
<th>Intragam P use pa (g)</th>
<th>Audit episodes</th>
<th>Population*</th>
<th>Intragam P use pa (g) per 1000 popula-</th>
<th>Average age (years)</th>
<th>Average weight (kg)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auckland</td>
<td>56,010</td>
<td>257</td>
<td>404,619</td>
<td>138</td>
<td>29</td>
<td>52</td>
<td>audited</td>
</tr>
<tr>
<td>Canterbury</td>
<td>31,995</td>
<td>141</td>
<td>466,407</td>
<td>69</td>
<td>39</td>
<td>59</td>
<td>audited</td>
</tr>
<tr>
<td>Capital and Coast</td>
<td>30,522</td>
<td>119</td>
<td>266,658</td>
<td>114</td>
<td>43</td>
<td>68</td>
<td>audited</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>12,351</td>
<td>75</td>
<td>433,086</td>
<td>29</td>
<td>44</td>
<td>62</td>
<td>audited</td>
</tr>
<tr>
<td>Hawke’s Bay</td>
<td>7,260</td>
<td>27</td>
<td>148,248</td>
<td>49</td>
<td>40</td>
<td>66</td>
<td>audited</td>
</tr>
<tr>
<td>MidCentral</td>
<td>9,630</td>
<td>41</td>
<td>158,841</td>
<td>61</td>
<td>45</td>
<td>70</td>
<td>audited</td>
</tr>
<tr>
<td>Northland</td>
<td>8,349</td>
<td>35</td>
<td>148,440</td>
<td>56</td>
<td>36</td>
<td>61</td>
<td>audited</td>
</tr>
<tr>
<td>Southern</td>
<td>21,063</td>
<td>80</td>
<td>286,224</td>
<td>74</td>
<td>53</td>
<td>67</td>
<td>audited</td>
</tr>
<tr>
<td>Tairawhiti</td>
<td>2,250</td>
<td>7</td>
<td>44,463</td>
<td>51</td>
<td>40</td>
<td>54</td>
<td>audited</td>
</tr>
<tr>
<td>Waikato</td>
<td>28,362</td>
<td>109</td>
<td>339,192</td>
<td>84</td>
<td>50</td>
<td>71</td>
<td>audited</td>
</tr>
<tr>
<td>Bay of Plenty</td>
<td>17,343</td>
<td>73</td>
<td>194,931</td>
<td>89</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Hutt Valley</td>
<td>5,571</td>
<td>21</td>
<td>136,101</td>
<td>41</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Lakes</td>
<td>7,251</td>
<td>30</td>
<td>98,319</td>
<td>74</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Nelson Marlborough</td>
<td>5,787</td>
<td>26</td>
<td>130,062</td>
<td>44</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>666</td>
<td>5</td>
<td>53,877</td>
<td>12</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Taranaki</td>
<td>5,043</td>
<td>22</td>
<td>104,277</td>
<td>48</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Wairarapa</td>
<td>2,889</td>
<td>8</td>
<td>38,613</td>
<td>75</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Waitakere</td>
<td>8,655</td>
<td>73</td>
<td>481,611</td>
<td>18</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>West Coast</td>
<td>855</td>
<td>4</td>
<td>31,326</td>
<td>27</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>Whanganui</td>
<td>2,583</td>
<td>9</td>
<td>62,211</td>
<td>42</td>
<td></td>
<td></td>
<td>not audited</td>
</tr>
<tr>
<td>In audit</td>
<td>207,792</td>
<td>891</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audited %</td>
<td>79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not audited</td>
<td>56,643</td>
<td>271</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* based on population data 2012

Primary and non-haematological secondary immunodeficiencies. It is also likely hospitalisation costs would be reduced if patients were under the care of a clinical immunologist. These fiscal benefits are in addition to the improvement in clinical care described previously.

**Hereditary angioedema (HAE)**

Hereditary angioedema (HAE) is a rare disorder resulting from mutations of the C1 inhibitor or FX11 genes. Patients are predisposed to recurrent angioedema and abdominal pain. Urticaria is absent. The vast majority of patients with C1 inhibitor deficiency have reduced complement component 4 levels, as well as reduced C1 inhibitor function, and/or antigen levels. HAE is currently considered a PID, even though predisposition to infections and autoimmunity are not a major feature of the disorder.

Standard treatment in New Zealand for C1 inhibitor deficiency is androgens (Danazol or Stanozolol). Fibrinolytic inhibitors have a minor role in management. Patients suffering an acute attack require infusions with purified or recombinant C1 inhibitor or Icatibant, which has now been funded. Treatment of an acute attack with purified C1 inhibitor or Icatibant costs approximately $2,500, plus costs of hospitalisation. Preventing attacks with attention to triggering factors and androgen therapy may result in major cost savings to healthcare services.
Table 4: NZBS audit showing compliance in treating PIDs. The NZBS data do not subcategorise the specific type of PID. Therefore, it is difficult to determine if this is the expected number of PID patients in New Zealand who should be receiving SCIG/IVIG.

<table>
<thead>
<tr>
<th>DHB</th>
<th>NBA compliant</th>
<th></th>
<th>NHS compliant</th>
<th></th>
<th>Overall use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
<td></td>
</tr>
<tr>
<td>Auckland</td>
<td>23,952 (100%)</td>
<td>70 (100%)</td>
<td>23,940 (100%)</td>
<td>69 (99%)</td>
<td>23,952</td>
<td>70</td>
</tr>
<tr>
<td>Canterbury</td>
<td>8,043 (100%)</td>
<td>22 (100%)</td>
<td>8,043 (100%)</td>
<td>22 (100%)</td>
<td>8,043</td>
<td>22</td>
</tr>
<tr>
<td>Capital and Coast</td>
<td>9,012 (91%)</td>
<td>22 (92%)</td>
<td>9,588 (96%)</td>
<td>23 (96%)</td>
<td>9,948</td>
<td>24</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>876 (81%)</td>
<td>6 (86%)</td>
<td>1,086 (100%)</td>
<td>7 (100%)</td>
<td>1,086</td>
<td>7</td>
</tr>
<tr>
<td>Hawkes Bay</td>
<td>972 (82%)</td>
<td>2 (67%)</td>
<td>1,188 (100%)</td>
<td>3 (100%)</td>
<td>1,188</td>
<td>3</td>
</tr>
<tr>
<td>MidCentral</td>
<td>1,650 (100%)</td>
<td>4 (100%)</td>
<td>1,650 (100%)</td>
<td>4 (100%)</td>
<td>1,650</td>
<td>4</td>
</tr>
<tr>
<td>Northland</td>
<td>4,386 (90%)</td>
<td>12 (92%)</td>
<td>4,386 (90%)</td>
<td>12 (92%)</td>
<td>4,854</td>
<td>13</td>
</tr>
<tr>
<td>Southern</td>
<td>1,563 (30%)</td>
<td>5 (36%)</td>
<td>1,563 (30%)</td>
<td>5 (36%)</td>
<td>5,211</td>
<td>14</td>
</tr>
<tr>
<td>Waikato</td>
<td>3,627 (63%)</td>
<td>9 (60%)</td>
<td>2,856 (49%)</td>
<td>7 (47%)</td>
<td>5,790</td>
<td>15</td>
</tr>
<tr>
<td>Overall</td>
<td>54,081 (88%)</td>
<td>152 (88%)</td>
<td>54,300 (88%)</td>
<td>152 (88%)</td>
<td>61,722</td>
<td>172</td>
</tr>
</tbody>
</table>

There is also a strong economic argument to allow HAE patients to administer Icatibant or to self-infuse C1 inhibitor to reduce the costs of hospitalisation. This is similar to haemophilia, where patients are encouraged to self-medicate. Early treatment of angioedema attacks reduces morbidity. C1 inhibitor (or Icatibant) is more effective when used early, before the onset of severe gastrointestinal edema. Laryngeal attacks require immediate treatment with C1 inhibitor or Icatibant. The ability of self-infuse C1 inhibitor or self-administer Icatibant has substantially reduced healthcare costs in Canada. Having a national PID service could significantly reduce costs by providing clinical advice on how to prevent acute attacks and by training patients to self-administer C1 inhibitor or Icatibant at home. A national service would also provide a uniform approach to the management of these patients throughout the country.

Genetic testing

In recent years there have been rapid advances in the understanding of PIDs.

Table 5: NZBS audit showing compliance with SCIG/IVIG use in secondary immunodeficiencies. The audit did not determine if patients had consulted with a clinical immunologist.

<table>
<thead>
<tr>
<th>DHB</th>
<th>NBA compliant</th>
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<th>NHS compliant</th>
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<th>Overall use</th>
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<tr>
<td></td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
<td>grams patients</td>
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</tr>
<tr>
<td>Auckland</td>
<td>3,396 (62%)</td>
<td>23 (56%)</td>
<td>987 (18%)</td>
<td>3 (7%)</td>
<td>5,448</td>
<td>41</td>
</tr>
<tr>
<td>Canterbury</td>
<td>3,954 (67%)</td>
<td>18 (67%)</td>
<td>384 (6%)</td>
<td>2 (7%)</td>
<td>5,928</td>
<td>27</td>
</tr>
<tr>
<td>Capital and Coast</td>
<td>912 (11%)</td>
<td>5 (14%)</td>
<td>363 (4%)</td>
<td>1 (3%)</td>
<td>8,451</td>
<td>37</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>1,749 (59%)</td>
<td>8 (53%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2,988</td>
<td>15</td>
</tr>
<tr>
<td>Hawkes Bay</td>
<td>852 (47%)</td>
<td>2 (67%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1,815</td>
<td>3</td>
</tr>
<tr>
<td>MidCentral</td>
<td>624 (39%)</td>
<td>3 (43%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1,608</td>
<td>7</td>
</tr>
<tr>
<td>Northland</td>
<td>531 (100%)</td>
<td>3 (100%)</td>
<td>228 (43%)</td>
<td>1 (33%)</td>
<td>531</td>
<td>3</td>
</tr>
<tr>
<td>Southern</td>
<td>2,277 (67%)</td>
<td>13 (57%)</td>
<td>690 (20%)</td>
<td>2 (9%)</td>
<td>3,405</td>
<td>23</td>
</tr>
<tr>
<td>Waikato</td>
<td>2,037 (29%)</td>
<td>8 (27%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6,912</td>
<td>30</td>
</tr>
<tr>
<td>Overall</td>
<td>16,332 (44%)</td>
<td>83 (45%)</td>
<td>2,652 (7%)</td>
<td>9 (5%)</td>
<td>37,086</td>
<td>186</td>
</tr>
</tbody>
</table>
Table 6: Advantages of molecular analysis for PID diagnosis. The original case
descriptions can be found in our review on PID genetic testing.  

<table>
<thead>
<tr>
<th>Diagnosis of PID</th>
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<tbody>
<tr>
<td>Distinguishing genetic from acquired disorders</td>
<td></td>
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<tr>
<td>Confirming the clinical diagnosis</td>
<td></td>
</tr>
<tr>
<td>Identifying novel presentations of PIDs</td>
<td></td>
</tr>
<tr>
<td>Identifying atypical presentations of PIDs</td>
<td></td>
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<tr>
<td>Urgent diagnosis in infancy where conventional diagnostic tests are unreliable</td>
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<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>Assisting treatment decisions</td>
<td></td>
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<tr>
<td>Gene therapy- identifying those who may benefit from gene based therapy</td>
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<tr>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Determining long-term outcome</td>
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<tr>
<th>Pre-symptomatic testing</th>
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</thead>
<tbody>
<tr>
<td>Where presymptomatic diagnosis (at any age) is not possible with protein based tests</td>
<td></td>
</tr>
<tr>
<td>Early identification of disorders which present later in childhood</td>
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<table>
<thead>
<tr>
<th>Screening</th>
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<tbody>
<tr>
<td>Cascade screening of at-risk relatives</td>
<td></td>
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<tr>
<td>Population based screening</td>
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<th>PID prevention</th>
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<tr>
<td>Prenatal diagnosis</td>
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<tr>
<td>Pre-implantation genetic diagnosis</td>
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<tr>
<th>Research</th>
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<tbody>
<tr>
<td>Characterising the role of molecules in cellular function</td>
<td></td>
</tr>
<tr>
<td>Assisting with the classification of primary immunodeficiency disorders</td>
<td></td>
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<tr>
<td>Identification of new genetic defects including animal models</td>
<td></td>
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</tbody>
</table>

The majority of PIDs are a consequence of monogenic disorders. Over 260 causative or predisposing genetic defects have been identified in PID patients. With the notable exception of CVID, genetic tests play a major role in patient management (Table 6). As well as confirming the diagnosis, these tests allow family studies, and may allow prevention of PIDS with prenat al diagnosis and pre-implantation genetic diagnosis. Genetic testing should now be considered the standard of care for most monogenic PID disorders (Table 6).

Genetic testing for PIDs has been undertaken in New Zealand for over 20 years. In the last decade, the immunology laboratory at Auckland Hospital has offered a customised genetic service for patients with PIDs. This service is accredited by the New Zealand laboratory accreditation agency, IANZ, and is publically funded for New Zealand citizens and residents. We currently offer full-length genomic (Sanger) sequencing for any published PID gene. The service offers a rapid turn-around, with results typically being available within 2–3 weeks, or sooner for urgent cases. This service is a cost-effective solution for a small, developed country. Genetic testing for PIDs is also available in Christchurch.

The customised genetic testing service is of particular significance to Māori, as it conforms to Tikanga Recommended Best Practice. It removes the need to send samples to overseas laboratories. Long-term storage of samples in overseas
research laboratories may be of concern to some Māori.

Currently, several regional and national services based in Auckland depend on two scientists for rapid sequencing of PID genes. These include adult and paediatric immunology (PID syndromes), adult and paediatric rheumatology (autoinflammatory disorders), adult and paediatric haematology (haematophagocytic lymphohistiocytosis, HLH syndromes), and adult and paediatric nephrology (atypical haemolytic uremic syndromes) services. It would seem appropriate to integrate a PID testing service into a national immunology service. This would not preclude other laboratories from offering PID genetic testing for local patients.

Immunopathology

Immunopathology is a subspecialty within clinical pathology. Laboratory testing for immunological disorders is complex. Many assays have not been automated, and a high level of operator skill is required for successful completion and interpretation of results.

While immunopathology is broader than PID testing, a national service could allow immunopathology supervision of laboratories with intermittent visits. Alternatively, a national immunopathology service could be considered separately. Considerable immunopathology expertise exists in Christchurch, which would be the hub for the South Island, and provide specialised testing nationally for specific autoimmune disorders.

PID research

New Zealand is currently involved in several PID research projects. Currently, most patients with CVID are enrolled in a long-term project evaluating their clinical features and outcomes. Over 80% of known CVID patients in New Zealand are part of this project. All patient notes and laboratory results have been thoroughly audited as part of the study. As seen in the NZBS audit, we believe such a thorough review should be undertaken for all PID patients on SCIG/IVIG, either as part of the study or as part of ongoing clinical care. Having such a database (once approved by the Ministry of Health ethics committee and current participants) linked to a national service would ensure patients are not lost to follow-up, and they continue to receive the appropriate care. Research is an essential part of a national PID service.

In addition, New Zealand has a long-term hypogammaglobulinemia study for patients not on SCIG/IVIG. This study seeks to identify the long-term prognosis for these patients. This cohort will also be used to validate CVID diagnostic criteria. Having a better understanding of the natural history of hypogammaglobulinemia is likely to save the health service large sums of money, as not all patients with hypogammaglobulinemia have CVID, and not all require SCIG/IVIG, especially if they are symptomatically well. Again, the project could be linked to a national PID service to ensure patients from around the country are enrolled and are not lost to follow-up.

The laboratory at Auckland Hospital has been undertaking whole exome sequencing (WES) as part of a research project. CVID families with more than one affected relative have been invited to join the WES project seeking to identify new genes. The program to date has identified two new genes associated with CVID-like disorders. Identification of the causative gene has profound implications for the patient and family members as discussed above (Table 6). Again, having a national PID service will ensure uniform access to research studies such the ones described here.

Discussion: advantages (and disadvantages) of a national service for patients with PID

A national service for patients with PID has many advantages (and a few disadvantages) as described above. Importantly, it will allow thorough and timely evaluation of patients with suspected primary and non-haematological secondary immune deficiency disorders. It may be difficult to distinguish between a primary and secondary immune deficiency until the patient is reviewed by a clinical immunologist. An immunology review will result in appropriate testing and a
confident diagnosis of a PID (or secondary immunodeficiency). Careful evaluation of these patients will result in major savings from more effective use of SCIG/IVIG. As outlined above, many patients with mild-moderate hypogammaglobulinemia remain well once other predisposing factors for recurrent infections are treated. These patients may not need to be treated with SCIG/IVIG. They will of course require long-term follow-up, as some will develop a symptomatic immune deficiency disorder over time. We believe these decisions, which carry substantial clinical risk, should only be made by an immunologist. If a secondary immune deficiency is identified, the patient can be treated or referred to the appropriate service. This would minimise the inappropriate use of IVIG, as seen in Table 5. This would result in more judicious and equitable use of SCIG/IVIG throughout New Zealand.

There has been a substantial increase in the use of SCIG/IVIG in recent years. The NZBS estimates there has been a 10.4% annual increase in demand for SCIG/IVIG over the last decade. As shown in Table 5, it is likely inappropriate use of IVIG has also contributed to the increased use of SCIG/IVIG in New Zealand. As a result, supplies of Intragam P, manufactured from local plasma donors, have not been able to meet this increased need. The NZBS has confirmed that New Zealand is no longer self-sufficient in the production of SCIG/IVIG. The NZBS has had to import SCIG/IVIG preparations, manufactured from overseas donors, at considerable cost to the taxpayer. This underscores the urgency to establish a national PID service which has oversight for SCIG/IVIG use in primary and non-haematological secondary immunodeficiencies. We would expect a national PID service to clinically review all primary and non-haematological secondary immunodeficient patients prior to the use of SCIG/IVIG. This will have the added clinical benefit of optimising management of these patients. SCIG/IVIG treatment decisions are by consensus at ADHB. We have shown how consensus decisions can work effectively in clinical practice. This would reduce the risk of inconsistent decisions being made by local NZBS services. We are very confident substantial immediate and sustained cost savings will result from the establishment of a national PID service with oversight for SCIG/IVIG prescriptions for immunodeficiencies.

A national PID service will secure the future of the customised genetic testing service, which has significantly improved health outcomes, and has also resulted in considerable cost savings to the New Zealand taxpayer. After intense counselling, several families are considering preimplantation genetic diagnosis, which will result in cost savings as well as alleviating suffering in future generations.

The future of genetic testing lies in the development of NGS-based gene panels. Gene panels are now offered by many diagnostic laboratories in the US. A diagnostic service, based on targeted next-generation sequencing (NGS) is being developed at LabPlus. Using targeted WES as a rapid screening method for known PID genes is a potential strategy, which could be much cheaper than sequentially testing multiple genes. Gene panels could be deployed when the genetic defect is not clear from the history or protein based laboratory testing. The development of functional studies is an essential part of this program.

If the causative gene is not clear from the initial targeted NGS panel, WES for gene discovery could be deployed in the context of a research program. WES has a major role in identifying novel genetic defects in patients with unknown clinical conditions. A recent study from the NIH identified the genetic defect in 24% of patients with undiagnosed disorders. These research assays are best performed within the framework of a national clinical immunology service with access to protein-based and functional studies.

Newborn screening for SCID will be implemented in New Zealand in the near future. Prompt identification and bone marrow transplantation of SCID patients before the onset of severe, life-threatening infections, will result in major improvements in patient outcomes and reduction in the cost from prolonged hospitalisation. The customised genetic testing program will play a key role in identifying the causative gene either through Sanger sequencing of a high probability genetic defect, or through
deployment of NGS-based targeted gene panels for SCID.

A national PID service could consist of a hub-and-spoke model. For adult patients, Christchurch would provide the hub for the South Island, while Auckland and Wellington would provide the hubs for the North Island. The unit at Starship would provide the service for the entire country. Regular immunology clinics in regional centres will reduce the need for patients to travel to larger centres.

The model proposed is unique in that both adult and child patients will be treated as part of the integrated national PID service. Such a national PID service may allow combined adult and paediatric immunology clinics in regional centres, which would help seamless transitioning of child patients to adult services, as well as upskilling local physicians on the management and monitoring required for these complex diseases. Currently, a seamless transition between child and adult services is only available in Auckland.

A national PID service, facilitated by the collegiality between adult and paediatric immunologists in New Zealand, will be of great benefit to patients and their families. A schism often exists in other services between provision of care for children as they progress through adolescence to adulthood. In some countries, paediatric immunologists continue care for their patients into late adulthood because of a lack of adult services for patients with PIDs.

Many countries are addressing the challenges posed by rare disorders. Ireland, England, France and the EU as a whole are developing national strategies to deal with patients with rare conditions. There have been similar calls for a national service for rare disorders in Australia. A national service for PIDs would support patient-centred management, allowing greater patient autonomy.

We accept there may be some disadvantages for the proposed national PID service. A national PID service will require immunologists having to visit regional centres on a regular basis. Extra immunology positions will be needed for each hub, in Auckland, Wellington, and Christchurch. There are currently several advanced trainees in immunology who could fill these positions over time. A national PID service will also require some investment in infrastructure to co-ordinate joint clinics in regional centres. Practical issues, such as reviewing laboratory results and typing clinic letters, will need to be addressed. These issues are not insurmountable and have been overcome by other national services, such as paediatric rheumatology. It is likely any additional costs for immunology positions and infrastructure will be easily offset by savings from the judicious use of IVIG/SCIG, and reduced hospitalisation costs.

Other models for a nationally co-ordinated service could be considered, where each region with an immunology service remains autonomous. There will be disadvantages with this model as there may be insufficient numbers of immunologists in some areas to provide a visiting service to regional cities. Funding formulas would also need to be carefully considered to ensure regions with fewer immunologists are not disadvantaged. Furthermore, there is only one public hospital paediatric immunology service (based at Starship) for PIDs, which has been providing a de facto national service for PID patients. It will be important for this service to be appropriately resourced.

In the past, there has been resistance to developing national services on account of each DHB having to financially contribute to the program. As we have shown here, smaller DHBs without an immunology service are likely to fiscally benefit most from a national PID service. We are very confident a strong business case could be made for our proposal. We hope the Ministry of Health and the National Health Board will engage with stakeholders, especially the New Zealand Clinical Immunology and Allergy Group (NZCIAG) for productive discussions on this proposal. Patient support groups (IDFNZ and HAE Australasia) will also play an important role in shaping a national PID service. The model proposed here may also be useful for other countries with a centralised government-funded health system.
Competing interests:
Rohan Ameratunga has received an unrestricted educational grant from Octapharma.

Acknowledgements:
We thank our patients for participating in our studies for the benefit of others. We hope this proposal will be implemented for the benefit of all PID patients in New Zealand. We thank Dr Richard Charlewood for allowing us to publish Tables 2–5 from the recent NZBS audit.

Author information:
Rohan Ameratunga, Departments of Clinical Immunology, Virology and immunology, Auckland City Hospital, Auckland; Richard Steele, Virology and immunology, Auckland City Hospital, Auckland, and Department of Clinical Immunology, Wellington Hospital, Wellington; Anthony Jordan, Department of Clinical Immunology, Auckland City Hospital, Auckland; Kahn Preece, Department of Immunology, Starship Hospital, Auckland; Russell Barker, Department of Clinical Immunology, Wellington Hospital, Wellington; Maia Brewerton, Department of Clinical Immunology, Auckland City Hospital, Auckland; Karen Lindsay, Department of Clinical Immunology, Auckland City Hospital, Auckland; Jan Sinclair, Department of Immunology, Starship Hospital, Auckland; Peter Storey, Department of Clinical Immunology, Auckland City Hospital, Auckland; See-Tarn Woon, Virology and immunology, Auckland City Hospital, Auckland, New Zealand.
All authors are part of the New Zealand Clinical Immunology and Allergy Group (NZCIAG)

Corresponding author:
Rohan Ameratunga, Departments of Clinical Immunology, Virology and immunology, Auckland City Hospital, Auckland, New Zealand.
rohana@adhb.govt.nz

REFERENCES:

URL:


CLINICAL CORRESPONDENCE

Unprovoked DVT, the clot thickens
Sophie Harmos, Tom Kai Ming Wang, Stewart Hawkins, Roger Reynolds

ABSTRACT
Deep vein thrombosis (DVT) is a common presentation to acute medical services. This paper describes the investigation and subsequent treatment of a patient who presented with an extensive lower limb DVT and was found to have congenital inferior vena cava agenesis (IVCA).

Case
Ms A., a 28-year-old female, presented to the medical service at Middlemore Hospital (Auckland) with a 12-hour history of right leg swelling. She denied recent infective symptoms or trauma, aside from a dog-scratch 4 days previously on her right shin. She had no chronic illnesses, no recent surgery, and no air travel. Ms A smoked five cigarettes per day, and her only medication was an oral contraceptive pill (OCP), containing ethinyloestradiol 30 mcg. On examination, marked swelling of the right leg was noted from ankle to groin, with a circumference differential of 6 cm at the upper thigh, and 5 cm at the tibial tuberosity. D-dimer was 1,440 ug/L and lower limb ultrasound showed a large right deep vein thrombosis (DVT) from the popliteal to the external iliac vein. Thrombophilia screen was negative.

Therapeutic enoxaparin was commenced at 70 mg twice daily. Given the severe swelling, surgical thrombectomy with possible venous reconstruction was initially considered, and CT venogram was performed. This revealed agenesis of the inferior vena cava (IVCA) associated with the DVT, presumed to be congenital, as Ms A had no history of vascular intervention in childhood. Referral was therefore made to interventional radiology and catheter-directed thrombolysis with urokinase was undertaken, initially to the occluded popliteal vein, followed by right external iliac vein 2 hours later and common femoral vein the next day. Following this, Ms A underwent pharmacomechanical thrombectomy of the femoral and external iliac veins. This was achieved by an AngioJet catheter, which directs pulses of a thrombolytic agent into the clot. Fragments of clot are then actively aspirated by a vacuum formed within the catheter. This led to significant improvement in swelling and no residual stenosis. Warfarin was then started, with enoxaparin cover until therapeutic levels were reached. The OCP was stopped on admission, and after discussion about contraceptive options, Ms A chose the Depo-Provera injection. Smoking cessation advice and support was provided. At her 4-month follow-up appointment, Ms A was back to running, and was only having occasional pain in the right leg on strenuous exercise. Anticoagulation had been therapeutic since discharge, and no complications had arisen. Ms A was educated further at this stage about the need for lifelong warfarin, and enoxaparin cover during any future pregnancies.

Discussion
IVCA is a rare congenital vascular anomaly identified in approximately 5% of patients with DVT under 30 years of age.1 The diagnosis covers several anatomic variations including the absence of the suprarenal, infrarenal or entire IVC.2 IVCA is proposed to be a risk factor for DVT because the vena azygous system does not adequately drain the lower limbs, leading to venous stasis and subsequent clot formation.3

The diagnosis of IVCA must be considered in DVT patients of younger age, with
**Figure 1:** CT venogram demonstrating lack of contrast uptake in the atresic IVC

**Figure 2:** Atresia of IVC parallel to the aorta
minimal risk factors, or with proximal DVT and extensive clot burden.\textsuperscript{1,4} Compressive ultrasonography is not sufficient to make the diagnosis of IVCA, and abdomino-pelvic CT, MRI or angiography is required.\textsuperscript{1} This can also guide treatment with catheter directed thrombolysis if required.

The diagnosis is important; IVCA is not a modifiable risk factor so there is significant risk for recurrent events. Treatment is with anticoagulation. There is no systematic follow-up data available regarding the rate of recurrence of DVT after stopping anticoagulation in patients with IVCA, although such cases have been reported.\textsuperscript{2,3} There are no guidelines for the duration of anticoagulation and most reported cases have been prescribed long-term vitamin K antagonists.\textsuperscript{4} Some authors report an association of IVCA with clotting disorders, although generally thrombophilia screening in these patients is not useful as it does not change the recommended duration of anticoagulation.\textsuperscript{2,5-7} In this case, the OCP was stopped and exchanged for the Depo-Provera injection. Evidence suggests that the risk of recurrent thrombus while anticoagulated is not increased by oestrogen containing contraceptives.\textsuperscript{8} However, given the teratogenicity of warfarin and the typical failure rate of the OCP (3\%) compared with the Depo-Provera injection (0.3\%), it makes sense to select a contraceptive method that minimises potential for unplanned pregnancy.

Long-term complications of DVT including oedema and post-thrombotic syndrome can lead to loss of mobility and inability to return to work. Recent trials have shown advantages of thrombolysis, particularly catheter-directed thrombolysis and pharmacomechanical techniques, over standard anticoagulation in terms of clot breakdown and venous patency.\textsuperscript{9} The long-term goal is to reduce the incidence of post-thrombotic syndrome (PTS). A recent Cochrane review of systemic and locoregional techniques demonstrated a number needed to treat of five to prevent one case of PTS, in patients who presented within 14–21 days of symptom onset.\textsuperscript{10} The newer pharmacomechanical techniques not included in the Cochrane review are proposed to have a lower bleeding risk through a reduced dose of thrombolytic, and improved venous patency by combining thrombolytic agent with mechanical techniques. These interventional procedures are particularly useful for patients with proximal iliofemoral DVT, a low bleeding risk, and good functional status who present within 3 weeks of symptom onset. Such techniques were therefore appropriate for Ms A, who fulfilled all of these criteria, and in whom post-thrombotic syndrome could have life-long implications.

IVCA is likely an under-diagnosed entity as CT is not a routine investigation for DVT, and IVCA is often found incidentally after imaging for suspected malignancy or occult sepsis.\textsuperscript{2,3} We need to consider IVCA in patients with DVT, especially young patients who have few risk factors, extensive clot burden and proximal location, such as Ms A. This could impact on both the duration of anticoagulation and the management in higher risk situations such as pregnancy. Further imaging also means that alternative acute treatments, such as thrombolysis or surgical thrombectomy, can be considered in appropriate patients.

**Author information:**
Sophie Harmos, medical registrar, Middlemore Hospital, Auckland; Tom Kai Ming Wang, medical and cardiology registrar, Middlemore Hospital, Auckland; Stewart Hawkins, interventional radiology consultant, Middlemore Hospital, Auckland; Roger Reynolds, general medical consultant; Middlemore Hospital, Auckland, New Zealand.
All authors are part of the New Zealand Clinical Immunology and Allergy Group (NZCIAG).

**Corresponding author:**
Sophie Harmos, 100 Hospital Road, Papatoetoe, 2025, New Zealand.
sophie.harmos@gmail.com

**URL:**
REFERENCES:


CLINICAL CORRESPONDENCE

Leukoencephalopathy in an HIV Patient

Joe James, James Jose, NK Thulaseedharan

Case

A 61-year-old male presented with progressive weakness of left upper and lower limbs, and slurring of speech of 2 months duration. He had focal seizures of right upper limb. He was an IV drug abuser. On examination he was disoriented and inattentive. His talk was irrelevant and psychomotor activity was reduced. He had grade II/V power of left upper and lower limbs. The plantar response was bilaterally extensor. He was tested positive for HIV and HBsAg. The CD4 count was 107/µL. MRI brain showed T1 hypointense and T2 and T2-FLAIR hyperintense asymmetrical lesions in bilateral frontoparietal regions with involvement of ‘U’ fibres, without any edema, mass effect or contrast enhancement. What is the diagnosis?

MRI showing hyperintense lesions in T2-FLAIR image in bilateral frontoparietal regions, which are asymmetric (Panel A, white arrows) with involvement of subcortical “U” fibres (arrowheads). The lesions are not contrast enhancing (Panel B).

Answer

Progressive multifocal leukoencephalopathy (PML). He was started on antiretroviral therapy, but his clinical condition rapidly deteriorated and he became bedridden. He was later shifted to a palliative care centre.

Discussion

PML is a subacute demyelinating disease of central nervous system caused by John Cunningham (JC) virus. After primary infection in the childhood, the virus remains latent in the kidneys and lymphoid organs and gets reactivated in the setting of immunosuppression as in HIV infection,
solid organ transplant recipients, lymphoproliferative neoplasms or therapy with natalizumab. Reactivated virus enters the blood stream and reaches the brain inducing a lytic infection of oligodendrocytes. Patients usually present with weakness, gait ataxia, visual field changes, dysarthria, seizures and progressive cognitive impairment with dementia. Typical MRI changes involve frontoparietal and occipital lobes, with white matter hyperintensities that are usually asymmetric, with involvement of subcortical ‘U’ fibres. HIV encephalopathy closely mimics PML with involvement of white matter. But the periventricular white matter is involved first and the lesions are more symmetric. Moreover, cerebral atrophy will be a prominent feature in HIV encephalopathy. In advanced stage when the whole of white matter gets affected, lesions of PML and HIV encephalopathy are indistinguishable and a definitive diagnosis of PML relies on detection of JC virus in the CSF by PCR or brain biopsy. There is no specific treatment for the disease other than initiation of antiretroviral therapy in HIV patients, but the disease is progressive and fatal.

**Learning points**

- PML is a progressive and fatal infection caused by reactivation of JC virus.
- It occurs in immunocompromised individuals especially HIV patients.
- It can also occur in Immunocompetent patients especially with natalizumab therapy for multiple sclerosis.
- MRI shows hyperintense lesions in T2-FLAIR image, which are asymmetric, involving subcortical ‘U’ fibres and spreads from periphery to centre, without mass effect or contrast enhancement.

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**Author information:**

Joe James, Resident, Department of Internal Medicine, Government Medical College Kozhikode, Kerala; James Jose, Professor and Head, Department of Neurology, Government Medical College Kozhikode, Kerala; NK Thulaseedharan, Professor and Head, Department of Internal Medicine, Government Medical College Kozhikode, Kerala, India.

**Corresponding author:**

Joe James, Department of Internal Medicine, Government Medical College Kozhikode, Njaralakatt House, Pottangadi Road, West Nadakkav Calicut 673011, Kerala, India. drjoejames@gmail.com

**URL:**


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**REFERENCES:**

1. Progressive Multifocal Leuкоencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis.

Survival benefit with kidney transplants from HLA-incompatible live donors

The problem examined in this study is whether there is a survival benefit for those having an incompatible live donor kidney transplant compared with those who remain on the waiting list or receive a transplant from a deceased donor.

In this multicentre study, the researchers estimated the survival benefits for 1,025 recipients of kidney transplants from HLA-incompatible live donors who were matched with controls who remained on the waiting list or received a transplant from a deceased donor. Recipients of kidney transplants from incompatible live donors had a higher survival rate than either control group at 1 year, 3 years, 5 years, and 8 years. All comparisons were found to be highly significant (p<0.001) in favour of the incompatible live donor transplants.


Management of ischaemic heart disease in those aged 80 years or older

Non ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris are frequent causes of hospital admission in the elderly. This study compares treatment with early invasive strategy versus conservative treatment.

Patients were randomly assigned to an invasive strategy (including early coronary angiography with immediate assessment for percutaneous coronary intervention, coronary artery bypass graft, and optimum medical treatment) or to a conservative strategy (optimum medical treatment alone). The primary outcomes sought were infarction, need for urgent revascularisation, stroke and death. The primary outcome occurred in 40.6% of the patients treated by invasive strategy and 61.4% of those treated conservatively (p=0.0001). Major and minor bleeding complications were infrequent and equal in occurrence in both groups.

An editorial commentary commends the study and regards the results as compelling evidence in favour of early invasive strategies for very elderly patients.


Pre-pregnancy potato consumption and risk of gestational diabetes mellitus

Is there an association between potato consumption before pregnancy and the risk of gestational diabetes mellitus?

This possibility is examined in this prospective cohort study which involved 15,632 women from the Nurses' Health Study in the US. None of them had previous diabetes or chronic disease prior to their pregnancy. Consumption of potatoes was recorded as 1 or less, 2–4, or 5 or more servings per week. Over a 10 year follow-up, there were 854 cases of gestational diabetes. The relative risks for the 2–4 and 5 servings per week were 1.27 and 1.50.

The researchers conclude that, “Higher levels of potato consumption before pregnancy are associated with greater risk of gestational diabetes mellitus, and substitution of potatoes with other vegetables, legumes, or whole grain foods might lower risk.”

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URL:
Present state of affairs in the lodge dispute in Wellington

Editorial: June 1916

As the April Journal went to press it was undecided, but expected, that a conference between the representatives of the Lodges and of the Wellington Division of the BMA would take place under the direction of the Minister of Internal Affairs, the Hon. GW Russell. This conference did eventually take place and lasted over three hours, but failed to agree on the question of the rate per member. The doctors offering the same terms as some of the lodges had already accepted, viz, 21s., and the representatives of the lodges promising to recommend to their lodges 20s., but no more. The doctors felt they could not grant better terms to the resisters than they had granted to those who met them and had come to a satisfactory agreement amicably. The chairman did his best to effect a settlement, but it was impossible.

During the discussion, it was pointed out inter alia that statistics had proved that the past remuneration from lodges had worked out at less than a shilling per attendance whether at surgery or at homes. This fact was seized upon and the other side wished us to consider a scheme of payment per visit basis instead of payment per member, and the chairman submitted the proposition to us. To anyone acquainted with medical practice numerous objections occur to such...
a proposition, but the major objections of such a scheme necessarily being only parochial and not of general application, and therefore no satisfactory solution; the bookkeeping that it would necessitate, the tendency for it to lower medical fees generally, and the fact that it would lead to medical men only having the serious and difficult cases to attend, and the fact that a few chronic long cases would deplete the funds; these objections were pointed out and the scheme refused.

To this we received a more or less reproachful letter from the Minister alleging bad faith and exploitation of the war conditions, and that negotiations were ended, and he would have to find other ways of providing medical service.

Thinking that the friendly societies might attempt to obtain men from England through the High Commissioner's office, correspondence passed between the various offices till we finally had the Minister's statement that the Government would not interfere further in the matter, nor instruct the High Commissioner to act for either party.

However, though it has been kept secret by the Friendly Societies, we understand that three or four medical men have been obtained from outside and are arriving shortly. If they are decent men, when they learn all the facts, they will not stay long, and, if of the other class, the lodge members will soon have enough of them.

Within the last week the dispute with the lodges has taken a much more interesting and possibly far-reaching turn, by reason of the discussion which has taken place in the House of Representatives. Mr JTM Hornsby (Wairarapa) and Mr R Fletcher (Wellington Central) assisted by Messrs Jennings, Harris, Witty and Poland denounced the BMA in scathing terms. They, with their followers, were under the impression that there was a rule implied, if not in black and white, to the effect that no member of the BMA was allowed to consult or assist a doctor who does not belong to the BMA. One can perhaps excuse this ignorance, when one learns that they nearly wiped out the Government subsidy in the back blocks, which enabled these districts to obtain medical service, which they cannot otherwise do, under the impression that these grants were made to the BMA. Arguing on these false premises it is no wonder that the deliberations reached an hysterical pitch and elicited from the Minister of Internal Affairs equally foolish threats against the profession. The only real thing that we have to learn from all this is that we must be alert lest this irresponsible minority in the House should be able to so impress the rest that some Gilbertian legislation should be rushed through and the country and this profession be placed in a ridiculous predicament. At the same time we must recognise that this present fight with the lodges which has gradually grown from a small affair to the present supreme test of strength, is to the medical profession all through the Dominion what the Verdun battle is to the belligerents in Europe. If we do not succeed in this effort to ameliorate the condition of contract practice, we need not attempt it again in the present generation. Also, what is happening in Wellington will be tried in all the other centres immediately if we do not succeed, and so it behoves all medical practitioners to help Wellington to win their dispute for the sake of the profession in New Zealand.

The Minister has stated that if Parliament gave him the power he would strike off the register any doctor who refused to consult or assist any duly registered medical practitioner. He does not realise that this would practically only debar a man from collecting his fees in court, and he could not sign death certificates and would have to report deaths occurring in his practice to the coroner, but no Act of Parliament can take away his medical diploma, nor any coroner say that the treatment that has been correct whilst he was on the register is necessarily incorrect now he is struck off. He would go on practising just as before with, in fact, a little more liberty.

Another threat by the Minister was to this effect: That if any doctor could not get another one to give an anaesthetic he would instruct a State paid doctor to do so. If these gentlemen have so much spare time and are so well paid already, no doubt they could easily undertake all the honorary work at the hospitals throughout the Dominion, and various other duties could be found them.

Of course, if we cared to put forth our whole strength, we could obtain sufficient
resignations from country lodges to make it impossible for the lodges to supply medical men throughout the country, but we do not think this is necessary at present. No doubt if we did so it would raise the question of either nationalisation of the profession or else a State medical service, after the Lloyd George scheme in England.

The idea of nationalisation is clearly only a dream. In a democratic country like New Zealand they would have to give us an eight hour service, requiring three shifts in the day. They could not offer us less than £500 a year, and they would either have to find us rooms and conveyances or provide another £500 for expenses of practice. Then there would be overtime fees and a great many smaller matters to be considered, so that however alluring the Utopian vision of a nationalised medical service may seem at is at most only a dream of the future.

As regards the State medical service, after the Lloyd George scheme at Home, it would be a bad jump for the lodges from the frying pan to the fire in the present instance. The British scheme is at the rate of 7s. per individual member, and this would mean 28s. to 30s. per member, according to the New Zealand interpretation of the term “member.” As we are at present only asking for 24s. and 21s. as a minimum the changes would not help the lodges, not even if Parliament shouldered a portion of the burden. Moreover it was plainly pointed out to the Minister that the present low rate of remuneration for lodge work is the result of sweating by unfair competition in the past, and that instead of starting negotiations at the present rate of 3d. per week, if any radical change were made we would not negotiate at less than double or treble that figure to begin with. The Minister has some idea of the difficulties of the situation, but still would use it as a threat, when we know that we would not only have nothing to fear if it were introduced but, as at Home, it would probably end in a less satisfactory medical service from the public point of view together with marked financial benefits to the medical profession.

We feel that it is a pity that this fight has arisen just now, but it had to come some time, and perhaps now as well as later. Few, even in Wellington, had the idea that the lodges would be so blind to their own interests or so unfair in recognising our just claims, but having once put forth our requests we must now make them demands, and it would be suicidal to retract one iota. We know we have the bulk of public opinion with us and even of the rank and file of the lodges, but the noisy minority in the lodge executive, as is common, override the others. The Wellington Division is absolutely unanimous in their action, and are confident of winning, and trust the other Divisions to assist, if only by abstaining from doing anything that might inadvertently hamper their actions. A further discussion is promised in Parliament on this question during the coming week when, with the full ventilation of the whole matter, we are confident that the justice of our cause and action will be vindicated.

URL:
Cognitive changes with adjuvant therapy for breast cancer: a longitudinal study

Ridmi Dissanayaka1, Jenny Boyd1, Robyn Segedin1, Barbara Hedge1, Michael Jameson1
1Oncology and Haematology, Waikato Hospital, Hamilton, NZ, 2Dept of Psychology, University of Waikato, Hamilton, New Zealand.

Background: Women with breast cancer are one of the largest groups of cancer survivors. Patients commonly report impaired mental function during and after chemotherapy (“chemobrain”), but this has proven difficult to characterise. These changes are stressful to individuals and are associated with a lower quality of life. Whether this may also be due in part to anxiety, depression, fatigue, menopause or subsequent hormone treatment for breast cancer is not clear. Existing studies all had major limitations, with the biggest flaw being lack of longitudinal evaluation starting before treatment, and not evaluating all the relevant factors that could influence mental functioning.

Methods: We designed a longitudinal study recruiting patients who were planned to receive any adjuvant therapy (radiation [RT], chemotherapy or hormonal therapy) from Waikato, Rotorua, Tauranga and Whakatane Hospitals. Each patient completed questionnaires and a battery of tests that focussed on the problem areas of mental functioning identified in other studies, as well as quality of life. Interviews were conducted at baseline (after surgery but prior to starting any adjuvant therapy), then 3, 6, 12 and 24 months later.

Results: 201 patients were recruited between November 2003 and September 2010. Median age was 51 years (range 21–81). The majority of patients were New Zealand European (79%; Māori 12%), married (62%), tertiary-educated (69%) and postmenopausal (45%) prior to their breast cancer diagnosis. Overall, about half of the patients had stage 2 invasive carcinoma and 45% of the patients received chemotherapy, radiotherapy and hormone therapy for their treatment. 76% of the patients reported taking alcohol, 88% reported caffeine intake and 16% reported cigarette smoking. Patients treated with RT alone had few changes in these tests. Chemotherapy or hormone therapy alone showed more disturbance, but the combination did not appear to be any worse than either treatment alone, nor did adding RT to hormones appear to add a burden. Combining chemotherapy with RT appeared worse and the greatest impact appeared to be in those patients who received all 3 treatments.

Conclusions: The results of these preliminary analyses show that the different systemic adjuvant treatments appear to have much more impact on cognitive function than RT alone, and their combination may be at least additive. The changes are also more marked over a longer duration of assessment, consistent with the prolonged treatment course in many of these patients. Further domain-specific analysis is planned including the speed and completeness of recovery.

Anaesthetic effects on infrared pupillometry

Liam McAskie, Dr. Amy Gaskell, Prof. Jamie Sleigh
Institution: Department of Anaesthetics, Waikato Hospital

Background: Pupillary size is determined by two groups of smooth muscle, sphincter pupillae and dilator pupillae. It is known to be affected by various factors in anaesthesia, including degree of noxious stimulation and drug concentrations. The aim of this research was primarily to determine if it was possible to demonstrate a link between intraoperative pupillary measurements and postoperative pain scores. In addition, we assessed the association of a variety of other possible explanatory variables—such as opioid doses, volatile concentrations and patient information (age, weight, height, etc)—with pupillary responses.

Methods: Adults undergoing general anaesthesia for general, gynaecological, urological, orthopaedic and plastic surgery procedures with access to the eye to take pupillometry readings would be possible. This study received ethics committee approval and written informed consent was obtained from all participants. Anaesthetic management was at the discretion of the treating anaesthetist who was independent from the study. Infrared pupillometry measurements were taken at the end of the surgery and patients were assessed for post-operative pain during their stay in the post anaesthesia care unit. The main pupillary responses were: maximum diameter, minimum diameter in...
response to a light flash stimulus and the rates of constriction and dilation. The influence of various factors on the pupilometry indices were assessed using correlation analysis.

**Results:** Ninety-two patients were studied. Older patients had smaller pupil sizes and were slower to react (R=0.5, p<0.001). Speed of pupillary reactivity is reduced by volatile anaesthetic agent (R=0.32, p<0.001), even when age is included as a partial correlation. Opioid concentrations had a minimal effect (p=0.06). There was poor univariate correlation between pupil indices and post-operative pain, but a multi-variate logistic regression model for post-operative pain score >4 identified regional anaesthetic technique and minimum pupil diameter as significant influences on post-operative pain (area under ROC curve=0.72).

**Conclusions:** Age and anaesthetic concentration had the most marked effects on speed of pupil reactivity. The minimum pupil diameter contributed to a composite predictive model of early post-operative pain.

**Thyroid disease and anaemia in the Waikato region**
Shekhar Sehgal, Jade AU Tamatea, John V Conaglen, Marianne S Elston
Waikato Endocrine Unit

**Objectives:** Anaemia and hyperthyroidism are both relatively common, but currently it is unclear as to whether thyrotoxicosis per se results in anaemia in the absence of other causes. The aim of this study was to determine the prevalence and characteristics of anaemia in a large cohort of patients with new onset hyperthyroidism. Patients: 355 patients referred to a regional endocrinology centre in New Zealand between March 2013 and November 2014 for new onset hyperthyroidism.

**Measurements:** All patients were evaluated by detailed clinical assessment including thyroid ultrasound, thyroid function tests, full blood count, inflammatory markers, thyroid antibodies, hematocrit parameters and coeliac serology. Anaemia was defined as a haemoglobin value <115 g/L (female) or <130 g/L (male). Patients were followed for a minimum 12 months.

**Results:** Anaemia was present in 31 (8.7%) patients at diagnosis. Of these 31 patients, pre-existing anaemia was present in 10 and a further 11 had a clearly defined underlying cause contributing to the anaemia. Only 10 patients (2.8% of the entire cohort) had anaemia not definitively attributable to another cause. Median free thyroid hormone levels were higher in those with anaemia of unknown cause compared to those with thyrotoxicosis alone (p=0.008). The median duration of anaemia was shorter in patients with unexplained anaemia compared to those with anaemia due to an underlying cause (1 vs 6 months, p=0.001). In all patients with unexplained anaemia the anaemia resolved either prior to, or when a euthyroid state was achieved.

**Conclusion:** Anaemia co-occurring with hyperthyroidism is less common than previously reported, usually normochromic, normocytic, and is mild and transient. Patients with thyrotoxicosis and significant anaemia should be investigated for other potential causes, particularly when anaemia persists.

**The implication of considering active surveillance as an option for men with low-risk localised prostate cancer: a cost analysis study.**

Chunhuan Lao, Richard Edlin, Paul Rouse, Charis Brown, Michael Holmes, Peter Gilling, Ross Lawrenson

**Background:** Active surveillance is increasingly being used as an option for men with low-risk localised prostate cancer. This study aims to compare the life-time costs of active surveillance with the costs of radical prostatectomy for men with low risk localised prostate cancer.

**Methods:** An economic model was constructed, using data from the New Zealand national datasets and published studies including the SPCG-4. The life-time costs of active surveillance and radical prostatectomy were estimated for men diagnosed with low risk localised prostate cancer at the age of 45-70 years.

**Results:** For men aged 45–50 years, the life-time costs of active surveillance ($21,115–23,396) were higher than the costs of radical prostatectomy ($20,991–22,316). For men aged 55–70 years, the life-time costs of active surveillance ($7,976–18,484) were lower than the costs of radical prostatectomy ($15,821–19,612). The life-time costs in both treatment arms increased with decreasing age at diagnosis. The life-time costs of active surveillance increased with increasing annual probability of having radical prostatectomy in the active surveillance arm.

**Conclusion:** The life-time costs of active surveillance were lower than the costs of radical prostatectomy for older men with low-risk localised prostate cancer, but not for younger men. The probability of active surveillance being cost-effective compared to radical prostatectomy decreased with increasing annual probability of having radical prostatectomy in the active surveillance arm.

**Whakangungu rākau: an increased incidence of thyrotoxicosis in Māori**

Tamatea JAU, Reid P, Elston MS, Conaglen JV

**Introduction:** The reported incidence of thyrotoxicosis in Western Countries ranges from...
22-81 per 100,000 per year.1-3 This variability is explained by differences to iodine intake as well as methods of measurement. The incidence of thyrotoxicosis in New Zealand has been reported to have dropped from 88 per 100,000 per year in 1928 to 26 per 100,000 per year in 1990,4 and this has been attributed to iodine fortification. No information is available regarding the incidence of thyrotoxicosis for Māori.

Aim: As part of a larger Kaupapa Māori methodology led project investigating the impact of thyrotoxicosis for Māori, the aim of this study was to calculate age-stratified incidence rates and age-standardised incidence rate ratios of thyrotoxicosis for Māori and Non-Māori.

Methods: All referrals to Waikato District Health Board (WDHB) Endocrinology Department and the sole private clinic in the region were recruited at presentation for inclusion to the study. Baseline demographic and clinical information was collected. WDHB census data from 2013 was used to calculate incidence rates. Incidence rates were age-stratified and age-specific incidence rate ratios were calculated using the Waikato DHB Māori population as a standard.

Results: 391 referrals were received from which 353 participants were recruited over a 20 month period. The annual incidence rate of thyrotoxicosis in Waikato was calculated at 68 (95%CI 61–76) per 100,000 people per year. Incidence rates (IR) were highest in women (IR 106 [95% CI 95–120] per 100,000 per year) and Graves’ disease was the most common diagnosis (IR 39 [95% CI 34–45] per 100,000 per year). Compared to Non-Māori, age standardised incidence rate ratios for Māori were 2.27 [95% CI 1.94–2.66; p<0.00001] for all cause thyrotoxicosis with the greatest difference seen in toxic multinodular goitre (age standardised IR 7.46 [95% CI 4.70–11.82; p<0.00001]). There was no difference in the gender distribution between the two ethnicity groups.

Conclusion: This is the first report of incidence of thyrotoxicosis in Māori and reveals an as yet unexplained, increased incidence of thyrotoxicosis for Māori when compared to the rest of the population.


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Dispensing data captures individual-level use of aspirin for cardiovascular disease prevention, despite availability over-the-counter

Vanessa Selak, Yulong Gu, Natasha Rafter, Sue Crengle, Andrew Kerr, Chris Bullen


In the first published version of this manuscript, Tables 1 and 2 contained an error. The Yes/No boxes titled "Dispensed" were inverted. This was resolved online and in the PDF on 2 June 2016.