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Infertility and outcomes for infertile women in Otago and Southland

Pacific Islands Families Study: Signs of puberty are associated with physical growth at ages 9 and 11 years

The experiences, motivations, and opinions of New Zealand's live liver donors

- Mandatory regulation or self-regulation in the age of the Volkswagen saga
- Fast, fair climate action crucial for health and equity
- Trends and patterns in medical student research and publishing in New Zealand
- Attitudes and risk of withdrawal in general surgical registrars

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Sydney Rae West
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The prevention of early-onset neonatal group B streptococcus infection: New Zealand Consensus Guidelines 2014

Brian Darlow, Norma Campbell, Nicola Austin, Adrienne Chin, Celia Grigg, Craig Skidmore, Lesley Voss, Tony Walls, Michelle Wise, Anja Werno

Group B streptococcal disease is the leading cause of infection in newborn babies in the first few days of life. The disease can usually be prevented by giving mothers intravenous antibiotics at the start of labour. The clinical problem is how best to identify mothers who might qualify for antibiotics and different approaches have been advocated. A multidisciplinary group including midwives, obstetricians, paediatricians and infectious diseases physicians met to review the 2004 New Zealand guidelines in the light of a recent two year audit on the incidence of early-onset GBS infection in the newborn and which showed New Zealand to have a relatively low incidence of the disease. The consensus guidelines are to continue to identify mothers, who should be offered antibiotics, by whether they have one of several clear risk-factors. The revised guidelines clarify the recommended approach in several obstetric circumstances and provide information about antibiotic choices.

Potential new regulatory options for e-cigarettes in New Zealand

Nick Wilson, Richard Edwards, Janet Hoek, George Thomson, Tony Blakely, Frederieke Sanne van der Deen, Brent Caldwell, Julian Crane

While e-cigarette usage has grown rapidly in New Zealand and around the world, the scientific evidence-base regarding the net benefits and risks of these types of products at the population level remains uncertain. The health-based policy experience is also minimal. In this article we analyse plausible future regulatory options for e-cigarettes that the New Zealand Government could explore, and that further research could help clarify. These options include: (1) a full free market (an option we doubt is desirable for multiple reasons); (2) controlled increased access through: (a) pharmacy only, (b) pharmacy only plus sales by prescription/to licensed vapers; (c) additional controls through non-profit supply/distribution (eg, public hospital pharmacies); (3) increased restrictions compared with currently (eg, a complete ban on self-imports and use).

Pacific Islands Families Study: Signs of puberty are associated with physical growth at ages 9 and 11 years

Elaine Rush, El-Shadan Tautolo, Janis Paterson, Victor Obolonkin

The Pacific Islands Families study is tracking the growth and development of Pacific Island children born at Middlemore Hospital in the year 2000. More than four out of five parents of both boys and girls reported growth spurts at both 9 and 11 years. Girls with a growth spurt at age 9 years weighed 250 g more at birth than those without a growth spurt. Factors that influence the rate of physical growth are complex but issues such as food security and supportive environments for children need to be addressed.

Mandatory regulation or self-regulation in the age of the Volkswagen saga

Nick Wilson, Rob Quigley, Osman Mansoor, Moira Smith, Louise Signal

This Editorial briefly discusses the issues around self-regulation and mandatory regulation of food marketing (partly in response to food industry claims around the value of self-regulation). It discusses how self-regulation can failure in some areas, and the value of mandatory regulation. But even when there is regulation, given situations like the Volkswagen saga, policy-makers should also consider better funding of regulatory science. Mandatory regulations, combined with science-based monitoring may then start to provide further protection of the public from unhealthy products – including the marketing of unhealthy food.

Is the statement that if a person is off work for 70 days the chance of ever getting back to work is 35% justified?

Gordon Purdie

Statements like, if a person is off work for 70 days, the chance of ever getting back to work is 35%, are being repeated by Government and non-Government agencies in New Zealand and Australia. The statements are not justified and appear to be based on an incorrect interpretation of a graph. The statements are being used to influence Government policies and doctors writing medical certificates. The statements should not be used.

Infertility and outcomes for infertile women in Otago and Southland

Antoinette Righarts, Nigel P Dickson, Lianne Parkin, Wayne R Gillett

Infertility, that is trying unsuccessfully to get pregnant for longer than 12 months or seeking medical help to conceive, was experience by a quarter of a sample of women aged 25–50 years in Otago and Southland surveyed in 2011 who had ever been or tried to get pregnant. Most women resolved their first episode of infertility with a live birth; however, a quarter had not done so. Furthermore, almost three quarters of women who had infertility accessed medical help for this. These results suggest infertility is an important problem, significant health resources are being used to address infertility and a substantial proportion of women are childless due to infertility and/or social circumstances (such as not having a male partner).

Renal replacement therapy associated with lithium nephrotoxicity in New Zealand

J Elisabeth Wells, Nicholas B Cross, Ruth L Savage, Lianne Parkin, Simon Horsburgh, Ann K Richardson

An uncommon consequence of long-term treatment with lithium can be kidney failure. We found that between 1996 and 2013 in New Zealand 35 patients had to start dialysis or have a kidney transplant because of kidney failure attributed to lithium treatment. Recently over 7,500 patients have been prescribed lithium each year. Dosing and monitoring of such patients should follow guidelines, not only to avoid future psychiatric episodes or acute toxicity, but because adherence to guidelines may avoid kidney damage.

Attitudes and risk of withdrawal in general surgical registrars

Rewena Keegan, Robyn Saw, Katie De Loyde, Christopher Young

Attrition during surgical training program is an important issue which affects individual doctors, the medical workforce and the community. This study found that more than half of the respondents had thoughts about withdrawing from their surgical training program. Those that thought of withdrawing were more likely to be female and to be locally educated in Australia or New Zealand. These registrars at attrition risk were less satisfied with many aspects of their education and training. This study may help us in the future to identify at risk trainees and institute strategies to improve training experiences and attrition rates.

The experiences, motivations, and opinions of New Zealand's live liver donors

Claire Gavin, Phillipa Malpas, Adam Bartlett

New Zealand's live liver donors offer their motivations and experiences of undergoing a risky procedure due to a lack of deceased organs for transplant. They have a unique and valuable perspective on New Zealand's current organ donation system. Most disagreed with the 'family veto' on deceased organ donation and thought education was important in encouraging people to donate. New Zealand's current organ donation system is unethical and needs balance from including a wider range of views including donors, potential recipients and the general public.

Intravenous magnesium sulphate as an adjuvant therapy in acute exacerbations of chronic obstructive pulmonary disease: a single centre, randomised, double-blinded, parallel group, placebo-controlled trial: a pilot study

S Mukerji, B Shahpuri, B Clayton-Smith, N Smith, P Armstrong, M Hardy, G Marchant, E Marsh

We were investigating whether magnesium sulphate could help treat an acute COPD attack in patients presenting to the emergency department. We gave about half of our patients magnesium sulphate whilst the other half received a placebo intravenously, on top of the standard treatment they would normally get currently in the emergency department. We found that Intravenous magnesium sulphate improved patients' breathing function when compared to the placebo group. Further studies should be carried out to investigate this effect further.

Prevention of neonatal early onset GBS sepsis: A clear protocol is better than none—or several

Michelle Wise, Norma Campbell, Brian Darlow

ABSTRACT

Revised New Zealand consensus guidelines on the prevention of early-onset group B streptococcus sepsis in the newborn are presented in this issue of the *Journal*. We provide some context for these recommendations and discuss issues considered by the multidisciplinary group in formulating the guidelines.

Presented in this issue of the *Journal* is the national consensus guideline on prevention of early-onset group B streptococcus (EOGBS) sepsis in newborns. Readers from other developed countries may wonder why New Zealand has chosen a risk-based approach to this preventable disease, over universal screening of pregnant women near term with antibiotic prophylaxis during labour for those who screen positive. Let's review the fundamental principles of a screening test, and then explain the rationale for this decision, which some might find controversial.

Principles of a screening test

In most high-income countries, GBS is the leading cause of sepsis in neonates within the first 48–72 hours of life and is accompanied by significant morbidity and mortality.[1,2] Concerns about EOGBS sepsis take up many clinical hours. Because the disease can progress very rapidly, most newborn infants who present with respiratory distress will have initial investigations and be treated with intravenous antibiotics until GBS disease can be discounted (usually by 36–48 hours). Thus, the burden of disease warrants a screening programme.

It was demonstrated in the 1980s that the risk of vertical transmission could be reduced by giving mothers intravenous intrapartum antibiotic prophylaxis (IAP). Although 50–75% of infants born to mothers who carry GBS are merely colonised with the organism, about 1% will develop sepsis.[3] Randomised controlled trials have shown that IAP does significantly reduce the incidence of newborn colonisation and most probably EOGBS sepsis, though there is no evidence for a reduction of neonatal mortality.[4] Thus, there is an intervention that is beneficial.

Maternal gastrointestinal and/or genital tract carriage of GBS is a prerequisite for neonatal infection and occurs in around 20–30% of mothers in the third trimester. A New Zealand study in 1998/99 found that 22% of pregnant women were carriers of GBS.[5] Screening for GBS is best done by collecting a lower vaginal and rectal swab at 35–37 weeks gestation, as swabs collected earlier do not predict carriage at term. The presence of GBS in the urine of pregnant women anytime in pregnancy is also predictive of colonisation at birth.

Lead maternity carers (LMCs) are in a unique position to counsel pregnant women about neonatal EOGBS sepsis and offer screening. Thus, screening for GBS within the New Zealand maternity system would reach those who would benefit most from it. The challenge for clinicians, though, is how best to identify mothers who should be offered IAP to prevent neonatal EOGBS

sepsis in the most efficacious and cost-effective way, whilst minimising potentially unnecessary exposure to antibiotics.

Two approaches to screening

The approach advocated in the current national consensus guideline is risk-based—where LMCs assess women during pregnancy and during labour for any risk factors for neonatal EOGBS sepsis and offer IAP only to women with a risk factor. This approach is also taken in the UK citing a lack of evidence-based data to support universal screening.[6,7] Analysis of UK epidemiological data also demonstrated that adopting universal screening would result in more women being treated to prevent one case and at a higher cost.[3] Importantly, the UK National Institute for Health and Care Excellence (NICE) guidelines processes ensure that stakeholder and consumer views are adequately considered and responded to.[6]

The alternative approach, as occurs in North America, is a recommendation for universal screening of all pregnant women at 35–37 weeks' gestation and to offer IAP only to women who screen positive.[8,9] The Centers for Disease Control made their recommendations following a retrospective cohort study in eight states which found a screening policy to be associated with a more than 50% lower risk of EOGBS sepsis compared with a risk-based policy.[10] These two strategies have not been directly compared in a randomised controlled trial.

Both strategies agree that IAP should be offered if one of three risk factors is present —preterm labour, GBS bacteriuria, or a previous infant with GBS sepsis.

Rationale for a risk-based approach

One reason for the New Zealand decision is that the incidence of neonatal EOGBS sepsis is low. A two-year survey of EOGBS carried out by the New Zealand Paediatric Surveillance Unit in 2009–11 reported a national incidence of 0.26 (95% CI 0.18–0.37) per 1,000 live births, equating to around 15 cases per annum.[11] This incidence is half that (0.5 per 1,000 births) reported in a similar 1998/99 national survey,[12] and compares well with the incidence reported from elsewhere ranging from 0.26–0.38 per 1,000 births.[8,13,14]

The multidisciplinary group considered other factors. Firstly, neither strategy will prevent all cases, for example, where there is a late presentation or a precipitous labour and delivery with no opportunity to provide IAP. Secondly, in everyday clinical practice there are missed opportunities for prophylaxis whichever strategy is adopted.[11,15-17] Of the reported cases of EOGBS sepsis in New Zealand in 2009–11, a maternal risk factor was present in 55%, but less than a third of these received IAP.[11] The authors estimated that if all mothers with risk factors had received IAP, the incidence of EOGBS sepsis might have been reduced to 0.17 per 1,000 births.[11] Even though there is evidence that universal screening as recommended can reach >90% of women who deliver at >36 weeks,[18] it is unknown what the uptake would be in New Zealand following the offer of screening in compliance with the Code of Consumer Rights on informed consent.[19] Lastly, the multidisciplinary group considered the costs and logistics of implementing a screening policy in New Zealand could be significant. There would be a greater chance to further reduce the incidence of EOGBS by enhanced support of the already recommended risk-based policy.

Update from 2004 consensus guideline

The current guideline recognises that some women will undergo screening at 35–37 weeks and provides guidance to cover that scenario. There is clarification of management following an incidental finding of urogenital GBS colonisation in early pregnancy. Several obstetric scenarios are discussed, and the guideline also explains the recommended antibiotic regimes in light of increasing antibiotic resistance. Because not all cases of EOGBS sepsis will be prevented, recommendations on neonatal management have been retained.

Future directions

Development of a rapid point-of-care test for GBS that can be used in early labour

will likely obviate both above approaches. Development of maternal immunisation would be another advancement that would also require future review of guidelines.

For the time being, better dissemination of the consensus guideline will improve prevention of EOGBS. It seems likely that one source of variation in practice is the confusion that arises from differing guidelines. One way to bolster compliance should be to have a single guideline that all are familiar with and can be locally promoted, in a similar way to resuscitation guidelines.[20] The authors would encourage district health boards to adapt their local protocols accordingly, and to directly link to the national consensus guideline. This effort must be coupled with strategies to maximise adherence, such as better information for women about GBS, and clarity in relation to documentation for either paper-based or electronic maternity records. There is always opportunity to reduce variation in practice through education of providers and women when the goal is to further reduce the burden of disease in our newborn babies.

Competing interests: Nil

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Mandatory regulation or self-regulation in the age of the Volkswagen saga

Nick Wilson, Rob Quigley, Osman Mansoor, Moira Smith, Louise Signal

A recent letter to the *NZMJ* by a food industry executive[1] states that past work (by some of us)[2] was "of historical interest only". Furthermore, the letter claimed that industry self-regulation of food marketing is "very effective and increasingly so". But there is evidence that the problem of marketing of unhealthy food in New Zealand remains a long-term, unresolved problem with significant consequences for health.[3,4] This is shown by a large number of New Zealand studies,[2,5-10] including ones published in 2013,[11] 2014[12,13] and an unpublished study in 2015 (described in a recent article in this *Journal*, which also provides a good overview of the food marketing problem[14]).

Furthermore, there are New Zealand examples where self-regulation has clearly failed. One is the inadequate response of the tobacco industry in New Zealand to follow guidelines around advertising, resulting in the Government eventually having to regulate this domain.[15]

Fortunately, New Zealand takes a mandatory regulations approach with many products, including pharmaceuticals, hazardous chemicals, firearms and product safety in general (eg, aspects of car design). Furthermore, the Government used regulatory powers to phase out asbestos imports, leaded petrol, and regulations have helped to eradicate various infectious diseases eg, hydatids and brucellosis.

In the food area, New Zealand uses regulations to prohibit microbiological contamination by some micro-organisms (such as *Salmonella*) and there is the illustrative case of the long-term, food-borne campylobacteriosis epidemic in New Zealand. Major progress in dealing with this epidemic only came once the New Zealand Government started to set regulations around campylobacter contamination levels in fresh poultry. This regulation triggered a marked 54% reduction in disease burden[16] and appears to have also reduced the burden of an associated neurological disease as well.[17]

Given the extent of the obesity epidemic in New Zealand,[4] and its preventable costs to the nation of at least three-quarters of a billion dollars a year,[18] it seems high time to follow these past successful approaches and start mandatory regulation of unhealthy food marketing.

Yet even when regulation is put in place, there is a risk that industry deception can still occur. The recent international situation with Volkswagen and its diesel emissions testing software is illustrative.[19] This suggests that even a very large company may attempt to risk its quality brand value by deceiving regulators.

So, not only should policy-makers be very cautious about industry claims for the value of self-regulation, but given situations like the Volkswagen saga, they should also consider better funding of regulatory science.[20] Mandatory regulations, combined with science-based monitoring may then start to have an impact around further protecting the public from unhealthy products—including the marketing of unhealthy food.

Competing interests: Nil

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Fast, fair climate action crucial for health and equity

Scott Metcalfe, for the New Zealand College of Public Health Medicine and OraTaiao: The New Zealand Climate and Health Council

Health equity underpins everyday medical practice[1,2]—and is a key motivator to set ambitious greenhouse gas (GHG) emissions targets at the impending United Nations climate conference in Paris (UN COP#21).[3-5] Fast-approaching, that conference is crucial to world health.[6-9] So, what does health equity mean for setting countries' climate targets—including ours?

Earlier this year *The Lancet* described climate change as a medical emergency threatening to undermine 50 years' progress in global health.[10] As part of the international effort to keep within 2°C—a carbon budget of 1 trillion tonnes remaining CO2 emissions (see Appendix note 1)—New Zealand has submitted GHG emissions targets as our contribution to Paris, setting a target of an 11% reduction on 1990 gross emissions by year 2030.[11-17]

Targets for, and patterns of, GHG emissions vary dramatically between countries.[18-21] For example, although China is now responsible for 30% of the world's annual fossil CO2 (fCO2) emissions, historically North America, Europe, the former Soviet bloc and Japan/Australasia have caused the bulk of the problem (eg, two-thirds of cumulative fCO2 emissions between 1950 and 2013). This compares with China's 13% cumulative emissions, while India (which has 18% world population) has 3%.[21] Per capita emissions vary a staggering 1,670 times between highest and lowest emitters (eg, Qatar 46.5 tonnes fCO2/person in 2013, vs Chad 0.028 tonnes/person).[23,24]

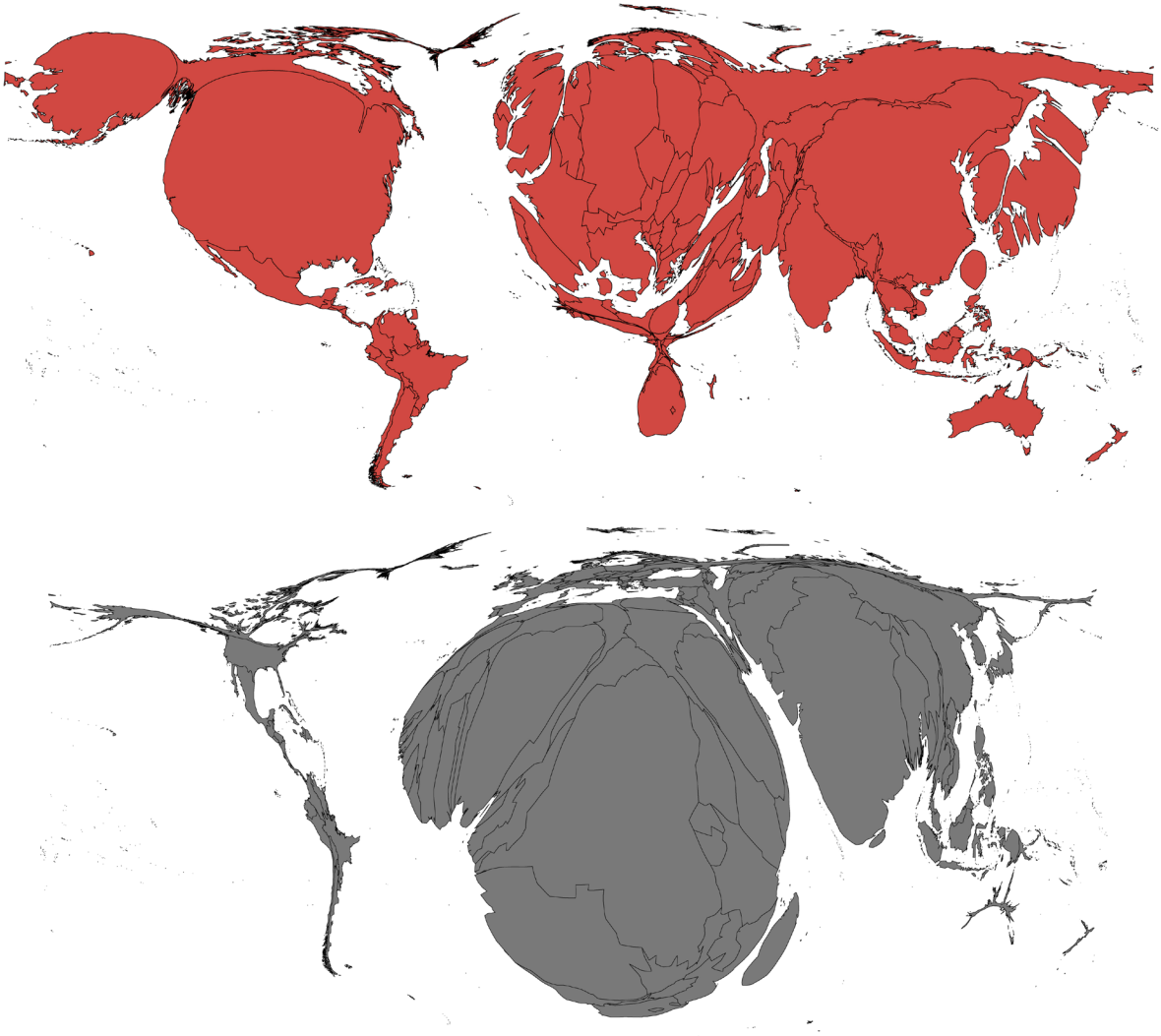
The differences in the likely health consequences of those emissions are just as large,[25,26] as is the potential for countries to reduce those emissions and/or adapt to those consequences.[27] Historic emissions correlate with both current per capita gross domestic product (GDP) and health (decreased disease burden) (see Appendix note 2),[21] with credible estimates of disease burden from climate change painting a bleak picture of inequity.[25,26] Although all countries will suffer, those hit earliest and hardest will be poorer countries, without the incomes or infrastructures to adapt—and who have contributed the least to this climate crisis (see Appendix note 3). Women and children there, especially girls, are and will be particularly affected.[28-30]

These differences are unfair.

What of New Zealand? We are both wealthy and a high emitter—both now and in the past. New Zealand accounts for 0.06% of the world's population, 0.15% of world GDP, 0.16% of world current annual gross GHG emissions, and 0.19% of cumulative gross GHG emissions.[23,24] Our per capita income, etc, is nine times that of our Pacific Island neighbours, and our per capita gross GHG emissions are eleven times as much[21,23] (see Appendix note 5)—yet they are being impacted first by sea level rises and ocean acidification, with the added risk of their lands becoming ultimately inhabitable, and their seas unfishable.

How should we share the ambitious global effort to reduce GHG emissions in time to keep well within the world's emissions budget? There are multiple ways, using multiple algorithms, to calculate countries' 'appropriate shares'. These can combine the level of global ambition (ie, how fast emissions must decline globally), current vs historic emissions, historical emissions starting from anywhere between 1850 and 1990, capitation vs population size, GDP, 'development thresholds' (base per capita emissions by rights), etc, all depending on what underlying value systems you choose.[32-44] The Contraction

Figure 1: The climate gap: those who have emitted most vs those impacted first and worst



Cumulative fossil CO2 emissions 1950–2013 [CDIAC via http://calculator.climateequityreference.org/]; additional deaths attributable to climate change from five climate-sensitive consequences, 2030 (under-nutrition, malaria, dengue, diarrhoeal disease, heat)—excluding coastal flooding (Hales, et al. WHO 2014).[25] Mapping by Mark Metcalfe. Details in Appendix note 4.

and Convergence model[42-44] is a widely-used example, the Climate Equity Reference framework (CERf, previously the GDRf)[27,45,46] is another, but there are many others still.[37]

New Zealand's small population and particular emissions profile makes it more sensitive to the choice of model and assumptions than many other countries.[12,21,22] However, under nearly all reasonable models,[12,21] our targets are very weak.[11] Where New Zealand proposes an 11% reduction on 1990 gross emissions by year 2030, the international allocation models calculate between 24% and 91% reductions on 1990 levels are required to be 'fair'.[12,21,22] Contraction and Convergence and key CERf scenarios, in light of other countries' efforts, both now estimate 63% reductions are needed (see Appendix note 6).[11,31] If most other countries were to follow New Zealand's approach, global warming would exceed 3–4°C.[12,19]

Fair is how much we rapidly reduce our greenhouse gas emissions to stay within the now tightly constrained atmospheric emissions budget. Fair is recognising that those who contributed the least emissions in the past, will ironically, now be hit first and worst. And fair is finance, both for climate loss and damage, which will be hardest for poorer countries, and to encourage their low emissions growth.[19]

Although the world can no longer afford other countries to emit GHG for growth like Western countries have, a fair approach recognises that every human has a right to good health and comparable health expectancy. This decade, the world confronts an

existential crossroads, where our best hope lies in working together fairly to rapidly reduce emissions and minimise human health costs from the climate changes already locked in.

Climate fairness also has a New Zealand face—where the most vulnerable New Zealand households will also be hit first and worst.[47] Children, Māori, Pacific peoples, older people and low-income households are all at greater risk from climate changes than other New Zealanders. Most of us will be in one or more of these groups at some stage. This year's South Dunedin, Whanganui, Kāpiti and Gisborne floodings are apt reminders of how more vulnerable households will bear more impact. Rapidly reducing climate risk is about fairness, both globally and within New Zealand. Creating a fairer country is future-proofing, in the face of climate changes already locked in.

Fair is also about future generations. We have the choice to stabilise climate changes over the next few years. Our children and the generations that follow do not have that choice; this is our responsibility, right now.

Yet as *The Lancet* Commission reminds us, tackling climate change presents the greatest global opportunity to improve people's health this century.[10] There are real practical solutions available to us that mean New Zealand can rapidly reduce emissions at a much faster rate,[11] consistent with a two-thirds chance of limiting warming to the globally agreed 2°C (or the safer limit of 1.5°C, which gives better odds and protects the lands of our Pacific neighbours and other vulnerable nations). In a world trending to zero emissions, rapid action also future-proofs our economy and our health sector, avoiding high-emitting stranded assets, and reducing health care demand. Importantly, many climate-protective measures can also generate immediate health gains in significant areas of concern,[47] which is a win-win for our health sector.

The key to success at the Paris talks, starting on 30 November, will be fairness and teamwork. No one country is too small to make a difference. This is about seizing unprecedented opportunities for better health[10]—and responding swiftly to our global medical emergency of climate change.

Competing interests:
Scott Metcalfe is on the Policy Committee of the NZ College of Public Health Medicine, the Executive Board of OraTaiao: The New Zealand Climate and Health Council, and the Board of the New Zealand Medical Association.

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Appendix

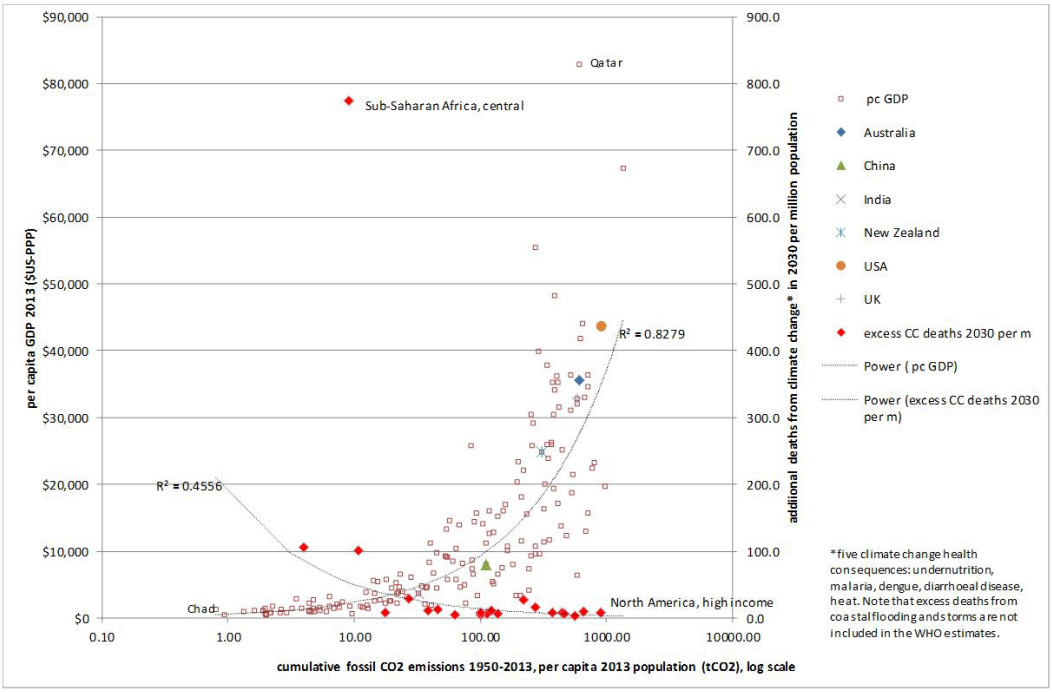
Notes:

1. The world needs to keep within the agreed 2°C guardrail (1.5°C for New Zealand's swamped Pacific neighbours), with a finite limit of the 1,010 billion tonnes (Gt) remaining net CO2 global carbon budget in the IPCC's recent 5th Assessment Report (at a very risky 66% confidence of keeping warming from CO2 alone to below 2°C).[48,49] At current rates of GHG emissions globally—let alone rates continue to rise each year—that budget will be breached by around the year 2035.[50]
2. Despite rapid growth in recent years, China and India remain relatively poor, when accounting for their large populations. Using per capita GDP (granted, a poor measure of true wealth), wealth varies 170-fold between richest and poorest (Qatar $82,000 per capita GDP in 2012, Burundi $474 ie $1.30 per day).[45] Likewise, health suffers; disease

burden varies 8-fold (United Arab Emirates 149.9 DALYs lost per 1000 in 2012, Sierra Leone 1251.3 per 1,000 DALYs lost from disability or early death).[51]

3. Sub-Saharan Africa is expected to suffer 77,760 additional deaths from just under-nutrition, malaria, dengue, diarrhoeal disease, and heat in year 2030—65% of the 241,000 of those climate deaths the World Health Organization (WHO) expects worldwide that year.[25] DARA predicts 650,000 such deaths in 2030, and estimates that already 400,000 excess deaths are caused now by climate change.[26] India and the other least developed countries (including sub-Saharan Africa) have half the world's population, but 15% of GDP and emit 13% of fCO2—and have been responsible for just 9% of 1950–2013 emissions, yet will suffer 88% of year 2030 additional climate deaths—that is 212,000 additional climate deaths just 15 years from now.[25]

Figure 2: Historic emissions, current per capita GDP and projected future excess death rates from climate change, by country[21,23,25]



4. Explanation of Figure 1:
Density-equalising cartograms. Comparison of (a) cumulative fossil CO_2 emissions by country for 1950–2013 vs (b) the regional distribution of deaths from five climate-sensitive health consequences (undernutrition, malaria, dengue, diarrhoeal disease, heat) estimated for year 2030.

Sources:

(a) analysis of CERP calculator data http://calculator.climateequityreference.org/ for cumulative fossil CO_2 emissions 1950-2013, sourced by CERP in turn from the UNFCCC dataset[1] for Annex 1 countries and the CDIAC dataset[2] for non-Annex 1 countries (see http://climateequityreference.org/calculator-information/gdp-and-emissions-baselines)

[1] Summary data from national reports to the UNFCCC are at http://unfccc.int/ghg_data/ghg_data_unfccc/items/4146.php

[2] Carbon Dioxide Information and Analysis Center (CDIAC), Oak Ridge National Laboratory, US Department of Energy. Its primary national level data set is available at http://cdiac.ornl.gov/ftp/ndp030/CSV-FILES/nation.1751_2010.csv, as Boden TA, Marland G, Andres RJ. Global, Regional, and National Fossil-Fuel

CO_2 Emissions. Carbon Dioxide Information Analysis Center, Oak Ridge National Laboratory, U.S. Department of Energy, Oak Ridge, Tenn., USA, 2013. doi 10.3334/CDIAC/00001_V2013.

(b) Hales S, Kovats S, Lloyd S, Campbell-Lendrum D (eds.). Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s. Geneva: World Health Organization, 2014. www.who.int/globalchange/publications/quantitative-risk-assessment/en/ Table 1.2.

Further data disaggregation to individual countries via linear scaling (as projected $deaths_{country}$ = projected $deaths_{region}$ × projected $pop_{country}$ / projected pop_{region}), solely for mapping software purposes.

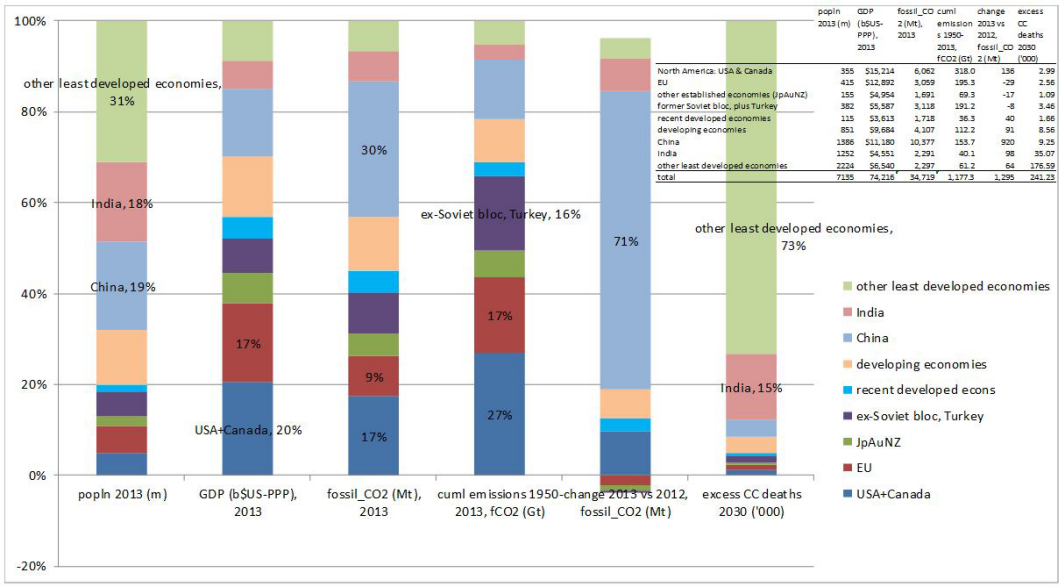
Note that excess deaths from coastal flooding are not included in these estimates.

(c) mapping by Mark Metcalfe

5. Analysis of CERP calculator data http://calculator.climateequityreference.org:[21,23]
New Zealand 2012 per capita GDP $24530 (US$-PPP) ÷ Pacific Islands (PICTs) $2826 = 8.7; New Zealand 2013 per capita gross GHG emissions = 17.1 tonnes CO2 (tCO2) ÷ PICTs 1.6 tCO2 = 10.8.
PICTs = Pacific Island Countries and Territories: Fiji, Kiribati, Marshall Islands, (Federated States of) Micronesia, Nauru, Niue, Palau, Papua New Guinea, Samoa, Solomon Islands, Timor-Leste, Tonga, Tuvalu, Vanuatu.
6. Climate Equity Reference Project Online Calculator (http://calculator.climateequityreference.org). Last modified 22 Oct 2015 00:46:51 PDT, Calculator version 3.0.0, Data version 7.0.0dev. 2o pathway, 1990 responsibility, mid-equity settings, gross GHG (fCO2 + nonCO2 GHG emissions, excludes LULCF):
New Zealand 1990 net GHG emissions 60.7 MtCO2-eq (note: this is unadjusted for new GWPs), allocation 22.3 Mt, 63% reduction.

Additional figures and tables:[21,24]

Figure 3: Population, GDP, current and historic emissions, and projected future excess deaths from climate change, by groups of countries



	popln 2013 (m)	GDP (b$US-PPP), 2013	fossil_CO2 (Mt), 2013	cuml emissions 1950-2013, fCO2 (Gt)	change 2013 vs 2012, fossil_CO2 (Mt)	excess CC deaths 2030 ('000)
North America: USA & Canada	355	515,214	6,062	318.0	136	2.99
EU	415	512,892	3,059	195.3	-29	2.56
other established economies (JpAuNZ)	155	54,954	1,691	69.3	-17	1.09
former Soviet bloc, plus Turkey	382	55,587	3,118	191.2	-8	3.46
recent developed economies	115	53,613	1,718	36.3	40	1.66
developing economies	851	59,684	4,107	112.2	91	8.56
China	1386	511,180	10,377	153.7	920	9.25
India	1252	54,551	2,291	40.1	98	35.07
other least developed economies	2224	56,540	2,297	61.2	64	176.59
total	7135	74,216	34,719	1,177.3	1,395	241.23

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Pacific Islands Families Study: Signs of puberty are associated with physical growth at ages 9 and 11 years

Elaine Rush, El-Shadan Tautolo, Janis Paterson, Victor Obolonkin

ABSTRACT

AIM: To prospectively observe, at ages 9 and 11, the relationship of parental report of pubertal signs with height, weight, body mass index and birth weight in children of the Pacific Islands Families cohort born in the year 2000.

METHOD: At ages 9 and 11 years a parental questionnaire assessed five gender-specific pubertal signs for 619 children and height and weight were objectively measured. At 9 years, body fatness was derived from frequency bioimpedance analysis. Birth weight was obtained from hospital records. Anthropometric measures of children with and without pubertal signs at each age were compared.

RESULTS: At both 9 and 11 years, more than 80% of both boys' and girls' parents reported the presence of a growth spurt. The growth trajectory between 9 and 11 years was steep compared to the Centers for Disease Control reference child. At age 11, girls showing pubertal signs had substantially greater height, weight and body mass indexes than girls who did not. Girls with a growth spurt at age 9 years (91%) had a heavier birth weight than those without; a difference of 250 g (95% CI 50, 450 g).

CONCLUSION: The relationships between birth weight, rapid growth in childhood and early pubertal signs are complex. In addition to biological factors, food security and socioeconomic factors need to be addressed to ensure that the children of these children are exposed to an environment that is supportive of healthy rates of growth and development.

There is very little research involving tracking body size from birth and how birth weight affects the relationship of changes in height and weight with the onset of puberty.[1] It is known that for girls, relatively high stores of body fat predict early puberty.[2] Although this relationship is not as clear for boys,[3] childhood obesity is a marker of adult obesity.[4]

In children, obesity and overweight are defined by body mass index (BMI) cut-offs that are age and gender dependent.[5] The positive relationship of BMI with fatness in children and adults varies both within and among ethnic groups, and for an individual BMI is not a good measure of body fat. For the same BMI, Pacific children[6] and adults[7] have less body fat than other ethnic groups. As a population the prevalence of obesity in Pacific children and adults is high.[8] Previous Pacific Island Families Study research has shown that from birth Pacific Island children living in Auckland, New Zealand experience more rapid physical growth than other child populations.[9]

Puberty is marked by a growth spurt in boys and girls—often defined as an increase in height,[10] but also in weight[2] and proportionally body fat.[11] In the 2002 New Zealand National Child Nutrition survey[12] at age 11 years 29% of Pacific girls reported having reached menarche, compared with 20% of Māori and 8% of New Zealand European girls.

Causes and predictors of early puberty require further explanation.[13] Longitudinal birth cohort studies, such as the Pacific Islands Families (PIF) study in Auckland, New Zealand,[14] may provide unique insights into relationships between growth, physical adaption and biological maturation.

The aim of this study was to examine, in the PIF child cohort, body size at ages 9 and

11 years, together with the onset of pubertal signs and the association of body size with signs of puberty. We hypothesised that cross-sectionally children, whose parents identified signs of puberty at ages 9 and 11 years, would be taller, heavier and have a greater BMI than those without reported signs. We also explored whether there was a relationship of rapid growth with the presence of pubertal signs at ages 9 and 11 years and if this was related to birth weight.

Methods

The study design and research methods for the ongoing longitudinal PIF study have been reported elsewhere.[15] Briefly, 1,398 children (born at Middlemore Hospital, South Auckland, New Zealand to 1,376 mothers in the year 2000) participated. Eligibility criteria included that at least one parent of the new-born child identified themselves as being of Pacific Island ethnicity and was a permanent resident of New Zealand. This child-cohort represented between a quarter and one-third of all eligible children born in the South Auckland region in 2000. South Auckland has the highest number of Pacific Island residents in New Zealand.[16] Birth weight was obtained from hospital records.

For this report weight (in light clothing to the nearest 0.1 kg) and standing height (without shoes, to the nearest 0.1 cm) were measured at the 9 and 11 year data collection phases, using standardised procedures[9] and scales and stadiometers that were calibrated against standard weights and lengths. BMI was calculated as weight in kilograms divided by squared height in metres.

At age 9 years, body fat was measured using hand to foot single frequency bioimpedance, and body fat derived using a prediction equation developed for Pacific, Māori and New Zealand European children.[17]

Puberty questionnaire

Parents were asked to report pubertal status on behalf of their child. This involved asking questions of the parent about whether their child had experienced a growth spurt in height, pubic hair and/or skin changes, together with facial hair growth in boys and the development of breasts and/or menarche for girls.[18] While each question had four possible responses and scores: no (0); yes, barely (1); yes, definitely (2); and development completed (3), the response to each question was recoded as either present (1, 2 and 3) or not present (0).

All procedures and interview protocols had ethical approval from the National Ethics Advisory Committee.

Statistics

For this analysis, children who were born preterm, were twins, or had mothers with diabetes were excluded. Only data for children whose parents answered the puberty questions at ages 9 and 11 years and for which anthropometric measures were obtained, were included.

Descriptive data were expressed as mean, standard deviation (SD) and 95% confidence intervals of the mean. Proportions were reported as percentages. Comparisons between those with and without observed pubertal signs were made using two-sample t-tests and equal variances were assumed. Fat mass was adjusted for body mass to compare the proportion of body fat between those with and without pubertal signs (ANCOVA). Z scores for height and weight were derived from ages 2 to 11 years following the LMS method of Cole and Green.[19] The advantage of z scores is that they account for the exact age of each measurement of the child. This method was previously used to document the growth of these children between 2 to 9 years of age[9] and has the advantage of accounting for age and gender when growth of children is considered cross-sectionally and longitudinally. The LMS parameters were derived using the R lmsqreg package with the R base package version R v2.15. (Repository at http://www.hsph.harvard.edu/carey/vcwww_4.html).

Results

Physical Measurement

A total of 627 children (305 girls and 322 boys) had complete physical measurements at age 9 and 11 years (Table 1). These 627 children were not different by birthweight, gender and Pacific ethnicity than those in the original cohort who were not measured (n=771, total cohort 1,398) for this report. At 9 years of age, boys were

Table 1: Physical characteristics of Pacific Island children at 9 and 11 years of age by gender

	9 years N=637 Mean (95% CI)	**11 years N=637 Mean (95% CI)**
Girls	**N=305**	**N=305**
Age, y	9.4 (9.3, 9.4)	11.2 (11.1, 11.2)
Height, cm	142.0 (141.2, 142.7)	154.2 (153.5, 155.0)
Weight, kg	44.2 (42.9, 45.5)	55.7 (54.1, 57.4)
BMI, kg/m2	21.7 (21.2, 22.2)	23.3 (22.7, 23.8)
Fat mass, kg	13.0 (12.3, 13.7)	-
Fat mass, %	28.1 (27.3, 28.8)	
Height, CDCSDS	1.09 (0.99, 1.20)	2.77 (2.65, 2.89)
Weight, CDCSDS	1.56 (1.46, 1.67)	2.28 (2.18, 2.37)
BMI, CDCSDS	1.39 (1.30, 1.48)	1.60 (1.51, 1.70)
Boys	**N=332**	**N=332**
Age, y	9.4 (9.3, 9.4)	11.2 (11.1, 11.2)
Height, cm	142.5 (141.8, 143.2)	152.5 (151.7, 153.2)
Weight, kg	47.2 (45.7, 48.7)	56.3 (54.6, 58.0)
BMI, kg/m2	23.0 (22.4, 23.5)	24.0 (23.4, 24.6)
Fat mass, kg	13.7 (12.9, 14.5)	-
Fat mass, %	27.1 (26.2, 27.9)	
Height, CDCSDS	1.06 (0.95, 1.16)	2.67 (2.55, 2.78)
Weight, CDCSDS	1.63 (1.52, 1.74)	2.27 (2.18, 2.37)
BMI, CDCSDS	1.47 (1.38, 1.57)	1.63 (1.53, 1.73)

Mean (95% confidence interval of mean)
BMI - Body mass index, CDCSDS (Centers for Disease Control 2000 Standard Deviation Score)

not taller than girls but were one BMI unit more than girls and 3 kg heavier. Boys and girls were similar in percentage body fat at age 9 years. At age 11 years girls were, on average, 1 cm taller than boys but did not weigh more. Over the two year period (9 to 11 years old) girls weight increased by more than 11 kg and boys by 9 kg; while in height girls increased by 12 cm and boys by 10 cm. Compared to the CDC growth reference the increases in height over the two years were more than one SDS for both boys and girls, and the increases in weight and height were also marked with the rate of increase of height, weight and BMI much steeper than for the CDC reference children.

Pubertal characteristics

The proportion of parents who reported the presence of pubertal characteristics in their children increased between 9 and 11 years of age. At both 9 and 11 years of age more than 80% of both boys and girls were recorded as having experienced a growth spurt (Table 2). The proportion of girls reported to have growth of breasts trebled from 25% at age 9 years to 85% at age 11 years. For boys, the proportion who had any pubertal characteristics identified, other than the growth spurt, was less than 10% at 9 years of age. At 11 years of age the largest changes were for pubic hair growth and deepening of the voice, which increased from 3% and 7% at 9 years to 16% and 18% respectively at age 11.

Physical characteristics with and without pubertal signs at age 9 and 11 years

Within gender differences between children with and without the discrete

Table 2: Prevalence of pubertal characteristics reported by parent for girls and boys at 9 and 11 years of age

	9 years		11 years	
	Total N responses	sign present %	Total N responses	sign present %
Girls				
Growth spurt	295	90.5	305	91.8
Pubic hair growth	294	6.5	298	44.6
Changes in skin	294	6.5	305	27.2
Growth of breasts	295	27.1	304	85.5
First period	291	0.7	305	14.1
Boys				
Growth spurt	321	82.2	329	83.6
Pubic hair growth	322	2.5	324	16
Changes in skin	322	1.2	329	9.1
Voice deepening	322	6.5	329	17.6
Facial hair growth	322	2.8	329	9.4

* number not same as anthropometric measures as not all pubertal questions were answered by parent

pubertal signs were compared by physical size characteristics (Tables 3 and 4). Girls and boys, whose parents identified the presence of a growth spurt, were substantially taller at both 9 and 11 years of age. At age 9 years, boys with a growth spurt were 3 kg heavier than those without, but for girls there were no difference in weight between those with or without a growth spurt. At 11 years of age girls, with a growth spurt or growth of breasts, height, weight and/or BMI had a substantially greater body size ($p<0.001$) (Table 3). For boys, differences in body size by pubertal sign were not as marked, with only change in voice associate with an increase in both height and weight at age 9 years, but not at 11 years of age. The large variance (SD) for height and weight of more than 4 cm and 10 kg (Tables 3 and 4) reflects the wide range of body size for children of the same age. A similar pattern of differences between presence and non- presence of pubertal characteristics were seen when cohort-specific anthropometric z scores were compared.

Fat mass (only measured at age 9 years) was adjusted for body weight. For girls, a higher proportion of fat mass was observed with the presence of pubic hair (0.97 kg), changes in skin (1.20 kg) and breast development (0.61 kg). For boys, only growth spurt at 9 years of age was associated with an increase in fat mass adjusted for body weight (0.68 kg).

Between ages 9 and 11 years the magnitude of the change in anthropometric measures of these children showed no pattern of association with pubertal characteristics presence or non-presence (Tables 3 and 4).

The birth weight of girls whose parents reported the presence of the growth spurt at age 9 years (91%) was 3.680 kg, 250 g (95% CI 50, 450g) heavier than those girls without the growth spurt (3.430 kg). This difference was not observed in girls at 11 years of age or in boys at either age 9 or 11 years.

We investigated if there were any differences between children with incomplete and complete measures for this analysis. No differences by gender, Pacific ethnic group or maternal smoking during pregnancy were seen however those measured at both ages were on average 3 to 4 weeks older than those whose pubertal signs were not recorded.

Table 3: Physical characteristics with and without pubertal signs at age 9 and 11years **for girls**

	Growth spurt	Pubic hair growth	Changes in skin	Growth of breasts	First period
	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)
Age 9 years	9.4(0.3);9.4(0.3)	9.5(0.4);9.4(0.3)	9.4(0.4);9.4(0.3)	**9.5(0.3);9.3(0.3)[c]**	9.6(0.7); 9.4 (0.3)
Height, cm	**142.2(6.6);139.4(6.3)[a]**	**146.4(7.1);141.7(6.5)[a]**	143.9(7);141.8(6.6)	**144.3(6.7);141.1(6.4)[c]**	136.9(9.3); 141.9 (6.6)
Weight, kg	44.5(11.6);41.7(10.7)	47.7(12.4);44.1(11.4)	41.8(9);44.5(11.6)	**46.6(10.0);43.4(11.9)[a]**	37.2(12.3); 44.2 (11.3)
BMI, kg/m²	21.8(4.5);21.2(4)	22(4);21.7(4.5)	**20(3.2);21.9(4.5)[a]**	22.3(3.8);21.5(4.6)	19.5(3.9); 21.7 (4.4)
Weight z	0(1);-0.3(1.2)	0.3(0.9);0(1.1)	**-0.2(0.8);0(1.1)**	0.2(0.8);-0.1(1.1) a	-0.9(1.2); 0 (1)
Height z	**0(1.1);-0.5(1.1)[a]**	**0.6(1.2);-0.1(1.1)[a]**	0.2(1.1);0(1.1)	0.2(1.1);-0.1(1.1) a	-1.1(0.8); 0 (1.1)
BMI z	0.1(1); -0.1 (1.1)	0.1(0.8); 0.0 (1.0)	**-0.3(0.8); 0.1 (1.0)[a]**	0.2(0.8); 0 (1.1)	-0.5(1.0); 0 (1.0)
Weight CDCSDS	1.1(1.0); 0.8 (0.8)	0.9(0.9); 1.1 (1.0)	1.1(0.6); 1.1 (1.0)	1.1(0.9); 1.1 (1.0)	2.5(0.4); 1.1 (1.0)
Height CDCSDS	1.6(0.9); 1.4 (0.7)	1.3(0.9); 1.6 (0.9)	1.4(0.8); 1.6 (0.9)	1.5(0.9); 1.6 (0.9)	2.6(0.3); 1.5 (0.9)
BMI CDCSDS	1.4(0.8); 1.3 (0.7)	1.2(1.0); 1.4 (0.8)	1.2(0.8); 1.4 (0.8)	1.3(0.8); 1.4 (0.8)	2.1(0.4); 1.4 (0.8)
Age 11years	11.2(0.2);11.1(0.2)	11.2(0.2);11.2(0.2)	11.2(0.2);11.2(0.2)	11.2(0.2);11.2(0.2)	11.2(0.2); 11.2 (0.2)
Height, cm	**154.7(6.7);149.5(4.4)[c]**	**156.4(6.8);152.5(6.2)[c]**	**157(6.4);153.2(6.6)[c]**	**154.8(6.7);150.9(5.8)[c]**	**159.7(6.7); 153.3 (6.3)[c]**
Weight, kg	**56.5(14.5);47.6(12.2)[b]**	**58.2(15.4);53.7(13.5)[b]**	57(13.4);55.3(14.9)	**57(14.3);48.4(13.2)[c]**	**61.3(15.1); 54.8 (14.2)[a]**
BMI, kg/m²	23.5(5.1);21.1(4.8)[a]	23.6(5.3);23(4.9)	23(4.5);23.4(5.3)	**23.7(5.1);21.1(4.6)[c]**	23.9(5); 23.2 (5.1)
Weight z	**0(1.0);-0.7(1.0)[b]**	**0.1(1.0);-0.1(1.0)[a]**	0.1(0.9);-0.1(1.0)	**0.1(1.0);-0.6(1.0)[c]**	**0.4(1); -0.1 (1)[b]**
Height z	**0.1(1);-0.7(0.7)[c]**	**0.3(1);-0.2(0.9)[c]**	**0.4(1);-0.1(1.0)[c]**	**0.1(1.0);-0.5(0.9)[c]**	**0.9(1.0); -0.1 (1.0)[c]**
BMI z	**0.0(1.0); -0.5 (1)[a]**	0(1.1); -0.1 (1.0)	-0.1(0.9); 0 (1)	**0.0(1.0); -0.5 (1.0)[c]**	0.1(1.1); -0.1 (1.0)
Weight CDCSDS	2.8(1); 2.7 (1.5)	2.8(1); 2.8 (1.1)	2.8(0.9); 2.8 (1.1)	2.8(1.0); 2.6 (1.1)	2.6(1); 2.8 (1.1)
Height CDCSDS	2.3(0.8); 2.1 (0.8)	2.3(0.8); 2.3 (0.8)	2.3(0.7); 2.3 (0.8)	2.3(0.8); 2.1 (1.0)	2.1(0.9); 2.3 (0.8)
BMI CDCSDS	1.6(0.8); 1.5 (0.7)	1.6(0.8); 1.6 (0.8)	1.6(0.8); 1.6 (0.9)	1.6(0.8); 1.5 (0.9)	1.5(0.9); 1.6 (0.8)
Change between 9 and 11 years	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.3)	1.8(0.3); 1.8 (0.4)
Height, cm	12.4(3.8); 11.5 (3.2)	**12.8(3.8); 11.8 (3.6)[a]**	12.8(4); 12.1 (3.7)	12.4(3.9); 11.5 (3.1)	13.1(4); 12.1 (3.7)
Weight, kg	11.8(7); 9.2 (8.2)	12(8.2); 11.3 (6.4)	11.7(7.7); 11.5 (7)	**12(7.2); 9.5 (6.3)[a]**	13.1(8.6); 11.3 (6.9)
BMI, kg/m²	1.6(2.4); 1.1 (3.3)	1.4(2.8); 1.7 (2.3)	1.4(2.9); 1.6 (2.4)	1.6(2.5); 1.2 (2.4)	1.7(3); 1.5 (2.4)
Weight z	0(0.5); -0.1 (0.7)	0(0.6); 0 (0.4)	0(0.5); 0 (0.5)	0(0.5); 0 (0.4)	0(0.6); 0 (0.5)
Height z	0.1(0.5); -0.1 (0.4)	0.1(0.5); 0 (0.5)	0.1(0.5); 0 (0.5)	0.1(0.5); 0 (0.4)	0.1(0.5); 0 (0.5)
BMI z	1.6(2.4); 1.1 (3.3)	-0.1(0.7); 0 (0.5)	-0.1(0.6); -0.1 (0.5)	-0.1(0.6); 0 (0.5)	-0.1(0.8); -0.1 (0.5)
Birth weight, kg	**3.7(0.5); 3.4 (0.4)[a]**	3.8(0.5); 3.6 (0.5)	3.6(0.5); 3.7 (0.5)	**3.5(0.5); 3.7 (0.5)[a]**	3.2(0.1); 3.7 (0.5)

Mean (SD) P [a]<0.05; [b]<0.01 ;[c]<0.001 two sample t test, z scores derived from study population, CDCSDS (Centers for Disease Control 2000 Standard Deviation Score)

Table 4: Physical characteristics with and without pubertal signs at age 9 and 11 years **for boys**

	Growth spurt	**Pubic hair growth**	**Changes in skin**	**Change in voice**	**Facial hair**
	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)	With Mean (SD); Without Mean (SD)
Age 9 years	9.4(0.4); 9.4 (0.3)	9.4(0.3); 9.4 (0.4)	9.5(0.4); 9.4 (0.4)	9.4(0.3); 9.4 (0.4)	**9.6(0.3); 9.4 (0.4)[a]**
Height, cm	**143.2(6.6); 139.5 (7)[c]**	141.6(9); 142.5 (6.8)	139.8(6.3); 142.5 (6.9)	**146.3(7); 142.2 (6.8)[a]**	144.6(7.4); 142.4 (6.9)
Weight, kg	**47.9(14.3); 44.1 (12.1)[a]**	46.5(18.9); 47.2 (13.9)	46.0(25.7); 47.2 (13.9)	**55.1(14.6); 46.6 (13.8)[a]**	56(16.5); 46.9 (13.9)
BMI, kg/m²	23.1(5.4); 22.5 (5.1)	22.6(6.9); 22.9 (5.3)	22.9(10.5); 22.9 (5.3)	**25.5(5.5); 22.8 (5.3)[a]**	26.5(6.6); 22.8 (5.3)
Weight z	**0.1(1); -0.2 (1.1)[a]**	-0.2(1.5); 0 (1.0)	-0.5(1.6); 0 (1.0)	**0.6(1.0); 0.0 (1.0)[a]**	0.5(1.2); 0.0 (1.0)
Height z	**0.1(1); -0.5 (1.1)[c]**	-0.2(1.3); 0 (1.0)	-0.6(0.6); 0 (1.0)	**0.5(1.0); -0.1 (1.0)[a]**	0.1(1.1); 0.0 (1.0)
BMI z	0.1(1.1); -0.1 (1.1)	-0.2(1.4); 0.0 (1.1)	-0.4(1.7); 0.0 (1.1)	**0.5(1.0); 0.0 (1.1)[a]**	0.6 (1.2); 0.0 (1.1)
Weight CDCSDS	1.0(1.0); 1.2 (0.9)	1.8(1.5); 1.0 (1.0)	1.9(0.6); 1.0 (1.0)	1.0(1.0); 1.1 (1)	1.5(1.1); 1.0 (1.0)
Height CDCSDS	1.6(1.0); 1.8 (0.8)	2(1.1); 1.6 (1.0)	2.1(0.6); 1.6 (1.0)	1.7(0.9); 1.6 (1)	1.8(1.1); 1.6 (1.0)
BMI CDCSDS	1.4(0.9); 1.6 (0.7)	1.6(0.9); 1.5 (0.9)	1.7(0.5); 1.5 (0.9)	1.5(0.8); 1.5 (0.9)	1.5(1.1); 1.5 (0.9)
Age 11years	11.2(0.2); 11.2 (0.2)	11.2(0.3); 11.2 (0.2)	11.2(0.3); 11.2 (0.2)	11.2(0.2); 11.2 (0.2)	11.2(0.3); 11.2 (0.2)
Height, cm	**153.3(7); 148.4 (7.1)[c]**	154.5(8.2); 152.1 (6.9)	154.7(8.2); 152.3 (7.1)	152.7(8); 152.4 (7)	**156.7(7.9); 152 (7)[b]**
Weight, kg	**57.4(16.4); 50.7 (12.7)[c]**	59.1(16.7); 55.7 (15.9)	57.2(17.4); 56.2 (15.9)	57.9(16.9); 55.9 (15.8)	60.1(13.6); 55.9 (16.2)
BMI, kg/m²	24.1(5.7); 23 (5.4)	24.5(5.7); 23.9 (5.6)	23.6(6); 24 (5.6)	24.5(5.7); 23.8 (5.6)	24.3(4.4); 23.9 (5.8)
Weight z	**0.1(1); -0.3 (0.9)[b]**	0.2(1); 0 (1.0)	0(1); 0 (1.0)	0.1(1.1); 0 (1.0)	**0.3(0.8); 0 (1.0)[a]**
Height z	**0.1(1); -0.6 (1.0)[c]**	0.2(1.1); 0 (1.0)	0.3(1); 0 (1.0)	0(1.1); 0 (1.0)	**0.6(1.0); -0.1 (1.0)[c]**
BMI z	0.0(1.0); -0.1 (0.9)	0.1(1.0); 0.0 (1.0)	-0.1(1.0); 0.0 (1.0)	0.1(1.1); 0.0 (1.0)	0.1(0.8); 0.0 (1.0)
Weight CDCSDS	2.7(1.1); 2.7 (1)	2.5(1.0); 2.7 (1.1)	2.4(1.3); 2.7 (1.0)	2.5(1.1); 2.7 (1.0)	2.4(1.0); 2.7 (1.0)
Height CDCSDS	2.2(0.9); 2.4 (0.7)	2.3(0.7); 2.3 (0.9)	2.2(1.1); 2.3 (0.8)	2.2(0.8); 2.3 (0.9)	2.2(0.7); 2.3 (0.9)
BMI CDCSDS	1.6(0.9); 1.8 (0.8)	1.7(0.7); 1.6 (1.0)	1.6(1.2); 1.6 (0.9)	1.6(0.8); 1.6 (0.9)	1.7(0.6); 1.6 (0.9)
Change between 9 and 11 years	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.4)	1.8(0.4); 1.8 (0.4)	1.7(0.4); 1.8 (0.4)
Height, cm	9.9(3.8); 10.2 (3.7)	10.3(3.9); 9.9 (3.8)	10.1(4.8); 10 (3.7)	9.9(4); 10 (3.7)	10.2(5.3); 10 (3.6)
Weight, kg	9.2(7.7); 8.4 (6.3)	9.3(7); 9 (7.6)	7.3(5.9); 9.2 (7.6)	9.8(7.6); 8.9 (7.4)	8.9(7.6); 9.1 (7.5)
BMI, kg/m²	1(3); 0.9 (3)	0.9(2.8); 1 (3)	**0(2.1); 1.1 (3)[a]**	1.2(2.7); 0.9 (3)	0.7(2.9); 1 (3)
Weight z	0(0.5); 0 (0.5)	-0.1(0.5); 0 (0.5)	**-0.1(0.3); 0 (0.5)[a]**	0(0.4); 0 (0.5)	0(0.4); 0 (0.5)
Height z	0(0.5); 0.1 (0.4)	0(0.4); 0 (0.5)	0(0.6); 0 (0.5)	0(0.5); 0 (0.5)	0.1(0.6); 0 (0.5)
BMI z	0.0(0.6); 0.0 (0.4)	-0.1(0.5); 0.0 (0.6)	**-0.2(0.4); 0 (0.6)[a]**	0.0(0.5); 0.0 (0.6)	-0.1(0.5); 0.0 (0.6)
Birth weight, kg	3.7(0.5); 3.7 (0.5)	4.0(0.5); 3.7 (0.5)	3.4(0.2); 3.7 (0.5)	3.8(0.5); 3.7 (0.5)	3.9(0.7); 3.7 (0.5)

Mean (SD) P [a] <0.05; [b] <0.01 ;[c] <0.001 two sample t test, z scores derived from study population, CDCSDS (Centers for Disease Control 2000 Standard Deviation Score)

Discussion

The principal finding of this study is that at 9 years of age more than four out of five parents had observed a growth spurt in their children. This was substantiated by sizeable differences in height, weight and BMI for girls, but not boys. The growth spurt in girls at 9 and 11 years was also associated with a higher birth weight. Moreover, new insights into the implications of rapid growth in childhood and early physical maturation in a unique population is provided. The tracking of growth from birth[20] and in this article the parental reports of pubertal signs at 9 and 11 years provides increased understanding of the origins of the high prevalence of adult obesity in this contemporary population.[8] Furthermore in girls, but not in boys, birth weight was strongly associated with parental reports of a growth spurt at age 9 years, which raises concerns about the compounding of intergenerational effects of obesity.[21] The girls in this cohort, when they become mothers, are more likely to give birth to larger babies,[22] as well as be predisposed to gestational diabetes.[23]

Comparisons with similar studies of puberty and growth identify three interrelated areas to be examined: relatively early puberty;[2] rapid physical growth; and the tracking of body size from birth. Each will be considered in turn.

Usually, pubertal development and maturity of boys occurs later than in girls.[24] In the Sorenson review, precocious puberty is defined for girls as before the age of 8 years and in boys before the age of 9 years. In Europe, the onset of breast development in girls was at the mean age 10 years and testicular volume of more than 3 mL was at a mean age of 11.5 years for boys. However, for these Pacific children the identification of a growth spurt in the majority of children at age 9 years, the development of breasts in 84% of girls at age 11 years, and pubic hair growth in 16% of boys and 45% of girls at age 11 years provides evidence of earlier maturation and puberty, particularly in girls, than reported for other ethnic groups[12] and in the past.[24] Evidence also suggests that early menarche in girls may be a predictor of childhood obesity, adult obesity and rapid infancy growth in the next generation.[25]

Very rapid childhood growth is of worldwide concern, given the prevalence of childhood obesity is increasing, and particularly for Pacific children as they have 3 times the prevalence of obesity of non-Pacific children.[8] Previously for this cohort we have shown that from birth through 4, 6 and 9 years of age, children born large grow faster than children born small.[9,26,27]

This investigation provides further evidence that birth weight is a predictor of more rapid growth, particularly the pubertal growth spurt of girls. On average, girls identified as having a growth spurt at age 9 years weight 250 g more at birth and almost 3 kg more at age 9 years than those who did not. This positive association with weight and earlier pubertal signs was not seen in boys, but should be examined further at subsequent measurement points of the PIF study. Knowledge of when rapid and/or critical periods of growth occur may provide intervention opportunities which may slow these adverse growth trajectories and possibly delay puberty.[28] Given many of these children will someday be parents, there is a life course argument that the point of intervention for the next generation should precede conception[29] and adolescence should be a target.

What was surprising was that between genders there was no apparent difference of proportion of body fat at age 9 years. Similar results were also found in a cross-sectional study undertaken in the year 2000 of a small number of Pacific children.[30] This is in contrast to Caucasian children, where the median body fat percentage in girls is higher than in boys between 9 and 11 years of age.[31] Similarly, in a study that measured Māori and European children over two years, girls were consistently found to have proportionally more fat mass than boys, but also that between ages 10 and 12 years, Māori girls increased their body fat more rapidly than European girls.[32] While these differences in growth trajectory by ethnicity should be explored further, such difference may merely be a function of the exceptionally fast growth rate of these contemporary Pacific children.

Limitations of this analysis include the relevance of pubertal scales developed in European populations and that the pubertal questions were answered by parents, not the child. Proxy reports of pubertal signs will be biased dependent on the ability of the parent to observe pubertal signs, particularly in boys where the features are less overt than, for instance, menstruation in girls. While more accurate measures of pubertal status, such as hormonal concentrations and testicular size, may give more information, culturally these measures are unlikely to be acceptable and the rapport with and continued retention of the families in the study may be compromised. At 9 years, 891 children were measured but at 11 years, 952 were measured—demonstrating that not every child is measured at each time point. Only 6% of the families have formally withdrawn from the study since the year 2000. Furthermore, the measurements were two years apart, so intermediate changes in body size were not recorded, and children were not measured exactly on their birth date. However, corrections for age were applied using cohort-specific z scores. Strengths of this study, however, are that it includes longitudinal data and a relatively large number of participants.

Measurements of height, weight and child-reported pubertal signs are now underway (age 14 years), and will add to the understanding of the physical development trajectory of this Pacific Islands cohort. The relevance of these findings to other populations, ethnic groups and environments needs to be explored further.

Other studies in this longitudinal study provide understanding of the social and physical environment of the families. Current studies are exploring the food environment and the relationship to the foods consumed, while past reports show, for example, high food insecurity,[33] food frequency,[34] the relatively high prevalence of damp and cold housing,[35] smoking,[36] middle ear disease,[37] and the association of acculturation, with child growth.[38]

This plethora of multifaceted stresses are clear markers of the disadvantage which these families suffer, and clearly signify that relationships between birth weight, rapid growth in childhood, and early pubertal signs are complex. In addition, to biological factors, food security and socioeconomic factors need to be addressed to ensure that the children of these children are exposed to an environment that is supportive of healthy rates of growth and development.

Competing interests:
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Intravenous magnesium sulphate as an adjuvant therapy in acute exacerbations of chronic obstructive pulmonary disease: a single centre, randomised, double-blinded, parallel group, placebo-controlled trial: a pilot study

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ABSTRACT

AIM: To investigate the effects on lung function of IV magnesium in acute exacerbations of COPD (AECOPD), when given in conjunction with standard bronchodilator therapy.

METHODS: This was a pilot study to a randomised, double-blinded, placebo-controlled trial. 30 patients presenting to ED with AECOPD were included. In addition to standard bronchodilator therapy, 17 patients were given saline, and 13 received 2 g of magnesium sulphate intravenously. Spirometry was carried out at presentation (TA), after initial standard bronchodilator therapy (TB) and immediately (T0), at 60 minutes (T60) and 120 minutes (T120) after trial drug infusion. Primary outcomes were percentage change in FEV1 and FVC at T0, T60 and T120. Secondary outcomes were admission rates, length of stay and requirement for NIV or mechanical ventilation. Trial registration (ANZCTR), ACTRN12613000837729.

RESULTS: Greater improvements were seen in FEV1 at T0, T60 and T120 compared to TB in magnesium group (at T120, mean percentage change in FEV1 was 27.07% with magnesium versus 11.39% in the placebo group, 95%CI 3.7 to 27.7, p=0.01). Similar significantly greater improvements were noted with FVC in the magnesium group, compared to TB.

CONCLUSIONS: IV magnesium sulphate used as an adjunct therapy to standard bronchodilators in AECOPD presenting to ED may improve lung function in the short term.

Magnesium's bronchodilatory effects in the airway have been long accepted. Its effects are attributed to various underlying mechanisms, including an inhibitory effect on acetylcholine release from cholinergic nerve terminals,[1] calcium antagonism[2] and histamine release from mast cells.[3] Magnesium has also been shown to inhibit bronchial smooth muscle contraction by its modulatory effects on calcium channels.[3]

As a result, magnesium has been proposed as a therapeutic option in asthma. Magnesium has been administered via intravenous[4-7] and nebulised[8-11] routes. The accepted understanding supports the use of intravenous magnesium in acute severe exacerbations of asthma,[5,6] but not via the nebulised route.[12,13] Although asthma and COPD share some pathophysiological characteristics as well as first-line treatment options in exacerbations,[14] there are only a handful of studies investigating magnesium use in COPD.

In stable COPD, treatment with intravenous (IV) magnesium has shown to not

only reduce lung hyperinflation[15,16] but when given with nebulised magnesium, increased forced expiratory volume in one second (FEV1).[17]

Only a handful of studies have investigated the sole use of IV magnesium in acute exacerbations of COPD (AECOPD) and all have supported its use.[19-21] One study investigated IV and nebulised magnesium versus nebulised ipratropium and showed similar outcomes in both groups, with slightly greater improvement in spirometry with ipratropium alone.[23] One study had investigated nebulised magnesium only and showed no difference in outcome compared to placebo.[22] However, the limited amount of evidence, confounding protocols, heterogeneity in doses and timing of administration of magnesium with respect to standard bronchodilators, and conflicting conclusions have led to significant uncertainty regarding the role of magnesium as a treatment option in AECOPD.

Our hypothesis was that IV magnesium sulphate administered as an adjunct to standard bronchodilator therapy in AECOPD patients presenting to the Emergency Department (ED) did improve lung function. This pilot study was conducted to assess the above hypothesis, as well as to assess feasibility and effectiveness of the protocol employed for a larger trial.

Methods

Participants

Patients presenting to Palmerston North Hospital ED with a primary diagnosis of AECOPD were invited to participate in this trial between July and October 2013. The period of three months was designated for data collection for this pilot study due to limitations in funding. The diagnosis for AECOPD was made clinically by the attending physician who was not one of the investigators. Clinical symptoms, such as shortness of breath, and signs, such as respiratory rates and wheezing, were used by the clinician to make their diagnosis, but this was not standardised. Patients above the age of 35 years, who had a previously documented diagnosis of COPD by either their general practitioner or in-hospital respiratory specialists were included. Non-infective and infective causes of AECOPD were included. Patients requiring mechanical ventilation or non-invasive ventilation (NIV) at presentation, anyone who was unable to do spirometry or had evidence of pneumothorax or hypotension or any other serious medical condition that would prevent their participation were excluded. Responders or 'asthma-type' COPD patients and those with a history of asthma were excluded by using previously carried out spirometry done at the respiratory outpatient department.

Randomisation, masking and ethical approval

Patients were randomly allocated in a double-blind fashion to receive either 2 g IV magnesium sulphate made up to 20 mls in 0.9% sodium chloride solution (saline) or 20 mls of IV saline as placebo. The senior ED pharmacist performed block randomisation and provided identical pre-made syringes with either trial drug or placebo, as per randomisation, to maintain investigator and patient masking. A block size of 20 was used with a 1:1 allocation ratio. Each batch of pre-made syringes expired after seven days and a new batch was made.

Ethical approval was granted by the Health and Disability Ethics Committee, New Zealand, approval number 13/NTA/58. The trial was registered with Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12613000837729).

Study Protocol

On presentation to the ED, all patients were clinically assessed and a venous blood sample was taken to check serum magnesium levels. At this time (TA), Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC) were measured using a handheld spirometer (EasyOne™, Diagnostic Spirometer. Model number 2001. SN54723/2005. NDD Medical Technologies, Andover, MA 01810, USA). Following this, patients received standard therapy:

- 5 mg Salbutamol and 500 mcg Ipratropium Bromide by jet nebulisation
- 60 mg of oral prednisone or 100 mg of IV hydrocortisone
- Oxygen: 2 litres per minute via nasal prongs if the patient's pulse oximetry revealed saturations of <90%

Informed consent was obtained by the investigator, who was not the treating clinician, during the first 20 minutes

between presentation to the ED and completion of the above standard therapy.

Following allocation and immediately after the initial nebulised treatment, a further spirometry was carried out (TB). Immediately after spirometry, all patients received either 2 g of magnesium sulphate or 20 mls of saline only, given via a peripheral vein over 15 minutes. This was given together with another 5 mg of nebulised salbutamol. Spirometry was carried out immediately following the end of the trial drug infusion (T0). A further 5 mg of salbutamol was given via nebulisation at 60 minutes (T60) and 120 minutes (T120) after the trial drug infusion had finished, and spirometry was carried out following each nebulisation. Both groups received the same amount of bronchodilator therapy until T120, after which further treatment was as per the attending physician's clinical judgment.

Heart rate, blood pressure, respiratory rate and oxygen saturations by pulse oximetry were monitored at each point to identify adverse reactions. All those performing spirometry had received training from the lung physiology department. Three FEV1 and FVC measurements were made at each time point and the value with two concordant results were used. The spirometer was calibrated weekly using a 3-L syringe provided by the manufacturer, following the manufacturer's guidelines. A brief questionnaire was administered at any time after randomisation to determine information regarding medication use, smoking status and flu vaccine uptake. Other interventions, such as further bronchodilator therapies after the spirometry at T120, chest X-rays, antibiotics and analgesia, were at the attending clinician's discretion. The attending clinician also assessed the patient at any time during the trial for the need for NIV or mechanical ventilation and admission into hospital.

Statistical analysis

Although this was a pilot study, a power calculation was performed using an estimated averaged FEV1 of 1.040 litres from a recent trial investigating IV magnesium in AECOPD.[21] 300 mls of absolute difference in FEV1 between the magnesium and placebo groups was chosen by expert opinion, rather than approximately100 mls suggested by the data from Gonzalez et al (2006). It was unclear what severities of COPD was investigated in the trial.[21] Since our trial was open to all severities of COPD, it was conceivable that reversal of bronchoconstriction may be greater compared to the referencing trial.[21] Due to a lack of prior data, a standard deviation (SD) of 0.75 litres was chosen by expert opinion. Using these figures for a power of 80% and an alpha error level of 5%, 77 participants were required in each treatment arm, and a sample size of 160 was planned for. Power calculation was carried out using an online calculator.[24]

The primary outcome was the percentage change in FEV1 and FVC at T0, T60 and T120. Baseline lung function is dependent on multiple factors, including age, height and degree of COPD severity. Since our recruitment was open to all severities of COPD, and due to the heterogeneity of lung function expected within each cohorts, mean absolute spirometry values would have been a poor indicator of clinical effect. Investigators believed that the percentage change in spirometry was a better measure to quantify degree of improvement in lung function. However, data was also presented to show the relative differences in the absolute improvements in spirometry at various time points. FEV1 and FVC values from different time points were compared to TB spirometry values, percentage differences were calculated and the means were produced with the SDs.

Secondary outcomes were hospital admission, episodes of NIV and/or mechanical ventilation and length of stay. Significance level was set at $P \leq 0.05$. A T-test was used to compare the groups at various time points with the baseline at TB (SPSS Statistics, Version 20.0.1. IBM Corporation, 1 New Orchard Road, Armonk, New York, USA). Data was checked for normal distribution and Mann-Whitney U test was applied to non-parametric data.

Results

Thirty-seven patients were assessed between July and the end of September, 2013, for eligibility. Three did not meet the inclusion criteria due to other primary causes of shortness of breath and presentation (congestive cardiac failure, asthma). One patient declined to participate in the trial. Thirty-three patients were randomised

Figure 1: Trial allocation profile

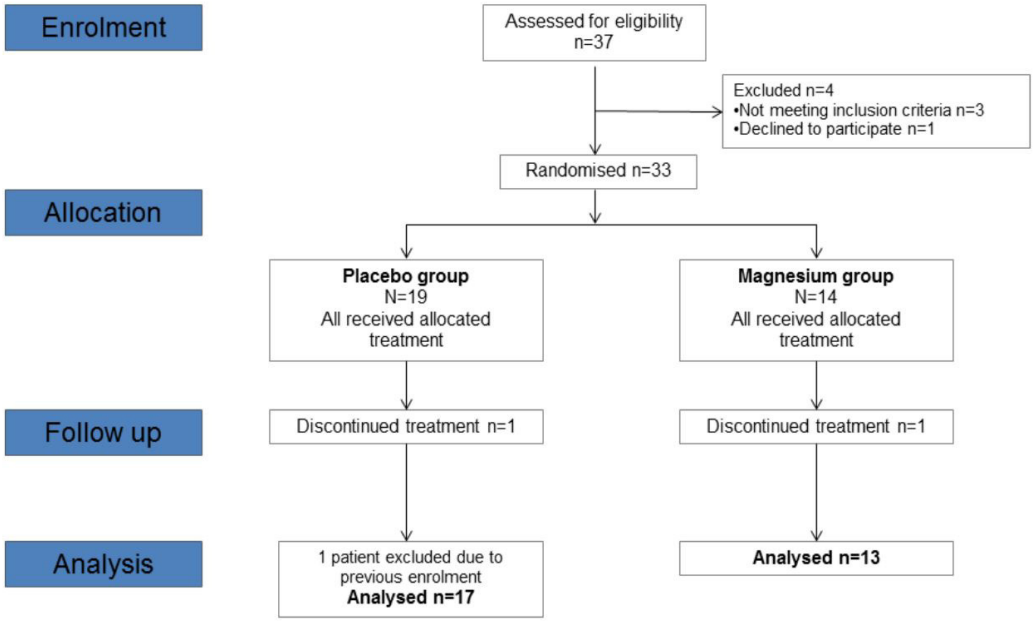

Table 1: Participants' baseline characteristics

Characteristics	Placebo (n=17)	Magnesium (n=13)	Difference (95% CI)	P Value
Mean (SD) age, years	72.9 (9.39)	76.1 (12.47)	3.2 (-12.4 to 6.1)	0.48
Female, n (%, 95% CI)	7 (41, 17.6 to 64.4)	2 (15, -4.4 to 34.4)	-	0.24
Current smoker, n (%, 95% CI)	5 (30, 8.2 to 51.8)	4 (31, 5.9 to 56.1)	-	0.75
Mean (SD) pack years	38.8 (18.2)	40.0 (27.9)	1.2 (-21.9 to 19.3)	0.82
Never smoked, n (%, 95% CI)	1 (6, -5.3 to 17.3)	1 (-6.8 to 22.8)	-	0.82
Long term oral steroids, n (%, 95% CI)	1 (6, -5.3 to 17.3)	1 (-6.8 to 22.8)	-	0.83
Home nebuliser use, n (%, 95% CI)	1 (6, -5.3 to 17.3)	2 (-4.4 to 34.4)	-	0.37
Home oxygen use, n (%, 95% CI)	1 (6, -5.3 to 17.3)	1 (-6.8 to 22.8)	-	0.24
Mean (SD) Serum Mg. at presentation, mmol/L	0.78 (0.1)	0.79 (0.1)	0.01 (-0.91 to 0.08)	0.91
Mean (SD) presenting FEV1, mL	691 (288)	637 (293)	54 (-184 to 292)	0.64
Mean (SD) presenting FVC, mL	1770 (719)	1681 (619)	88 (-468 to 644)	0.75
Mean (SD) presenting heart rate	103 (12)	98 (12)	5 (-5.19 to 14.64)	0.34
Mean (SD) Presenting respiratory rate	21 (3)	20 (2)	1 (-2.06 to 2.69)	0.79
Mean (SD) presenting oxygen saturations	91 (4)	90 (4)	1 (-2.71 to 3.44)	0.81
Patients with presenting FEV1<50% predicted, n (%)	17 (100)	13 (100)	-	-

SD: Standard deviation. FEV1: Forced Expiratory Volume in 1 Second. FVC: Forced Vital Capacity. Mg: Magnesium. mL: Millilitres.

Table 2: Mean absolute improvements of FEV1 and FVC at various time intervals

FEV1				
Time Points	**Placebo/ mL (SD)**	**Magnesium/ mL (SD)**	**Difference (95% CI)**	**P Value**
TA-TB	16.0 (108.81)	30.0 (56.57)	14.0 (-60.37 to 88.37)	0.7
TB-T0	18.0 (50.03)	41.8 (53.82)	23.82 (-18.5 to 66.1)	0.26
T0-T60	43.3(66.83)	46.36 (52.21)	3.03 (-47.1 to 53.1)	0.9
T60-T120	18.7 (28.0)	78.18 (84.6)	59.52 (11.47 to 107.56)	0.02
TB-T120	80.0 (102.82)	166.36 (104.72)	86.36 (1.48 to 171.25)	0.04
FVC				
	Placebo/ mL (SD)	**Magnesium/ mL (SD)**	**Difference (95% CI)**	**P Value**
TA-TB	20.6 (213.32)	106.36 (162.87)	85.7 (-73.16 to 244.56)	0.28
TB-T0	16.7 (142.61)	140.9 (71.06)	124.2 (27.42 to 221.07)	0.01
T0-T60	36.7 (156.33)	100.9 (84.32)	64.24 (-43.26 to 171.75)	0.23
T60-T120	96.0 (112.49)	91.82 (74.94)	4.18 (-76.60 to 84.96)	0.92
TB-T120	149.3 (223.97)	333.6 (106.14)	184.3 (33.33 to 335.27)	0.02

Time points: TA: at presentation. TB: post initial bronchodilator therapy. T0, T60, T120: Immediately after and at 60 and 120 minutes post-trial drug infusion. SD: Standard deviation. FEV1: Forced Expiratory Volume in 1 Second. FVC: Forced Vital Capacity.

and 19 were allocated to the placebo group, while 14 were allocated to get magnesium sulphate (Figure 1). Treatment was stopped in one patient in both groups, who were assessed to require NIV therapy shortly after randomisation and prior to the end of the trial drug infusion, hence no further spirometry was carried out on these patients. One patient was excluded from the final analysis in the placebo group due to the patient having previously been enrolled within a period of one week in the magnesium arm of the trial. All other patients received their allocated treatments. All patients included in the final analysis had completed all measurement stages.

Table 1 details the baseline characteristics of the two groups. There was no difference in mean age, mean pack years, long-term corticosteroid and home nebuliser use. There was no difference in serum magnesium levels, heart rate, respiratory rate, oxygen saturations and mean FEV1 and FVC at presentation (TA). A retrospective analysis revealed that all patients included in the final analysis had a presenting FEV1 of less than 50% predicted.

Mean absolute changes in FEV1 and FVC

There were wide variability of data points indicated by the large standard deviations (Table 2). There was no statistically significant improvement in absolute changes in FEV1 between TA and TB, TB and T0 and T0 and T60. However, there was significantly greater improvement in FEV1 in the magnesium group between 60 minutes and 120 minutes post drug infusion (Table 2). Further, overall, there was significantly greater improvement in FEV1 in the magnesium group at 120 minutes post infusion compared to baseline (166.36 mls vs 80.0mls, Difference of 86.36 mls, P=0.04).

Statistically significant improvement in FVC was noted between TB and T0. Similar to FEV1, there was significant improvement in FVC in the magnesium group at 120 minutes post infusion from baseline (333.6 mls vs 149.3 mls, difference of 184.3 mls, P=0.02)

Analysis by percentage change

Both groups presented (TA) with similar FEV1 values (691 mL in placebo vs 637 mL in magnesium group, P= 0.64) (Table 1). The response in FEV1 after standard bronchodilator therapy were similar in both groups (percentage change placebo vs magnesium; 1.52% vs 5.05%, P=0.51). Immediately after trial drug administration (T0), the magnesium group showed greater improvement in FEV1 compared to the placebo group (percentage change of 8.02% vs 2.04%) (Table 3), although

Table 3: Mean percentage change in FEV1 and FVC

Time Points	Placebo	Magnesium	Difference (95% CI)	P Value
TA, TB	1.52 (15.0)	5.05 (10.3)	3.53 (-7.3 to 14.3)	0.51
TB, T0	2.04 (5.7)	8.02 (10.3)	5.98 (- 0.03 to 12.3)	0.06
TB, T60	8.35 (13.6)	15.87 (14.9)	7.52 (-4.0 to 19.2)	0.19
TB, T120	11.39 (13.6)	27.07 (16.0)	15.68 (3.7 to 27.7)	0.01
Time Points	**Placebo**	**Magnesium**	**Difference (95% CI)**	**P Value**
TA, TB	-1.24 (14.4)	5.73 (9.6)	6.97 (-3.4 to 17.3)	0.18
TB, T0	2.74 (7.9)	9.80 (7.7)	7.06 (0.7 to 13.5)	0.03
TB, T60	4.59 (13.1)	16.40 (12.1)	11.81 (1.4 to 22.2)	0.03
TB, T120	12.94 (24.5)	22.82 (15.3)	9.88 (-0.5 to 27.3)	0.25

Time points: TA: at presentation. TB: post initial bronchodilator therapy. T0, T60, T120: Immediately after and at 60 and 120 minutes post-trial drug infusion. SD: Standard deviation. FEV1: Forced Expiratory Volume in 1 Second. FVC: Forced Vital Capacity.

Table 4: Secondary outcomes in magnesium and placebo groups

Outcome	Placebo (n=17)	Magnesium (n=13)	Difference (95% CI)	P Value
Requirement for NIV, n (%, 95% CI)	1 (6, -5.3 to 17.3)	0	-	0.3
Requirement for mechanical ventilation, n (%)	None	None	-	-
Admitted to hospital from ED, n (%, 95% CI)	16 (94, 82.7 to 100)	11 (85, 65.6 to 99.7)	-	0.8
Mean (SD) length of hospital stay, days	5.47 (5.03)	3.18 (3.19)	2.28 (-1.28 to 5.85)	0.11

NIV: Non-invasive ventilation. SD: Standard deviation.

this did not attain statistical significance (P=0.06). However, 120 minutes following the administration of the trial drug, the magnesium group showed significantly greater improvement in FEV1 compared to placebo (Table 3).

Response in FVC mirrored FEV1 with baseline FVC at TA and percentage change at TB being similar. However at T0 and T60, there were significantly greater improvements in FVC in the magnesium treated patients when compared to TB (Table 3).

Secondary outcomes

Most participants were admitted into hospital from ED, with one patient in placebo group and two from magnesium group discharged from ED (Table 4). None required mechanical ventilation, whereas one patient was given NIV in the placebo group after all spirometry was completed. Length of hospital stay (LOS) was not significantly lower in the magnesium group (3.18 days compared to 5.47 days, p=0.11). One patient reported hands and facial flushing feeling in the placebo group. No other adverse events were noted by clinicians or reported by patients.

Discussion

We had conducted a pilot study for a future, randomised, double-blind, placebo-controlled trial to investigate the effects of IV magnesium as an adjunct therapy to current standard treatments for AECOPD in ED. Our pilot study was the first to investigate the effects of IV magnesium on lung function in AECOPD at a duration longer (120 minutes) than in previous studies (45 minutes).[19-21] Thirty patients were included in the final analysis and baseline characteristics were similar in both groups.

Data was presented and analysed in two formats to better elucidate an accurate picture; relative differences in absolute

improvements in spirometry at each time point, and relative differences in percentage change from baseline. Comparison of absolute change in spirometry is usually the accepted approach. However, given the small participant numbers and the heterogeneity of lung functions within the groups, it would be difficult to detect effects using absolute values for spirometry. Percentage change better quantified lung function changes since it standardised values, which made the results more comparable between cohorts and therefore a better quantification of the effects.

Results revealed that there were some significant improvements in FEV1 and FVC in the magnesium group at various time points. Results indicated that IV magnesium seemed to have some immediate beneficial effect on lung function and it may also have a prolonged effect on FEV1 up to two hours post magnesium infusion.

This is supported by the handful of studies that have investigated magnesium in AECOPD. Treatment with magnesium seemed to have improved patients' symptoms,[19] increased PEFR at 45 minutes and almost halved admission rates.[20] When given concurrently with salbutamol, intravenous magnesium significantly increased FEV1 compared with control patients.[21] One study investigated the combined use of IV and nebulised magnesium against nebulised ipratropium and showed that there was a trend of reduced dyspnoea scores in both groups.[23] Furthermore, a retrospective analysis of stable COPD and AECOPD patients revealed that those in the latter group had significantly lower serum magnesium levels.[25] Indeed, lower serum magnesium levels seemed to be an independent predictive factor for higher admission rates with acute exacerbations.[18]

Results indicated that the magnesium group had a reduced LOS (3.18 vs 5.47 days), which mirrored another study comparing magnesium with placebo (4.27 vs 7.33 days, $p<0.05$).[20] Our results indicated that a patient presenting with an AECOPD with approximate FEV1 of 700 mL and FVC of 1600 mL, at 2 hours post magnesium infusion, could experience an improvement of 100 mL of FEV1 and 250 mL of FVC greater than just standard therapy. Although this is a clinically significant degree of improvement in lung function in the short term, linking this result to reduced LOS, without supporting spirometry data, would be presumptuous.

Indeed this magnitude of bronchodilation is surprising in COPD. We had an 'all comers' approach to recruitment. This was done for two reasons. Firstly, in the acute presentation setting, clinicians do not always know whether it is an infective cause for AECOPD. Secondly, it was unclear from previous studies whether magnesium would have a beneficial effect in all AECOPD severities and hence, no restriction was made regarding severities. Our data revealed a wide variability in baseline spirometry indicating varying severities of AECOPD, although all had a presenting FEV1<50% predicted, indicating all had severe exacerbations. However, no data was collected regarding the severities of these patients' baseline COPD. It was conceivable that the magnesium group had patients whose baseline COPD were not as severe as those in the placebo group and hence could have skewed the data.

Furthermore, although attempts were made to recruit patients 24 hours a day, there were times when recruitment was not carried out due to lack of investigators or departmental workloads. It was estimated retrospectively that 52 patients had presented with a possible diagnosis of AECOPD over the three months, out of whom 37 were assessed for suitability. It was uncertain whether this could have affected the generalisability of the results, given that no baseline COPD severity data was collected. Future trials will require better definition of patient groups regarding causes of AECOPD and severities of baseline COPD as well as better round-the-clock recruitment.

And finally, the original study was planned to be much larger with an n=160, hence a block size of 20 was selected. The authors expected large numbers of patients for the pilot study, using previous year's COPD presenters to ED as a guide. Hence the block size of 20 was maintained. Unfortunately, the pilot study was only able to recruit much smaller numbers. The large block size of 20 led to unequal numbers in both cohorts. This may have led to a degree of bias given the small numbers.

In conclusion, this pilot trial added to the limited amount of data that indicated that IV magnesium given in conjunction with standard bronchodilator therapy may improve lung function immediately after drug infusion and the effects may have been prolonged for up to two hours post drug infusion. However, future trials will need to ensure adequate patient numbers and stricter patient group definitions. Further, increased duration of spirometry measurements, for example up to 24 hours post magnesium infusion, could be useful in understanding magnesium's effects over prolonged periods.

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Infertility and outcomes for infertile women in Otago and Southland

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ABSTRACT

AIM: To establish the burden of infertility in women residing in Otago and Southland.

METHODS: A survey of women aged 25–50 years residing in Otago and Southland was conducted to determine the proportions that experienced infertility, sought medical help and resolved their infertility, and to assess the determinants of these outcomes.

RESULTS: Of the 1,125 participants, 21.7% (95% CI 19.1–24.4%) had experienced infertility, defined as ever having tried unsuccessfully to conceive for at least 12 months, increasing to 25.3% (22.6–28.1%) when seeking medical help was included in this measure. Seeking medical help to conceive among those having difficulties was very common and most women resolved their first episode of infertility with a live birth. Infertility was more common with extremes of body mass index, higher education and not being in a heterosexual relationship. Infertility resolution was less likely for those over 35 years at onset of infertility and with increasing social deprivation.

DISCUSSION: Infertility was common in women residing in Otago and Southland. Despite high levels of infertility resolution overall, those with higher deprivation appeared disadvantaged. Further research is needed to provide national estimates and investigate factors influencing infertility outcomes.

The experience of infertility can have a major impact on individuals, families and relationships, as most people have life plans that involve children. In addition, it can result in a considerable cost to both individuals and health services. The aetiology of infertility is complex, with many factors affecting an individual's risk of infertility. Age is an important determinant, especially for women, with increasing age strongly correlated with decreasing fertility for women older than 30 years.[1] Due to social changes over the past few decades, many women/couples in New Zealand are delaying the start of their families, with the median age of childbearing now around 30 years.[2] Concurrent with this trend of delayed childbearing, there have been changes in the frequency of health conditions that may have a negative impact on fertility. These include increases in obesity and sexually transmitted infections such as *Chlamydia trachomatis*,[3,4] which have most likely impacted on the number of women experiencing infertility. There is already evidence that childlessness is increasingly common in women aged more than 40 years; in the 2006 New Zealand Census, 16.7% of women over 40 years were childless and this is projected to rise to over a quarter by the next census in 2018.[5,6]

Despite the importance of infertility and social changes that may be impacting on its prevalence, population-based estimates are limited to one study, a cohort born in Dunedin, New Zealand, in 1972/3, who were last interviewed when aged 37–39 years.[7] Just over a quarter (26.0%) of these 458 women had ever tried to conceive for at least 12 months, or needed medical help to conceive. This estimate is higher than the few comparable studies in high-income countries and the commonly quoted statistic of 1 in 6 couples experiencing infertility;[8,9] one probable reason for the higher proportion in the Dunedin study being that information was obtained on more than one occasion.

Given the paucity of information on infertility prevalence and the use of

treatment services in New Zealand, a population-based survey of women aged 25–50 years was undertaken in Otago and Southland. From this survey data the aim was to estimate the prevalence of infertility, describe both the uptake of infertility services and the frequency of infertility resolution, and examine factors associated with infertility.

Method

Population and data collection

A random sample of 2,200 women aged 25–50 years was drawn from the general and Māori electoral rolls in the Otago and Southland electorates in December, 2010. Women were invited to participate in a survey on fertility and infertility using a computerised questionnaire. This method has been shown to be particularly useful when studying sensitive issues.[10,11] A link to the secure online questionnaire was provided in the letter, as well as a pre-paid return slip allowing participants to alternatively request a telephone interview or decline to participate. Non-responders were sent one reminder letter and, if there was still no response, where possible they were contacted by telephone after searching for their details in the public telephone directory. Remaining non-responders were sent a brief paper-based questionnaire with a final reminder letter.

The online fertility questionnaire was adapted from three surveys: The US Fertility and Family Growth Survey; the North East of Scotland Fertility Study; and the Dunedin Multidisciplinary Health and Development Study.[11-13] Demographic questions were refined for the New Zealand context. Data were collected between June and December, 2011.

The Southern Regional Ethics Committee granted ethical approval for this survey in November 2010 (reference number LRS/10/EXP/054).

Measures of infertility and childlessness

Infertility measures were those widely used, based on (a) length of time trying to conceive, which historically was 24 months but is now more commonly 12 months (the period generally waited before intervening clinically), and/or (b) seeking medical help to conceive.[8] Successful resolution of infertility was considered as having a live birth during or after the first infertile period. Women aged 40 years or more with no previous births, whose infertility was not resolved with a live birth, were defined as having primary unresolved infertility. Childlessness, a commonly used demographic fertility measure,[14] is distinct from the above as it is independent of a woman's fertility history. It is defined as never having had a live birth and was determined among all participants aged 40 years or more. Childlessness was considered involuntary if the woman reported trying to conceive and/or wished she had had a child, and otherwise considered voluntary. Involuntary childlessness has multifactorial aetiology, including women who have not had the opportunity to form relationships and those who have primary unresolved infertility.

The denominator for the infertility analyses included all women who had ever conceived or had tried to conceive. For the analyses of resolution of first infertility, the denominator was women who had tried for 12 months or more and/or sought medical help to conceive. For childlessness, the denominator was all women over the age of 40 years, irrespective of whether they had ever tried to conceive.

Demographic variables

Age at the time of participation, ascertained from the electoral roll, was grouped into 5-year age bands. Māori descent was also ascertained from electoral roll data. Self-identified ethnicity was collected from participants using Census New Zealand questions and, where multiple ethnicities were reported, the woman's ethnicity was prioritised into one group in the following order: Māori; Pacific; Asian; Other; or otherwise European.[15] Area-level relative deprivation decile, calculated using 2006 Census data (NZDep06 score),[16] was determined for each participant using the mesh block area code associated with the residential address. Deprivation deciles were then grouped as follows: Low (deciles 1–3); medium (deciles 4–7); and high (8–10). Highest educational qualification, household income, body mass index (BMI) and smoking status were collected via the questionnaire. BMI was grouped according

Table 1: Demographic characteristics of participants and non-participants

		Participants, n (%)		Non-participants, n (%)*		χ^2 test P-value
Total		1,125		901		
Age group (years)*	25–29	215	(19.1)	210	(23.3)	
	30–34	159	(14.1)	98	(10.9)	
	35–39	208	(18.5)	177	(19.6)	
	40–44	277	(24.6)	203	(22.5)	
	45–50	266	(23.6)	213	(23.6)	0.047
Current relationship status†	Living with male partner	837	(74.4)	–		
	Male partner, not cohabiting	49	(4.4)	–		
	Living with female partner	5	(0.4)	–		
	Not in a relationship	151	(13.4)	–		
Māori descent*	Yes	109	(9.7)	133	(14.8)	
	No	1,016	(90.3)	768	(85.2)	<0.001
Prioritised ethnic group†	European	981	(87.2)	–		
	Māori	78	(6.9)	–		
	Pacific peoples	3	(0.3)	–		
	Asian	20	(1.8)	–		
	Other	15	(1.3)	–		
Deprivation (NZDep06)*	Low (deciles 1–3)	512	(45.5)	338	(37.5)	
	Medium (deciles 4–7)	429	(38.1)	335	(37.2)	
	High (deciles 8–10)	184	(16.4)	228	(25.3)	<0.001
Highest qualification level†	High school or less	436	(38.8)	–		
	Post high school, not university	255	(22.7)	–		
	University	338	(30.0)	–		
Annual household income†	Low (≤ $30,000)	124	(11.0)	–		
	Medium ($30,001–$70,000)	392	(34.8)	–		
	High (>$70,000)	479	(42.6)	–		
Smoking status†	Current smoker	148	(13.2)	–		
	Past smoker	307	(27.3)	–		
	Non smoker	593	(52.7)	–		
Body mass index (BMI), kg/m²†	Underweight, <18.5	14	(1.2)	–		
	Normal, 18.5–24.9	484	(43.0)	–		
	Overweight, 25.0–29.9	233	(20.7)	–		
	Obese class I, 30.0–34.9	139	(12.4)	–		
	Obese class II, 35.0–39.9	74	(6.6)	–		
	Obese class III, ≥40.0	31	(2.8)	–		

– These data were not available for non-participants.
* Data on non-participants were derived from the electoral roll.
† Due to women not always answering all questions in the questionnaire, these variables have missing data and, therefore, the total responses are less than 1,125.

Table 2: The prevalence of infertility and childlessness

Definition	N	n	%	(95% CI)
Ever tried to conceive for 12 months or more	974	211	21.7	(19.1–24.4)
Ever tried to conceive for 24 months or more*	911	117	12.8	(10.7–15.2)
Ever sought medical help to conceive	974	171	17.6	(15.2–20.1)
Ever tried for 12 months or more and/or sought medical help to conceive	974	246	25.3	(22.6–28.1)
Primary unresolved infertility†	476	9	1.9	(0.9–3.6)
Involuntary childlessness‡	518	35	6.8	(4.8–9.3)
Voluntary childlessness‡	518	36	7.0	(4.9–9.5)

* Only 911 women who had conceived or tried to conceive answered the full questionnaire allowing definitions to be calculated using a 24-month period.
† Limited to women aged 40 years or more who had ever tried to become or had been pregnant.
‡ Limited to women aged 40 years or more, irrespective of whether they had attempted or had previously conceived.

to the World Health Organization guidelines as: Underweight (<18.5 kg/m^2); normal (18.5–24.9 kg/m^2); overweight (25.0–29.9 kg/m^2); obese class I (30.0–34.9 kg/m^2); obese class II (35.0–39.9 kg/m^2); or obese class III (≥40.0 kg/m^2).[17]

Statistical analyses

Data were analysed in STATA 12.1/SE. The demographic characteristics of participants and, where information was available, non-participants were described. The prevalence of infertility according to various definitions was calculated with 95% confidence intervals (CI). Service seeking behaviours, diagnoses, help received, and outcomes were described for the participant's first episode of infertility and were summarised across multiple episodes of infertility. All differences between categorical data were tested using Pearson's χ^2 tests.

Infertility (using a definition of 12 months or more duration and/or seeking medical help to conceive) was examined by demographic factors, using Poisson regression to measure the relative risk (RR) of infertility, ever seeking medical help and the likelihood of resolving the first episode of infertility.

Results

Participation and demographic profile

Of 2,200 women drawn from the sampling frame, 174 were found to be ineligible and a further 154 did not receive the survey as they were no longer at their registered address and could not be located, giving an estimated eligible total of 1,872. After the initial invitation and two further attempts to contact non-responders, 1,125 completed questionnaires were received, including 63 from women who completed the shorter paper-based version, a response rate of 60.1% (1,125/1,872). There was lower participation amongst those aged 25–29 years, those of Māori descent and those from high deprivation areas (all p≤0.05). The demographic profile of participants and non-participants is shown in Table 1.

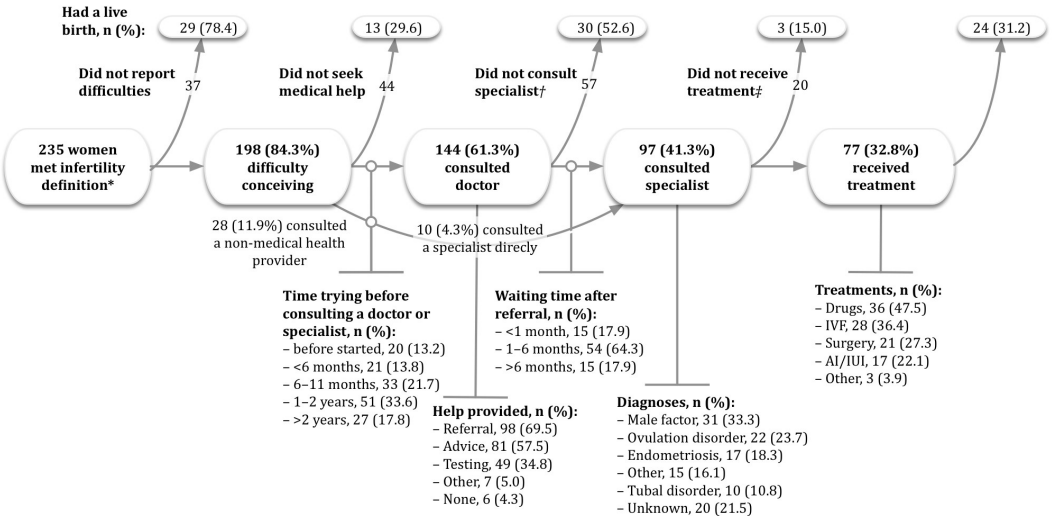
The prevalence of infertility

Of the 1,125 participants, 974 (86.6%) had ever tried to become or had been pregnant; the proportion who had done so increased markedly with age, from 63.3% in those aged 25–29 years to 94.2% in those aged 35–39 years (p<0.001). Of those in the 25–29 year age group, 70.2% intended to have (more) children in the future, a significant proportion of women in their thirties also reported future fertility intentions (34.2% and 11.5% in those aged 30–34 and 35–39 years, respectively). This decreased to 3.9% in the 40–44 year-olds, with no one older than this intending to conceive in the future.

The measures of infertility and childlessness are shown in Table 2.

Of those women who had tried to become or had become pregnant, 211 (21.7%, 95% CI 19.1–24.4%) had ever tried to conceive for 12 months or more; just over half (55.4%, 117/211) of those women having tried for 24 months or more.

Figure 1: Access to services, uptake of treatment and resolution for the first experience of infertility



* Defined as 12 months or more trying and/or seeking medical help to conceive.
† Includes 11 referred women (11.3% of the 98 referred) who conceived before seeing specialist, 10 of whom eventually had a live birth and one who did not.
‡ Includes four women who conceived before starting any treatment, all of whom eventually had a live birth.

Including those women who had sought medical help for conceiving increased the 12-month estimate of infertility to 25.3% (22.6–28.1%). Of the 476 women over the age of 40 years at the time of participation who had tried to conceive, nine (1.9%, 0.9–3.6%) had primary unresolved infertility. However, substantially more (13.8%) of all 518 women aged 40 years or more were childless; 35 (6.8%, 4.8–9.3%) were considered involuntarily and 36 (7.0%, 4.8–9.5%) voluntarily childless.

Uptake of services for infertility and infertility outcomes

There were 235 who women who had at least one episode of infertility (using the 12 months trying and/or sought medical help to conceive definition) and completed all service use questions. Figure 1 summarises the first experience of infertility for these women. This initially shows those with self-defined difficulty, followed sequentially by services sought and received. Whether this first episode of infertility ended with a live birth has been indicated at each stage for those women who did not progress to the next stage of the care pathway.

Of the 235 infertile women, 37 (15.7%) did not consider that they had a fertility problem for their first episode of infertility. All of these 37 women eventually conceived, with 29 having a live birth.

Of the 198 women who reported having difficulties, 144 sought help by initially consulting a non-specialist, and 10 by consulting a specialist directly. Of the women who saw a non-specialist medical provider, over half reported receiving advice (81, 57.5%) and just over two-thirds (98, 69.5%) were referred to specialist services.

A total of 97 women saw a specialist. Male factors were the most common cause of their infertility (33.3%), followed by ovulation disorder (23.7%), unknown cause (21.5%) and endometriosis (18.3%). Twenty of these 97 women reported not having any treatment, although four reported getting pregnant before any treatment could be started. The remaining 77 women received treatment for their first episode of infertility, the most frequent treatments being drugs (47.5%), *in vitro* fertilisation (IVF) (36.4%), surgery (27.3%) and artificial insemination (AI)/intra-uterine insemination (IUI) (22.1%). It is possible that the prevalence of treatment with surgery has been inflated by women reporting surgery as a treatment when it may have been for diagnostic purposes (eg, laparoscopy).

For 99 (42.1%) of the 235 women, their first episode of infertility ended with a live birth, another 79 had a live birth after this attempt; ie, they reported a pregnancy ending in a live birth, which they self-defined as a subsequent fertility event—this may have involved a change of partner

Table 3: Unadjusted and adjusted relative risk of infertility* by selected demographic factors and risk determinants

Determinants (measured at time of participation)	Number of women who experienced infertility* (Prevalence, %)			Unadjusted			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Relationship type	Heterosexual	216	(27.4)	Reference					
	Same-sex/no relationship	15	(13.6)	0.50	(0.31–0.81)	0.005	0.50	(0.28–0.90)	0.020
Age group (years)	25–29	19	(14.0)	0.52	(0.32–0.83)				
	30–34	38	(27.5)	1.02	(0.71–1.45)				
	35–39	53	(27.0)	Reference					
	40–44	79	(30.2)	1.12	(0.83–1.50)				
	45–50	57	(23.6)	0.87	(0.63–1.20)	0.017			
Māori descent	No	227	(25.9)	Reference					
	Yes	19	(19.2)	0.74	(0.49–1.13)	0.159			
Ethnic group	European	221	(25.9)	Reference					
	Māori	13	(18.8)	0.73	(0.44–1.20)				
	Other	6	(20.0)	0.77	(0.37–1.59)	0.373			
Educational level	Lower than university	148	(23.7)	Reference					
	University	80	(30.3)	1.13	(1.01–1.27)	0.036	1.19	(1.04–1.35)	0.010
Household income	Low (≤ $30,000)	17	(17.4)	0.65	(0.41–1.03)				
	Medium ($30,001–$70,000)	89	(26.1)	0.98	(0.78–1.24)				
	High (>$70,000)	112	(26.7)	Reference		0.179			
Deprivation	Low (deciles 1–3)	116	(25.7)	Reference					
	Medium (deciles 4–7)	94	(25.9)	1.01	(0.80–1.28)				
	High (deciles 8–10)	36	(22.6)	0.88	(0.64–1.22)	0.714			
Smoking status	Current smoker	36	(28.1)	1.04	(0.76–1.43)				
	Past smoker	65	(22.8)	0.85	(0.65–1.10)				
	Non-smoker	132	(26.9)	Reference		0.372			
BMI category, range (kg/m^2)	Underweight, <18.5	5	(55.6)	2.47	(1.34–4.55)		2.61	(1.43–4.79)	
	Normal, 18.5–24.9	91	(22.5)	Reference					
	Overweight, 25.0–29.9	54	(26.2)	1.16	(0.87–1.56)		1.19	(0.88–1.61)	
	Obese class I, 30.0–34.9	30	(25.2)	1.12	(0.78–1.60)		1.17	(0.80–1.69)	
	Obese class II, 35.0–39.9	23	(34.3)	1.52	(1.04–2.22)		1.78	(1.19–2.65)	
	Obese class III, ≥40.0	11	(36.7)	1.63	(0.98–2.70)	0.019	2.01	(1.19–3.37)	0.004

* Infertility definition used: 12 months or more trying and/or sought medical help to conceive.
† Simultaneously adjusted for all variables reported in the adjusted analysis and for household income, variables that were not significantly associated with infertility are not presented in the adjusted model.

and/or a break from trying to conceive. Therefore, in total 178 (75.7%) women had a live birth subsequent to their initial infertility. Those who were aged 35 or more years when they first experienced infertility were significantly less likely to have resolved it than those aged less than 35 years (57.1% vs 79.0% respectively, p=0.005).

When considering all episodes of infertility, 166 (70.6%) infertile women had sought non-specialist and/or specialist medical help at least once, and treatment was received by 89 (37.9%) infertile women.

Factors associated with infertility, service use for infertility and resolution of infertility

Unadjusted analyses revealed statistically significant associations between having experienced infertility and relationship type, age, education and BMI (all of which were at the time of survey participation) (all p<0.05) (Table 3). Women aged 25–29 and 45–50 years had a lower prevalence of infertility, especially compared to women aged 40–44 years at the time of the survey. However, after simultaneously adjusting for these factors, age group was no longer a significant determinant of infertility risk.

The adjusted relative risk of infertility was reduced (RR 0.50, 95% CI 0.28–0.90) amongst women who were single or in a same-sex relationship compared with women in a heterosexual relationship at the time of the survey. Women who were underweight were 2.61 (1.43–4.79) times more likely to report infertility compared with women with a normal BMI, while women in the obese class II and class III categories had 1.78 (1.19–2.65) and 2.01 (1.19–3.37) times the risk respectively. Women who had a university level qualification had 1.19 (1.04–1.35) times the risk of infertility than those without.

After investigating the likelihood of seeking medical help for infertility, using the determinants listed in Table 3 for modelling, only two significant factors were found: Education and income. However, these models (and that for resolution of infertility) were of limited power, having just 235 cases. Infertile women with a university-level qualification were slightly more likely than those without to seek non-specialist care (RR 1.10, 1.01–1.21). Household income predicted seeking specialist help; those with low and medium incomes were less likely to do so than those in the high-income bracket (RR 0.70 [0.39–1.26] and RR 0.67 [0.49–0.90] respectively).

Only two factors were associated with the resolution of the first episode of infertility in the adjusted model: Reported age at the onset of the first infertility experience and deprivation. Those aged 35 years or more when they first experienced infertility were less likely (RR 0.71, 95% CI 0.53–0.96) to resolve their infertility compared with those aged less than 35 years. For each level of deprivation there was a modest but significant decrease in infertility resolution (RR 0.89, 0.80–1.00), such that those in the highest deprivation deciles (deciles 8–10) were 22% less likely to resolve their infertility compared with those in the lowest deprivation deciles (deciles 1–3).

Discussion

Infertility was very common amongst women aged 25–50 years in Otago and Southland, with one in four who had ever tried to conceive or had conceived having tried for at least 12 months and/or had sought medical help to conceive. The prevalence of infertility was highest amongst those aged 40–44 years (30.2%), but was still common amongst women aged 30–34 and 35–39 years (27.5% and 27.0%, respectively). This suggests that women aged 30–39 years in the survey will eventually have an even greater burden of infertility than those women in the older birth cohorts, as many of these women intend to have children in the future and may yet experience infertility issues.

An increased risk of infertility was associated with being underweight or very obese, and a more modestly increased risk was detected for women with a university-level qualification. Among women who had tried to conceive, the risk of infertility was reduced amongst women who were single or in a same-sex relationship compared with women in a heterosexual relationship at the time of the survey; this may be explained by women who were not in a heterosexual relationship having less exposure to pregnancy risk and, therefore, infertility.

Amongst infertile women, over two-thirds had sought medical help to conceive on at least one occasion; doing so was modestly associated with university level education and having high household income. Over a third of infertile women reported receiving infertility treatment.

Whilst the proportion of women who resolved their infertility with a live birth was high, with three-quarters resolving their first episode, a relatively high proportion of women (6.7%) over the age of 40 years were involuntarily childless. Resolution of infertility was found to be less likely in those over 35 years old at first experience of infertility and with increasing deprivation.

This was a population-based study with a well-characterised sampling frame that had very good coverage in the age group relevant to this study. Basic demographic information was available for both the survey responders and non-responders. The use of a computer-based questionnaire minimised data coding and entry errors, standardised the way in which answers were elicited and possibly provided more complete disclosure of sensitive data. Another advantage of using a computerised questionnaire was that a comprehensive set of fertility questions could be asked, with the programming being able to avoid questions to women that did not apply. This comprehensive assessment uniquely allowed for the resolution of infertility to be examined at each point along the pathway from the first experience of infertility, to contact with various services, to treatment.

The survey had a modest response rate of 60.1%, with lower response rates in sub-groups with a slightly lower prevalence of infertility. However, the estimate of infertility from the Dunedin birth cohort, a study with notably high retention rates, and the prevalence of childlessness from the 2006 New Zealand Census were both very similar to the survey findings;[5,7] suggesting that non-participation did not create a substantive selection bias.

There is some evidence that recall of detailed fertility events may not be complete; van Roode et al (2015) found some infertility events that were reported at age 32 in the Dunedin birth cohort were not reported again when participants were asked about all past infertility events at age 38.[7] To reduce information bias in the present cross-sectional study, infertility was measured using both a fertility history method and specific questions on infertility. Thus, women not self-defining as having had difficulties conceiving, but who had taken longer than 12 months to conceive a pregnancy, were included as infertile.

Due to the cross-sectional design, important factors that influence infertility (such as age, BMI and smoking) were ascertained either during the current experience of infertility or after the experience of infertility. It is not known whether reported BMI and smoking reflected the status prior to experiencing infertility. On average, women's BMIs may increase after having a child, therefore, measuring BMI subsequently may mask the effect of BMI on infertility and resolution of infertility. Furthermore, modelling these potential determinants of infertility was constrained by the sample size; and even more so when modelling the determinants of service use and resolution amongst the infertile women.

The overall estimate of the burden of infertility (25.3%), and that of having tried to conceive for 12 months or more (21.7%), is similar to findings from recent studies in New Zealand and other high-income countries. van Roode et al (2015) reported that 26.0% of women had experienced infertility by age 38 in the Dunedin cohort study.[7] Amongst women of reproductive age (ranging from 28–50 years old), estimates from surveys of infertility based on a definition of ever having tried for 12 months or more to conceive were 17.3%, 17.5%, 19.9% and 21.2% in Scotland, Australia, Finland and the USA respectively.[13,18-20] The most common causes of infertility in the present study were very similar to the most common self-reported causes in Scotland.[13]

The estimate of childlessness in the current study (13.8%) was consistent with that of the 2006 New Zealand Census (16.7%);[5] the Census did not, however, provide information on whether childlessness was involuntary. Involuntary childlessness, estimated at 6.8% in this study, was higher than that measured in infertility surveys in the United Kingdom, Denmark and Finland (these ranged from 4.1–4.3%).[18,21-23]

An increased risk of infertility amongst those with very low or high BMI corresponds with findings of Hassan and Killick (2014).[24] Study findings on infertility and education replicate those associations previously described in Finland and New Zealand.[7,25]

Implications and conclusions

Overall, the findings from this study illustrate that infertility has the potential to be an even greater health burden in New Zealand, especially for older women, women with particularly low or high BMI and those who are often less privileged, which could include those from more deprived areas and non-European ethnic groups. Many women in this survey may yet experience infertility, suggesting that infertility will become even more prevalent. Medical assistance was also common and the burden on the healthcare system is likely to be greater if prevalence of infertility increases.

Age, BMI and specific clinical information, such as severity of diagnosis, have long been known to impact on infertility and the resolution of infertility. However, BMI limits for public funding of infertility treatment are the same for all women in New Zealand, since high and low BMI reduce the efficacy of treatment and also impose additional risks for pregnancy; this might disadvantage Māori and Pacific women who have higher BMIs for the equivalent body fat percentage compared with Europeans.[26] The impact of higher BMIs on infertility and pregnancy within these populations needs further investigation to determine whether the criteria for funding need to be adjusted.

Care is needed in generalising these finding to the whole New Zealand population. Some population groups with a slightly lower prevalence of infertility are relatively less common in the lower South Island (such as women of Māori ethnicity and women from more deprived areas). However, especially as some participants may yet experience infertility, this study provides further evidence that probably more than 1 in 6 New Zealand women experience infertility. The findings regarding the importance of age, BMI, deprivation, and male factor infertility are also likely to be common to the rest of New Zealand, though the relative importance may vary.

A national Ministry of Health survey, investigating sexual and reproductive health, is currently underway and will provide basic national data on the prevalence of infertility. This may allow for further assessment of whether the more detailed infertility results from this study in Otago and Southland can be further generalised.

Competing interests: Nil

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The experiences, motivations, and opinions of New Zealand's live liver donors

Claire Gavin, Phillipa Malpas, Adam Bartlett

ABSTRACT

AIM: To explore the motivations and experiences of New Zealand's live liver donors, and their opinions on New Zealand's current organ donation system.

METHOD: An anonymous questionnaire was sent to all 45 of New Zealand's live liver donors in November 2012.

RESULT: 21 responses were collated with an even gender split. Half of the participants were parents of the recipient. Despite the risks of surgery and associated post-surgical pain, all participants were satisfied by how the transplant went for the recipient and for themselves. 90% thought people should save lives if they can, with 18 (86%) disagreeing with New Zealand's current method of allowing family members to veto the deceased person's wishes on organ donation (on their driver's license). 95% thought that education was important in encouraging people to donate.

CONCLUSION: This unique and informed group have experienced both what it means to have a loved one waiting for a transplant and how it feels to be an organ donor. If New Zealand is serious about wanting to increase deceased organ donation rates, we should consider the experiences such as those who have undergone live donation.

There have been studies on New Zealand's liver transplant programme regarding the medical outcomes of recipients and to a lesser extent the medical outcome for donors;[1] no studies have explored the motivations or opinions of live liver donors. Furthermore, there is minimal data internationally.[2] Information from live donors about their experiences is rare, yet such experiences can provide valuable insights into the motivations of donors as well as how to motivate organ donation within the community.

Participants have experienced a loved one needing an organ and donating part of their liver in response to that need. Although results are not generalizable this study aims to contribute to a wider discussion on increasing organ donation rates in New Zealand.

Live liver donation is a high-risk operation that has been described as "one of the most invasive procedures that could be contemplated for healthy individuals."[3] Despite the risks, 5% of adult and 50% of paediatric liver transplants in New Zealand are done using live donors.[4] The lack of deceased donors, a high mortality rate for those with liver failure, and no equivalent of dialysis all drive the need for live donation. Our hands are forced into considering live donation in New Zealand because of our low deceased donation rates.[5]

Methods

An anonymous questionnaire was sent by post from Auckland Hospital's liver transplantation unit to all 45 of New Zealand's live liver donors in November 2012. A Participant Information Sheet was included and explained the study. Consent was assumed when a participant sent back the completed questionnaire in an addressed envelope.

The questionnaire had two parts, the first dealing with participants' own experiences of organ donation, and the second seeking responses regarding wider concerns about

Table 1: Demographic data for all participants

ID	Age now	Sex	Ethnicity	Occupation	Religion	Donor's relationship to recipient	Time to make decision to donate
1	30–49	M	European	Service	None	Parent	3 months
2	30–49	M	European	Business	None	Parent	Days
3	30–49	F	European	Professional	None	Friend	3 weeks
4	30–49	F	European	Professional	Anglican	Parent	Months
5	30–49	F	Māori	Clerical	AOG	Niece	2 months
6	30–49	F	European	Labourer	None	Parent	2 days
7	30–49	M	European	Professional	None	Parent	None
8	30–49	F	European	Mother	None	Sibling	2 days
9	30–49	M	European	Tradesperson	None	Parent	2 weeks
10	30–49	F	European	Professional	None	Friend's child	2 months
11	20–29	F	Indian	Home-maker	Hindu	Child	1 day
12	20–29	M	Albanian	Chef	None	Sibling	6 months
13	30–49	F	Chinese	Clerical	None	Parent	0 days
14	20–29	F	European	Telemarketer	None	Partner's cousin's daughter	12 months
15	50–69	M	European	Manager	None	Parent	3 months
16	20–29	M	European	Tradesperson	None	Child	Immediate
17	30–49	M	European	Professional	Catholic	Parent	1 week
18	50–69	F	European	Retired	Anglican	Grandparent	2 weeks
19	30–49	F	Māori	Labourer	None	Aunt	Few days
20	30–49	M	European	Tradesperson	None	Child	3 months
21	30–49	M	European	Professional	None	Parent	6 months

New Zealand's organ donation methods. The study received approval from the University of Auckland Human Participants Ethics Committee, reference 8682.

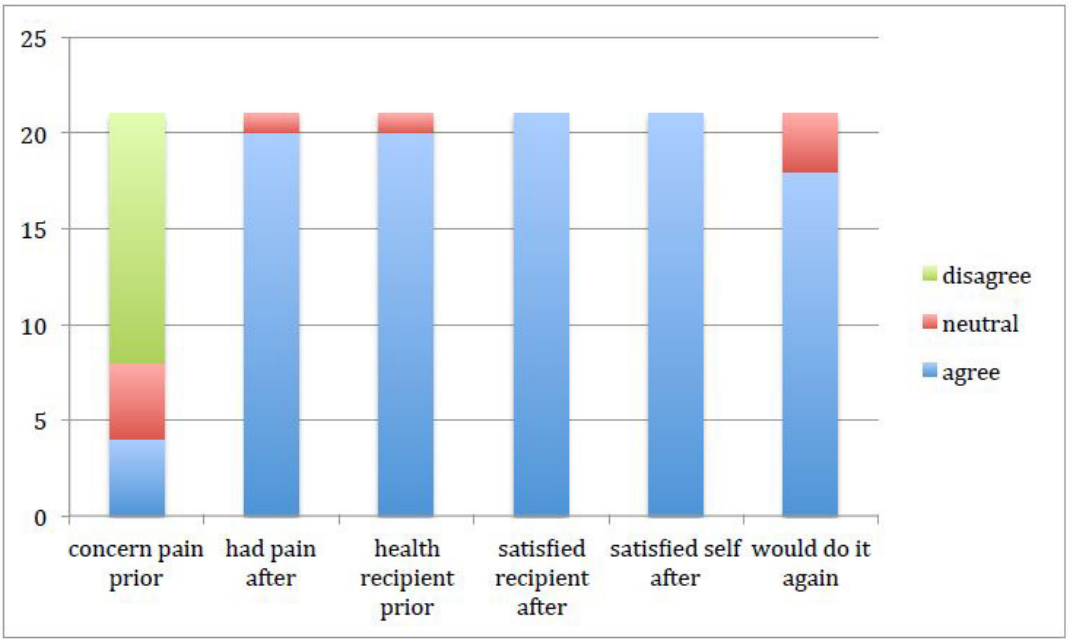
The questionnaire was divided into five sections. Section A requested participants' demographic information, including their relationship to the recipient and the amount of time within which they had to make their decision to donate. Section B asked questions about their experiences of the transplant procedure, including any concerns prior to and feelings after donation.

Responses were captured on a Likert Scale. (The Likert scale scales responses to give a better range of answers such as: strongly agree, agree, neutral, disagree, and strongly disagree.) Section C enquired about donors' motivation to donate to both their particular recipient and donating in hypothetical situations. Section D asked for their opinions about New Zealand's current system for deceased organ donation. The final section, E, related to participants' opinions on why they thought other people should donate organs, why people might refuse to donate, and how best to encourage more people to donate. Qualitative comments were sought from participants.

Results

Of the 45 questionnaires sent out, three were returned due to out-of-date addresses.

Figure 1: Comparison of donor concerns, before and after organ donation



Of the 42 remaining, 21 were completed making a 50% response rate.

Demographic data

Fifteen (71%), live liver donors, were aged 30–49 at the time of donation and gender was evenly split. The time they had to decide to donate ranged from days to months, with six (29%) having only a few days (including some who had only hours) to make the decision to donate. The relationship of donors to recipients covered a wide range, but ten (48%) were parents, three (14%) were children, and two (9.5%) were siblings. Fifteen (72%) were therefore immediate family members. Six (29%) of the donors had a more distant relationship (outside the immediate family) and all were female. Males made up seven (70%) of those donors who were parents of recipients

Experiences of the donation procedure

Prior to the procedure 17 (81%) were not "worried about their own death during the surgery", 16 (76%) were not "concerned about their future health after the surgery", and 4 (20%) were "concerned about pain after the surgery". However, 20 participants (95%) were always or often "concerned about the health of the person they were donating to".

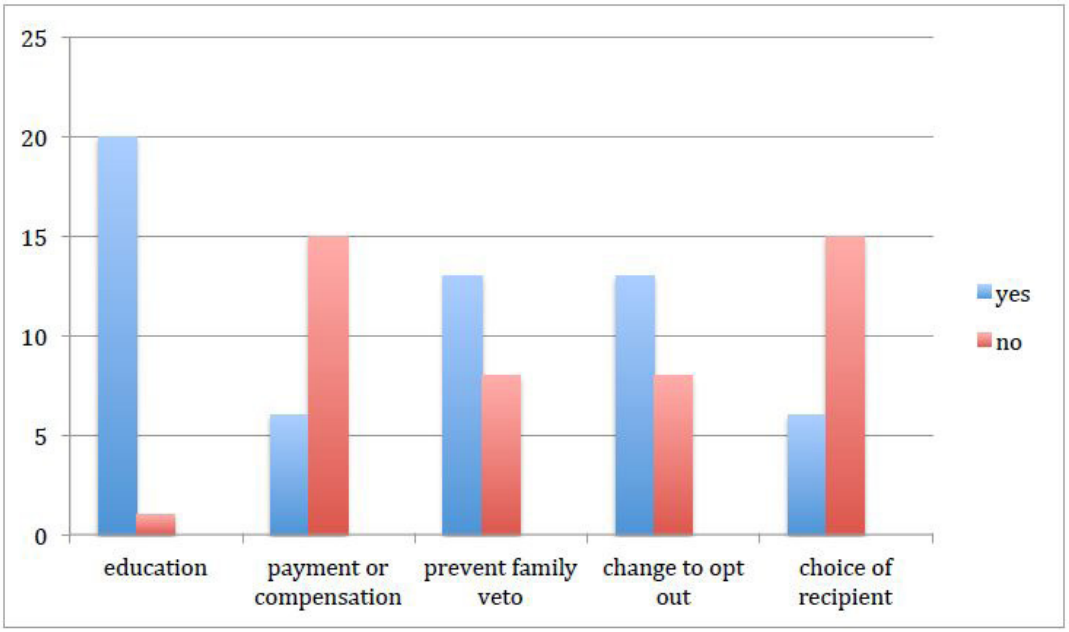
Although 4 participants (20%) had been "concerned about pain after surgery" prior to the procedure, all but one, (95%), "experienced pain" after the surgery. Nine participants (44%) agreed with the statement "I have on-going health concerns". Despite this, all 21 (100%) participants agreed or strongly agreed with the statements "I am satisfied with how the liver transplant went for me", and "I am satisfied with how the liver transplant went for the recipient". Eighteen (86%) participants agreed, "That if it were possible, I would donate a part of my liver again".

Motivation to be a donor

Participants were then asked about their motivations to donate to their recipient, and whether in hypothetical situations, they would donate to others. They were all motivated by "wanting the recipient to live", and nearly all (90%), "felt close to the person who needed a liver transplant". There was strong disagreement with statements relating to pressure from recipients or families to donate. 19 participants (90%) disagreed that they were "asked by the person who needed the transplant", and 18 (86%) disagreed with being "asked by my family". All participants disagreed with having been persuaded either "by the person I was donating to", or "by my family". While 14 participants (66%) disagreed with the statement "I felt I had no choice".

Regarding their motivations to donate to others in a hypothetical situation (living

Figure 2: Strategies to encourage organ donation



donation), 5 participants (24%) agreed that they "would donate to a stranger". This percentage was not altered "if I could choose who it was". Three participants (14%) indicated they would donate to a stranger, "if I was compensated for it". Regarding deceased donations, 20 (95%) said they would be "a deceased donor", while 16 (76%) said "I would agree to donate a deceased family member's organs to a stranger".

New Zealand's Current System

Sixteen participants (76%) were "currently an organ donor on their driver's licence", with 9 (43%) having previously "donated blood". When asked about New Zealand's current policy of allowing families to veto organ donation even if an individual had indicated their preference to donate on their driver's licence, 18 participants (86%) disagreed that "the family's wishes should override the deceased person's wishes". Sixteen (76%) participants thought that changing to an opt-out system was a good idea. (Opt-out systems mean donation is the default position unless you state otherwise, in contrast to opt-in systems where the default is non-donation, unless requested.)

Societal reasons for organ donation

When asked, "What reasons do you think people *should* donate living or deceased organs?", 19 participants (90%) agreed with two statements: "We should do for others what we would want others to do for us"; and "We should save lives if we can." Participants could tick as many options as they wished.

When participants were asked, "What reasons do you think people refuse to donate living organs?", 18 (86%) stated "religious reasons", and 19 (90%), stated "fear for their own health." Most participants (71%) disagreed with the statement that refusal may be because "they should be paid or compensated in some way." Similar figures were found regarding "reasons for refusing to become deceased donors", with 18 (86%) participants stating "religious reasons", and 15 (71%) participants "not wanting to further upset family at this time". Sixteen (76%) participants disagreed with the statement "because they get nothing in return" for donating.

The final question asked participants, "Which factors do you think will encourage more people to donate organs?" Education was the most significant response for 20 (95%) participants, followed by "assume everyone is a donor unless they object" and "stop families going against the wishes of a deceased donor." Six participants (29%) disagreed with the statements, "donors get a say on who gets their organs" and "payment or compensation for donating."

Overall, qualitative comments revealed

that participants thought it was important to have conversations about donation before death, and to be very clear to family members about one's wishes. There were also preferences that a prospective donor's choice on their driver's licence should be upheld. Other comments reflected that it was a good feeling to be able to help.

> *"I was in my early* [fifties] *when I gave my baby grandson his new liver.* NOTHING *gives me more joy than to see him now (11yrs) leading a healthy life. So many lives can be transformed by donation. We have leading experts that can save so many lives by people donating. Words cannot express the personal feelings of helping to save my grandson*[']*s life.* YES *I would do it again."* Participant ID #18

Discussion

Living donors are in the unique position of experiencing the needs of potential recipients and undergoing surgery for the benefit of someone other than themselves. While it is not surprising that this group were very concerned about the health of the recipient (95%), and had plenty of incentives to want to help, one might also expect that undergoing surgery would also result in concern about their own health. There were, however, low levels of concern about the risk of death (19%), or their future health (24%) as a result of the surgery. Studies show that donors are influenced by the large potential benefits to the recipient,[6] rather than themselves, and that donors often decide to donate rapidly without a thorough consideration of risks.[7]

There are concerns in the medical profession regarding the level of acceptable risk, particularly for live donors.[8] In our study, all participants were satisfied with how the procedure went, with a majority saying they would do it again if it were possible. It is important to note though, that these respondents only represent half of all possible live liver donors. It is possible those who did not participate in the study were less positive with their experiences.

Nevertheless, these results are similar to those observed in other quality-of-life studies following live donor liver transplant, where nearly all stated that they would donate again, irrespective of donor outcome.[3] There is a need to safeguard against donors' potential desperation and lack of concern for personal risk, while balancing the great benefit that comes with donating and the need to respect the autonomous decision of the donor.

New Zealand's living donor rates are relatively high compared to other Western countries, however deceased donation rates in New Zealand are comparatively very low.[10] If New Zealand could increase deceased donation rates, the difficulties and risks of live organ donation (particularly that of live liver donation) would be greatly reduced, and only required in emergent situations.

Regarding strategies to promote and increase deceased and living organ donation, there are numerous ethical concerns that need to be considered. No participants in this study reported any persuasion to donate and only a few were asked by the recipient or a family member to donate. Paula Martin's study of New Zealand patients waiting for kidney transplantation showed that the task of finding a living donor is usually the responsibility of recipients.[11] She found that asking people to consider donation is consistently reported by (potential) recipients as being extremely difficult and many wait for potential donors to approach them.

Another strategy to increase organ donation would be to consider some form of payment, either for organs or for time off work and related costs.[12] The majority of participants in this study were against such a strategy. Although, if a payment scheme increased deceased donation rates, this may have negated the need to consider live donation. The participants in this study were a select group who were willing to be a living donor, and who were very altruistic. Other potential recipients and their families might feel differently towards reimbursement.

There is an important distinction to be made here between receiving money as compensation for losses incurred and money used as an incentive to encourage people to consider donating when they otherwise may not.[14] Several comments

reflect participants' views that potential donors should have sufficient compensation to help with income loss and expenses:

> *"I feel that compensation support for live donors is insufficient. For donors that are travelling from outside of Auckland, it is important that they do not have to leave family or recipient in Auckland because they need to return to work to cover living costs. ....While I was lucky enough to be able to do this, and stay with my family, others may not be so lucky and in a worst case scenario unable to donate because of this reason."* (ID# 7)

With regard to written qualitative comments, most were in response to the family veto question ("the family's wishes should override the deceased person's wishes"). Most participants (86%) did not agree with this statement. In regard to the hypothetical question (being a deceased donor themselves), 95% of participants were willing to be a deceased donor but this decreased to 76% when considering donating another family member's organs. This may illustrate the difficulties families have with consenting on behalf of others for donation, especially when they do not know the wishes of the deceased individual. A UK study looking at this question from the families' perspective, found that families found it significantly easier to consent if they knew the donor had registered their wish to donate.[6] Participants in this study felt strongly that the decision of an individual to be a donor should be respected by their loved ones. Participants' comments emphasised that individuals should make their wishes clear to their family before death and that if a decision to donate had been made, that this should be upheld:

> *"If the deceased person has made their wishes to donate clear, then their wishes should not be able to be overturned by their family."* (ID# 6)

These views mirror those found in a 2012 New Zealand poll of 1,029 people, which showed that 87% were adamant that the wishes of a deceased individual must be followed by the family.[14] The comments from the poll included, "The needs of the many are far more important than the wishes, for whatever spiritual or other reason, of a surviving relative."

International comparisons indicate that a change to New Zealand's organ donation system is overdue.[15] Currently, New Zealand policy is promoting living organ donation which is both risky and costly, but little is being done to promote deceased donation, which not only helps more recipients, but also does not place additional demands and risk on recipients' healthy supporters. Two areas in which progress could be made include decreasing the power given to the family veto and educating the public about the process of deceased organ donation. Organ Donation New Zealand medical staff express concerns about both of these strategies. Streat and Silvester write that the previously expressed wishes of the deceased should not be used to influence the family,[16] and Judson commented that, as only a small percentage of the population will ever be in a position to donate, there was no need to educate everyone.[17] These views are not supported by the results of this study, a poll of the New Zealand public,[9] nor by overseas practice.[18] A wider ethical lens needs to be used in order to represent more views, such as those of other medical staff and the New Zealand public. Rates of deceased and living organ donations are interrelated, as are the lives of potential recipients, living donors, and deceased donor families. If, as a society, New Zealand is serious about wanting to increase organ donation rates, we should consider the experiences, insights, and views of those individuals who have been living donors.

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Attitudes and risk of withdrawal in general surgical registrars

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ABSTRACT

AIMS: To determine the risk of withdrawal from training of Australian and New Zealand general surgical registrars, and to investigate factors associated with increased risk.

METHODS: An invitation to participate in an online survey was distributed to all Australian and New Zealand general surgical registrars by the Royal Australasian College of Surgeons.

RESULTS: 142 of 550 (26%) participants completed the survey. Overall, 54% (n=77) of respondents had considered leaving surgical training. Female trainees were significantly more likely to consider leaving training compared to males (65% vs 47%, *p*=0.036, OR 2.1). Respondents who studied in Australia or New Zealand, compared to overseas, were also significantly more likely to consider leaving surgical training (59% vs 35%, *p*=0.023, OR 2.7). The most common reason for potential withdrawal was poor lifestyle and quality of life during surgical training. Trainees at risk of withdrawal felt less supported, less satisfied with teaching and less confident in their operative skills.

CONCLUSION: Female and locally-trained general surgical registrars are at a higher risk of withdrawal during their training programme for a number of reasons. At risk trainees are also less satisfied with their programme.

Attrition during surgical training is a critical issue, as the loss of a training registrar represents a waste of resources and effort as well as having implications for future workforce planning. Workforce modelling has predicted that unless there is a substantial increase in the number of graduating surgeons, Australia will face a surgical workforce crisis within the next 15 years. It has been conservatively estimated that at least 264 new surgeons will be needed each year between now and 2025, which equates to at least an additional 80 per annum in addition to the current 184 already graduating.[1] It is therefore critical to ensure that we retain as many surgical trainees and fellows as possible, and prevent attrition.

The literature regarding the rate of attrition from surgical training is limited, and there have been no studies in Australasia concerning either the incidence of attrition or the reasons contributing to it. Attrition is defined as a decrease in the surgical workforce due to all causes, including voluntary withdrawal, transfer to other programmes or dismissal. In the US, several studies have reported trainee attrition rates (including all trainees who have left or been dismissed for any reason), with fairly consistent figures of 17–30%.[2-7] In Australia and New Zealand, the withdrawal rate for general surgical trainees during the 5 years from 2010–2014 was 5.9% (with 5.8% for male trainees, and 6.2% for female trainees) due to personal reasons or transfer to another specialty.[8] These figures do not include trainees who were dismissed from training.

Few studies have considered the factors contributing to a trainee's decision to leave. It is perceived that attrition is the result of the highly demanding and stressful climate that trainees and their families endure in the postgraduate years. It has been demonstrated that dissatisfied physicians are 2 to 3 times more likely to leave medicine than those that are satisfied.[9] A 2005 study by Dodson et al[2] considered reasons for attrition and found that 65% of residents

who left their programme withdrew from training for 'life-style' reasons (other reasons included opportunity for early specialisation, emotional issues or performance difficulties and desire to leave medicine altogether).

It has been reported previously that gender may play a role in attrition. This is certainly an important consideration in the context of increasing feminisation of the surgical workforce, with 33% of current general surgical trainees in Australasia being female.[8] In the US, Bergen et al[10] reported that women were 2.26 times more likely to voluntarily withdraw from general surgical training than men, and this was predominantly due to family commitments or health reasons. Similarly, the study by Dodson et al reported attrition rates for females as being double that for males (27% vs 13%). However, a comprehensive study of 6,303 US trainees by Yeo et al found no gender difference in attrition rates.[3] This same study found that the only independent predictor of attrition was post-graduate year level, with the highest rates in the first and second years of specialty training.

The aim of this study was to examine both the satisfaction and attitudes of Australasian general surgical trainees toward their training programme and to assess the number and characteristics of trainees at risk of withdrawal.

Methods

Ethics approval for the project was obtained from the ethics committee of the Sydney Local Health District and approval to distribute the survey was obtained from General Surgeons Australia (GSA) and the New Zealand Association of General Surgeons (NZAGS). An invitation to participate in a survey was extended to all Australian and New Zealand General Surgical trainees. Trainees were emailed a link by the Royal Australasian College of Surgeons to an online survey delivered via the Survey Monkey website. The survey comprised socio-demographic questions and a 44-item questionnaire implementing a 5-point Likert scale response (modified version of survey developed by Yeo et al at the Yale University School of medicine[11]). Trainees were given 8 weeks to respond with a reminder letter e-mailed four weeks following initial invitation. The voluntary responses were submitted online via Survey Monkey.

Outcomes

The primary outcome was the prevalence of risk of withdrawal from general surgical training. This was established by determining how many participants responded in the affirmative to the question, "Have you considered leaving surgical training?" The secondary outcomes were to investigate reasons for leaving surgical training and to explore satisfaction and attitudes towards surgical training. Firstly, respondents who identified themselves as being at risk of withdrawal were asked whether or not 12 factors influenced their decision to leave surgical training (n=77 respondents identified themselves as being as at risk of attrition, see Table 2). These 12 factors were presented as a list of common concerns formulated by the authors based on previous experience with surgical trainees who had left or thought about leaving surgical training. Secondly, all respondents were asked to rate 44 statements regarding attitudes towards surgical training on a five-point Likert scale (strongly agree–strongly disagree). Analysis was performed to determine statistically significant differences between at risk and not at risk groups (a difference was found for 21 of the 44 statements). These answers are presented in Table 3, stratified by whether or not trainees identified themselves at risk of withdrawal from training.

Statistical analysis

Statistical analysis was conducted using SPSS 20.0 (IBM, US). The level of significance for all tests was $p<0.05$. Differences in outcomes between categorical groups were analysed using Chi-square test or Fisher's exact test if cell counts were <5.

Results

A total of 142 survey responses were received of 550 general surgical registrars in Australia and New Zealand (26% response rate) in 2013. Of the respondents, 56% were male and 44% female, with females relatively over represented, given that in 2013 only 35% of general surgical trainees were female. Half the responses received were from trainees in their first

Table 1: Characteristics of survey respondents

Participant Characteristics		Frequency (%)		
		Total†	Considered leaving training‡	
			No	Yes
Age	25–29	31 (22)	15 (48)	16 (52)
	30–34	70 (50)	31 (44)	39 (56)
	35–40	40 (28)	18 (45)	22 (55)
Gender	Male	79 (56)	42 (53)	37 (47)
	Female	63 (44)	22 (36)	40 (65)
Year of SET	1	40 (29)	19 (48)	21 (52)
	2	31 (22)	14 (45)	17 (55)
	3	24 (17)	16 (67)	8 (33)
	4	19 (14)	5 (26)	14 (8)
	5	26 (18)	10 (39)	16 (62)
Medical degree completed	Australia/NZ	115 (81)	47 (41)	68 (59)
	Overseas	27 (19)	17 (65)	9 (35)
State/Country of SET training	NSW	56 (40)	25 (45)	31 (55)
	VIC	35 (25)	14 (40)	21 (60)
	QLD	16 (11)	6 (38)	10 (63)
	WA	10 (7)	5 (50)	5 (50)
	SA	9 (6)	5 (56)	4 (44)
	NZ	15 (11)	9 (60)	6 (40)
Marital Status	Single	41 (29)	15 (37)	26 (63)
	Married	73 (52)	38 (52)	35 (48)
	De Facto	24 (17)	10 (42)	14 (58)
	Divorced/ separated	3 (2)	1 (33)	2 (67)
Children	Yes	54 (39)	29 (54)	25 (46)
	No	86 (61)	35 (41)	50 (46)

† Column %, ‡ Row %, SET – Surgical Education and Training Programme

or second of five years of training. The socio-demographic characteristics of survey participants are summarised in Table 1.

Overall, 54% (n=77) of respondents had considered leaving surgical training, with 43% (n=61) considering this within the previous year. Females were more than twice as likely to consider leaving surgical training compared to males; OR=2.1(95% CI 1.0–4.1), p=0.036 (Table 1). Respondents who studied in Australia or New Zealand were also significantly more likely to report considering leaving surgical training compared to those who studied in another country (p=0.023, OR=2.7 [95% CI 1.1–6.7]); 59% vs 35% respectively. Other factors—including age, gender, year of training, location of training, marital status and whether respondents had children—were not found to be significantly associated with attrition risk (Table 1).

Reasons for considering leaving surgical training and the response frequency are listed in Table 2. The most common reason for considering leaving was poor lifestyle and quality of life during surgical training

Table 2: Reasons for leaving surgical training (n=81 respondents)

Reason	Frequency. (%) of Respondents agreeing or strongly agreeing
Poor lifestyle and quality of life during training	38 (47)
Lack of support (home or work)	30 (37)
Excessive working hours	28 (35)
Job dissatisfaction	27 (33)
High levels stress/anxiety/pressure	26 (32)
Domestic or social reasons/family commitments	19 (24)
Excessive workload/work intensity	18 (22)
Poor lifestyle and quality of life as a consultant	15 (19)
Desire to travel	10 (12)
Financial/lack of job security	3 (4)
Lack of flexible training/work opportunities	3 (4)
To pursue training in another field/specialty	3 (4)

(47% respondents). The next most cited reason was a perceived lack of support, either at work or home (37%), and this was followed by a concern over excessive working hours (35%). Males were significantly more likely to consider leaving surgical training because of poor lifestyle and quality of life as a consultant compared to females (p=0.001). There were no other significant differences between genders in reasons why respondents had considered leaving surgical training.

Table 3 shows differences in satisfaction and attitudes towards surgical training between trainees at risk of withdrawal and those not at risk. Respondents who identified themselves at risk of withdrawal from training were significantly less likely: to be satisfied with their training; to think their opinions were important; to agree that the programme had support structures in place; to feel like they could turn to senior colleagues; to look forward to going to work; to be happy at work; to feel their operating skills were appropriate; to feel they fitted well into their training programme; and to feel they could count on other registrars to help them. Respondents who reported risk of withdrawal were also significantly more likely to: worry they were not confident enough; agree that the hours they were working were causing strain on their personal life; agree that the personal cost of training was not worth it; and agree that surgeons do not make as much money as they used to.

Discussion

This study, the first of its kind in Australasia, found that 54% (n=77) of respondents had considered leaving their surgical training and demonstrates that thoughts of discontinuing surgical training are prevalent amongst trainees. While this study captured responses from only 26% of the cohort of general surgical trainees, this number still represents a high absolute number of trainees who had considered leaving. The available data on attrition in Australian general surgical trainees shows a current attrition rate of 5.9%, and whilst this is much lower than the potential attrition rate of trainees, it remains concerning that 1 in every 17 general surgical registrars will not complete their training programme.

The most common reason given when considering withdrawal is poor lifestyle and quality of life during surgical training. This is in agreement with previous American studies by Morris et al[12] and Kelz et al,[13] where poor lifestyle was given as the most common reason for voluntary resignation form surgical training. Interestingly, in the US, the introduction of restricted

Table 3: Satisfaction and attitudes towards surgical training (n=142 respondents)

Attitudes	Those that agree or strongly agree n* (%)			
	Total (n=142)	Thought of leaving surgical training		P value between groups †
		No (n=64)	Yes (n=77)	
I am satisfied with my training programme	74 (52)	40 (63)	33 (43)	**0.020**
As a surgical registrar, my opinions are important	90 (63)	51 (80)	38 (49)	**<0.001**
My training programme has support structures in place which provide me with someone to turn to when I am struggling	51 (36)	34 (53)	16 (21)	**<0.001**
I feel I can turn to my consultants and senior colleagues when I have difficulties in my training	69 (49)	39 (62)	29 (38)	**0.005**
I look forward to coming to work every day	73 (51)	41 (64)	31 (40)	**0.005**
I am satisfied with the teaching in my training programmeme	53 (37)	35 (55)	17 (22)	**<0.001**
I am satisfied with the operative experience in my training programme	63 (44)	37 (58)	26 (34)	**0.004**
I have considered leaving my training programme in the last year	61 (43)	5 (8)	56 (73)	**<0.001**
I am happy when I am at work	89 (63)	48 (75)	41 (54)	**0.010**
I often feel that "I am in over my head"	20 (14)	5 (8)	15 (20)	**0.045**
I feel that my operating skill is level appropriate	71 (50)	41 (64)	30 (39)	**0.003**
I worry that I will not feel confident enough to perform procedures by myself before I finish training	89 (63)	32 (51)	57 (74)	**0.004**
The hours I am working are causing a strain on my personal and family life	88 (62)	32 (51)	55 (71)	**0.012**
My consultants will think worse of me if I ask for help when I do not know how to do a procedure	35 (25)	11 (17)	24 (32)	**0.045**
I really care about my patients	133 (94)	61 (95)	71 (92)	**0.453**
The personal cost of surgical training is not worth it to me	26 (18)	3 (5)	23 (30)	**<0.001**
I feel that I fit in well in my training programme	88 (63)	49 (78)	38 (50)	**0.001**
I am committed to completing my general surgical training	123 (87)	61 (95)	61 (79)	**0.005**
My operative experience so far has helped me develop my skills well	92 (65)	52 (81)	39 (51)	**< 0.001**
If I have a problem, I feel I can count on other registrars to help me out	88 (62)	46 (72)	41(53)	**0.023**
Surgeons do not make as much money now as they used to	52 (37)	17 (27)	34 (44)	**0.030**

* Where n ≠ total data is missing † Only significantly different results included in this table

working hours has not been associated with any improvement in the wellbeing of surgical residents.[14]

We found that female trainees were significantly more likely to consider leaving, and this is in agreement with previous findings in the literature.[2,10,15] The reasons women are more likely to withdraw are multi-factorial, but include pregnancy and childcare responsibilities. There are currently steadily increasing numbers of female doctors entering surgical training, and it is imperative that these trainees are retained as they represent a valuable resource and ever increasing percentage of the surgical workforce. Interestingly, despite female trainees being at higher risk of withdrawal, the reasons that trainees chose to leave were not significantly different between genders other than more men attributing poor lifestyle as a consultant as a factor in potential attrition.

This study found that locally-educated registrars (those completing their medical education in Australia or New Zealand) were at a significantly higher risk of attrition than their counterparts who underwent medical training overseas. The reasons for this trend are not entirely clear, but may be related to different expectations and perceptions, as well as the fact that international trainees have often chosen to move to Australasia (particularly from more disadvantaged nations) and therefore may be more committed to completing training and more willing to accept the challenges that training presents. They have usually made a significant financial sacrifice to go through the Royal Australasian College of Surgeons International Medical Graduate pathway, and this, coupled with the associated sequelae, is likely a significant driving force against consideration of withdrawal.

In addition to establishing withdrawal risk, we also questioned attitudes toward and satisfaction with training and significant differences were identified between trainees at risk of withdrawal and those who had not considered it (Table 3). Overall, we found that 52% of trainees agreed or strongly agreed that they were satisfied with their training programme. This is significantly less than the 85.2% of US general surgical trainees who felt satisfied with their training in the survey by Yeo et al.[9] We do, however, acknowledge that our sample may be inherently biased by the fact that a relatively high proportion of dissatisfied trainees or those at withdrawal risk may have responded to the survey.

While it is beyond the scope of this paper to consider every difference in detail, there were broad themes of dissatisfaction that emerged amongst the cohort of at risk trainees. Registrars contemplating withdrawal felt unsupported and undervalued by their colleagues and seniors, with only 21% of at risk trainees vs 53% of other trainees agreeing or strongly agreeing their programme had structures in place to provide them with someone to turn to when they felt they were struggling ($p<0.001$). This is in comparison to 71.6% of US residents in the survey from Yeo et al. Overall, only 22% of at risk trainees felt satisfied with teaching in their training programme, compared to 55% of remaining respondents ($p<0.001$). Trainees who identified themselves at risk of leaving also felt that their operating skills were not appropriate for their training level, and 74% were worried they would not feel confident performing procedures independently before they complete their training programme. Similar studies in the US showed higher rates of confidence in operating skills, with a recent study by Fonseca et al of 653 final year US general surgical trainees reporting that approximately 25% of respondents had a significant lack of confidence in performing a variety of open surgeries[16].

While the largest American study by Yeo et al found year of training to be significantly associated with attrition risk (most withdrawals occurring in the first or second year), this was not the case in our study. To the contrary, we found the highest percentages of trainees considering withdrawal were in their penultimate or final training year (74% and 61% respectively), although this was not statistically significant. We postulate that this may be due to the very high levels of stress and sacrifice related to study and completion of the general surgical fellowship exam at the beginning of the final year of training.

This study has several limitations, most of which are due to the nature of survey-based research. Our response rate was low (26%)

and we acknowledge that we only have received data from a minority of trainees. Whilst the rate of withdrawal risk in this study population was found to be 54%, the true rate amongst trainees may be much higher or lower. It is also possible that there was a selection bias in the type of trainees who replied, with those who are inherently less satisfied or struggling being overrepresented. Our sample also had a higher rate of female trainees than the overall training cohort, and as female trainees are at higher risk of withdrawal this may have had an influence on the high attrition risk rate. Despite these limitations, this study is the first to consider this issue in Australian and New Zealand general surgery trainees, and we hope the results will be used as impetus for further research in this area.

It would be of great value to survey trainees who have actually withdrawn to elucidate the reasons they did so, as this would be helpful in further determining the factors that place individuals at attrition risk. In addition, it would be interesting to know what paths these trainees took following leaving surgery—whether they transferred to another specialty, took a position in a non-clinical field or left medicine altogether. If a negative experience in surgical training is resulting in abandonment of any medical career, this would be a cause of significant concern. There is clearly potential for further research in this field, and results will be of great use in terms of workforce planning and development, surgical educational reform and in the broader context of gender and generational cultural shifts in medicine.

Conclusion

Attrition in surgical trainees presents a significant concern for all those involved in surgical education and training as well as workforce planning. The current 5 year training programme entails commitment and sacrifice on behalf of the trainee, and there is no doubt that the stressors and difficulties encountered during these years will leave some trainees questioning whether they can complete their surgical education. This study is the first of its kind in Australasia, and has allowed estimation of withdrawal risk compared to actual attrition rate and the factors contributing to it. Whilst this study may have been affected by a responder bias, with dissatisfied trainees being more likely to reply, it has identified that female trainees are significantly more at risk of withdrawal than their male counterparts and that thoughts of attrition are prevalent amongst a proportion of trainees. Overall, the majority of trainees we surveyed were satisfied, but problems relating to lack of support, perceived poor teaching, lack of appropriate operative skills and excessive working hours were expressed by all trainees, regardless of whether or not they had considered withdrawal from training. Pleasingly, despite these issues, the vast majority of trainees felt committed to completing their training. From here, we must focus on identifying the group of at risk trainees, particular female locally-trained registrars, and start considering how the modifiable risk factors for attrition can be addressed. We need to listen to the concerns of current general surgical registrars and find ways to improve the quality of their training to ensure we have not only adequate numbers for our future surgical workforce, but a cohort of surgeons who have enjoyed their training experience and will strive to create a similar one for their own trainees in the future.

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The prevention of early-onset neonatal group B streptococcus infection: New Zealand Consensus Guidelines 2014

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ABSTRACT

AIMS: Group B streptococcal (GBS) disease is the leading cause of early-onset neonatal sepsis in New Zealand. Disease follows vertical transmission of GBS from the mother, which can largely be prevented by intravenous intrapartum antibiotics. A 2004 New Zealand guideline recommended using clinical risk factors to identify mothers who would qualify for intrapartum antibiotics. An expert multidisciplinary group met to reconsider these guidelines in the light of a two year survey of the incidence of early onset GBS neonatal sepsis.

METHODS: Representatives from the New Zealand College of Midwives, the Fetus and Newborn Committee of the Paediatric Society of New Zealand, the Royal New Zealand College of General Practitioners, the New Zealand Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the New Zealand sub-Committee of the Australasian Society of Infectious Diseases, and the Canterbury Home Birth Association met to review the literature and the most recent New Zealand data.

RESULTS: The multidisciplinary group noted that the estimated incidence of early-onset GBS sepsis had halved over a 10-year period to be 0.26 per 1,000 live births in 2009–11 and that there were missed opportunities for preventing GBS infection. Consensus was reached that adoption of a national guideline on prevention and management of early onset GBS neonatal sepsis by all practitioners and District Health Boards would have the greatest potential to further reduce the incidence.

CONCLUSION: A risk-based GBS prevention strategy continues to be recommended as being the most clinically and cost effective for the New Zealand context. Universal routine antenatal GBS screening is not recommended.

Early-onset neonatal group B streptococcus (EOGBS) infection is acquired by the baby by vertical transmission from the birth canal around the time of birth and is an important and largely preventable public health problem.

Two strategies for identifying women at increased risk of giving birth to an affected baby have been used; one based on universal antenatal screening and the other on clinical risk factors. In both strategies, mothers identified as at risk are offered appropriate intravenous antibiotics from when labour is established. This intrapartum antibiotic prophylaxis (IAP) has been shown to be effective in preventing vertical transmission of GBS.[1]

In 2004, an expert multidisciplinary group reviewed the evidence on IAP and the results of a national two year surveillance study of EOGBS in New Zealand (1998–9).[2] The group agreed a set of guidelines appropriate for New Zealand, which recommended a risk factor-based prevention strategy.[3]

A repeat, national, two-year study of EOGBS infection was completed in 2011 through the New Zealand Paediatric Surveillance Unit.[4] This showed that the incidence

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of EOGBS had halved in the 10 years since the first survey, when it was 0.5 per 1,000 live births,[2] and was estimated as 0.26 per 1,000 (95% CI 0.18–0.37) live births.[4] The study also found there were missed opportunities for preventing GBS infection.[4]

In late 2012, the multidisciplinary group was reconvened to review the current literature and the New Zealand data. The group comprised representatives from the New Zealand College of Midwives, the Fetus and Newborn Committee of the Paediatric Society of New Zealand, the Royal New Zealand College of General Practitioners, the New Zealand Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the New Zealand sub-Committee of the Australasian Society of Infectious Diseases, and the Canterbury Home Birth Association. The group considered that the adoption of a national guideline by all practitioners and District Health Boards (DHBs) would have the potential to improve prevention of EOGBS infection.

The group noted that the most recent recommendation from North America[1] was for universal screening, whilst that from the UK[5] was for a risk-based approach. Neither will prevent all cases of EOGBS and factors such as the practicalities and cost-effectiveness need to be considered. Screening has to be carried out at the right time (35–37 weeks) with the correct technique (vaginal and anorectal swab), reach the laboratory where selective media and enrichment broth are required, and the results need to be available and acted upon. A recent study[6] has shown that 10% of women with negative screening were actually positive for GBS when in labour, whilst 50% of women with a positive screen result were negative for GBS when in labour. The screening approach is more expensive and exposes more women to antibiotics than the risk-based approach. Lastly, it is likely that the approach to GBS prevention will need to be reviewed again and potentially significantly altered as rapid diagnostic testing in labour and maternal immunisation are developed and become cost-effective.[4]

The following guidelines on the prevention and management of EOGBS infection represent the consensus statement from this group.

Recommendations

1. A risk-based EOGBS prevention strategy continues to be recommended, as it is the most clinically and cost effective for the New Zealand context. Universal routine antenatal GBS screening is not recommended.

Risk factors

The risk-based approach recommends that all women with one or more of the following factors be offered intravenous intrapartum antibiotic prophylaxis (IAP):

   a. a previous GBS-infected baby
   b. GBS bacteriuria of any count during the current pregnancy
   c. preterm (<37 weeks) labour and imminent birth
   d. intrapartum fever $\geq 38^0$C
   e. membrane rupture $\geq$ 18 hours

2. Women who have had an incidental finding of GBS on a vaginal swab earlier in pregnancy need to have this repeated between 35–37 weeks. If this has not occurred, then this should be considered a risk factor and she should be offered IAP.[5]
3. All maternity providers need be updated about these current GBS recommendations, to improve practice and outcomes, and achieve national equity.
4. All hospitals should have an accessible and agreed protocol, based on the current recommendations and which should be followed by all practitioners.
5. GBS information needs to be developed for pregnant women and their whānau/family, using both written and web-based material. Accurate and appropriate information will help decision making.

Practical Applications

1. Antenatal management of group b streptococcus (GBS)

i. Incidental finding of GBS on vaginal swab

An incidental finding of vaginal and/or rectal GBS colonisation during pregnancy does not require treatment with antibiotics antenatally, as GBS cannot be eliminated from its reservoir in the large bowel.

An incidental finding of GBS in pregnancy greater than 5 weeks before labour is unreliable[1,7] and may result in unnecessary intervention in labour.

If the woman has had a previous GBS-infected baby or GBS bacteriuria in the current pregnancy she should be offered intrapartum antibiotic prophylaxis (IAP).

In other cases, it is recommended the woman is re-swabbed at 35–37 weeks' gestation if an incidental finding has occurred, using the following technique:

- **Low vaginal and rectal swab** (use same swab for both; clinician or patient collected)
- **The request form must clearly state "GBS screen" and "use selective broth process".**

This result informs labour management. If this swab returns positive the woman should be offered IAP. If the swab returns with no evidence of GBS colonisation, IAP is not required.[1] (However, if intrapartum fever occurs there should be an assessment for chorioamnionitis).

If the woman has had an incidental vaginal GBS positive swab early in the current pregnancy and has **not** been re-swabbed at 35–37 weeks, this should be considered a risk factor and she should be offered IAP.[5]

ii. GBS bacteriuria or GBS urine infection during pregnancy

GBS bacteruria of any count and at any stage in pregnancy is a risk-factor for early onset GBS infection. Most experts will only treat the bacteruria with appropriate antibiotics when the colony count is $>10^5$ colony forming units.ml.[1,8]

There is no need to take or repeat a GBS vaginal swab when GBS bacteriuria has been diagnosed—this is a sufficient risk-factor in itself.

IAP is recommended even when GBS bacteriuria has been successfully treated. (The only exception to this is if caesarean delivery is performed before the onset of labour in a woman with intact membranes).

2. Principles of GBS management in labour

All women with risk factors for early onset neonatal GBS infection (listed above) should be offered treatment, when labour commences, with IAP. **Oral antibiotics are ineffective in this context.**

Women with clinical signs of chorioamnionitis require immediate treatment with intravenous broad-spectrum antibiotic therapy, instead of the prophylaxis regimen.

IAP is intended to have a narrow spectrum, to reduce the risk of antibiotic resistance and unwanted side effects.

Penicillin allergy may be significant in this context. Penicillin allergy may occur in 0.7%–4% (usually a maculopapular rash), but the risk of anaphylaxis is estimated to be in the range of 4/10,000 to 4/100,000.[1] Documentation of details of any previous, immediate (within 24 hours), hypersensitivity reactions (eg, anaphylaxis, angioedema, laryngospasm, bronchospasm or urticaria) is an important part of antenatal assessment.

3. Timing of IAP for EOGBS in active labour

IAP is recommended for all women with GBS risk factors **in active/established labour, or at the commencement of intervention (eg, oxytocin induction or augmentation)**, whether or not they have ruptured membranes.

The evidence suggests that IAP may still be effective if there is likely to be at least one hour before the birth.[9-11]

It is recommended that IAP be continued until the baby is born.

4. Pre-labour caesarean section

Women with risk factors for GBS, other than those with signs of infection, and who have intact membranes and require **pre-labour** elective or emergency caesarean section **do not require** IAP for EOGBS infection.[12]

5. Pre-term labour

As preterm babies are at increased risk of GBS sepsis, IAP for GBS is recommended for all women who are in established progressive preterm labour, with or without ruptured membranes.

If preterm labour is established, continue IAP.

If preterm labour does not establish and membranes are intact, discontinue IAP.

If preterm labour is not established but there are prolonged premature ruptured membranes, consider appropriate antibiotics are recommended to prolong pregnancy (as per local DHB guidelines).[13]

6. Pre-labour rupture of membranes (ROM) at term—with no GBS risk factors

A comprehensive assessment of all women with pre-labour ROM at term, to check maternal and fetal wellbeing is recommended.

Women with signs of infection or chorioamnionitis should have immediate treatment with intravenous broad spectrum antibiotics and appropriate intervention.

Women who are well, and the fetus is healthy, with pre labour ruptured membranes and no risk factors for GBS **do not require** IAP.

- Women who go into spontaneous labour and give birth before 18 hours has elapsed since ROM **do not require** IAP.
- Women who go into spontaneous labour but do not give birth within 18 hours of rupturing their membranes have developed a risk factor for EOGBS infection and **IAP is recommended**.
- Women who do not go into spontaneous labour within 18 hours of rupturing their membranes have developed a risk factor for EOGBS infection.[5] **The offer of an induction of labour, and then for IAP** once labour is established, is recommended.
- Women with signs of infection in association with pre-labour rupture of membranes at term require careful assessment and the **immediate consideration of intravenous broad spectrum antibiotic therapy**. If vaginal birth is appropriate it is recommended that they are offered an induction of labour as soon as possible.

7. Pre-labour rupture of membranes at term—with GBS risk factors

Women with **risk factors** (see previous section for these) for EOGBS infection, who are well and have pre-labour rupture of membranes (ROM) at term, are at higher risk of having a baby affected by EOGBS infection. It is recommended that they are offered an induction of labour as soon as practicable, with IAP **at commencement of the induction**.

8. Maternal fever and suspected chorioamnionitis

Maternal fever is a special risk category which requires consideration of broad spectrum antibiotic therapy and additional monitoring, including fetal monitoring. Ruptured membranes are not necessary for the diagnosis of chorioamnionitis. Women with a fever or signs of chorioamnionitis require immediate treatment and intervention.

Clinical signs of chrioamnionitis include maternal fever (≥38oC) with ≥2 of the following:

- abdominal tenderness
- fetal tachycardia
- maternal tachycardia
- vaginal discharge
- offensive liquor

Where there are clinical signs of infection, appropriate specimens including blood cultures are required before commencing empirical broad spectrum antibiotic treatment.

Recommended antibiotic regimes for intrapartum antibiotic prophylaxis (IAP)

1. Maternal GBS risk factors with no clinical signs of infection—standard IAP[#]

Intravenous benzyl penicillin.

Initial dose **1.2g** and then **0.6g, 4 hourly** until birth.

(If iv benzyl penicillin is unavailable, amoxycillin is an acceptable alternative. **2g** initially and then **1g, 4 hourly** until birth)

Allergy to penicillin—YES *(Low risk of anaphylaxis—Women who **do not** have history of anaphylaxis, angioedema, respiratory distress or urticaria after penicillin or a cephalosporin)*

cephazolin 2g iv initially, then 1g 8 hourly until birth

Allergy to penicillin—YES *(High risk of anaphylaxis—Women who **do** have a history of anaphylaxis, angioedema, respiratory distress or urticaria after penicillin or a cephalosporin)*

vancomycin 1g iv and repeat 12 hourly until birth

(Erythromycin and clindamycin not recommended because of increasing resistance patterns)

[#]When the risk factor is established labour <37 weeks, some DHB's will use more broad spectrum antibiotics including coverage for GBS

2. Maternal GBS risk factors with clinical signs of chorioamnionitis (see above)

Broad spectrum antibiotic treatment for chorioamnionitis, including coverage for GBS, as per local DHB guidelines.

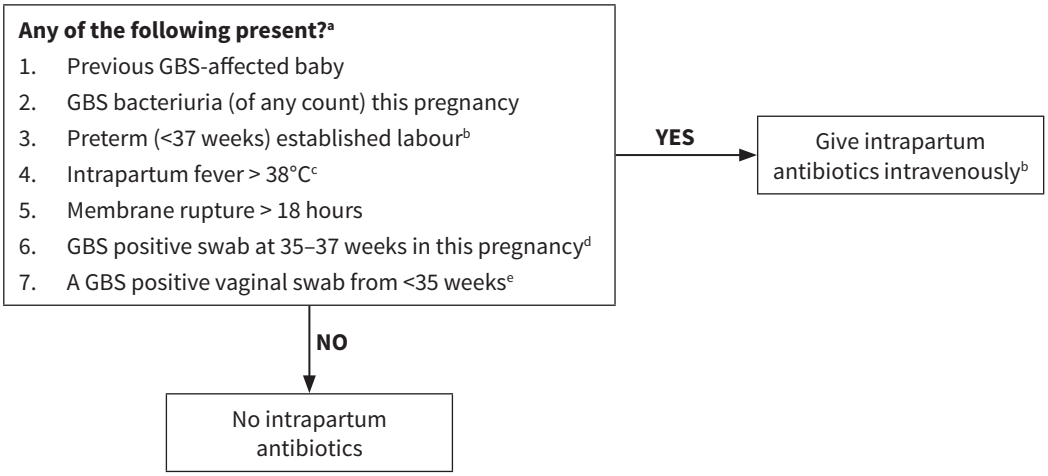
Newborn babies guidelines

- All newborn babies should be observed as outlined in the Ministry of Health Guideline *Observation of mother and baby in the immediate postnatal period: consensus statements guiding practice*.[14]
- Newborns of mothers who have risk factors, regardless of whether the mother has received intrapartum antibiotic prophylaxis (IAP), also require close observation for signs of sepsis, particularly during the first 24 hours. Women and their families need to understand this so they also know what signs to look for in their baby.
- Signs of sepsis in the newborn may be non-specific and include respiratory distress, apnoea, temperature instability, tachycardia, lethargy, poor feeding, shock or "unwell".
- If the baby is showing signs of sepsis immediate evaluation is required (at least a full blood count and blood cultures) and they should receive empiric therapy for at least 48 hours while culture results are awaited. The antibiotics are usually a penicillin and an aminoglycoside as this combination is active against common neonatal pathogens, including GBS and *E. coli*.
- When feasible a lumbar puncture should be performed on all septic newborn babies and especially when blood cultures are positive or when, because of clinical instability or other evidence of sepsis, therapy is continued beyond 48 hours since up to one-third of neonates with meningitis will have sterile blood cultures.[15]
- Maternal chorioamnionitis is associated with an increased risk of invasive disease, even if intrapartum antibiotics have been given. Some authorities recommend that all babies of women with chorioamnionitis should receive immediate evaluation and empiric antibiotic therapy. However, as the risk of an asymptomatic baby having sepsis is still very low no additional recommendation has been made.[16]

Management of asymptomatic newborns when a woman is identified as needing GBS prophylaxis in labour

- If mother **has received appropriate** intrapartum GBS prophylaxis (> 4 hours of appropriate antibiotic before delivery) the infant should be observed for at least 48 hours. This does not require admission to a neonatal unit. Some infants may be able to be considered for discharge at 24 hours after delivery with good parental understanding of the situation.
- If mother **did not receive** GBS prophylaxis at all or did not receive it for at least 4 hours prior to birth:
  - If 37 weeks gestation or more, ideally the baby needs close observation (TPR) for 24 hours in a maternity facility.
  - If < 37weeks then a full blood count, blood cultures and CRP is recommended and the baby needs close observation (TPR) for 48hours in a maternity facility. Antibiotics are not required unless other risk factors are present or as guided by the laboratory results.
  - If signs and symptoms of sepsis develop a full diagnostic evaluation is required with initiation of appropriate antibiotics—usually amoxycillin or penicillin and gentamicin + cefotaxime (if meningitis suspected).[17]

Figure 1: Risk-based group B streptococcus (GBS) strategy



[a] Except in women with intact membranes undergoing pre-labour elective caesarean section and have no fever.

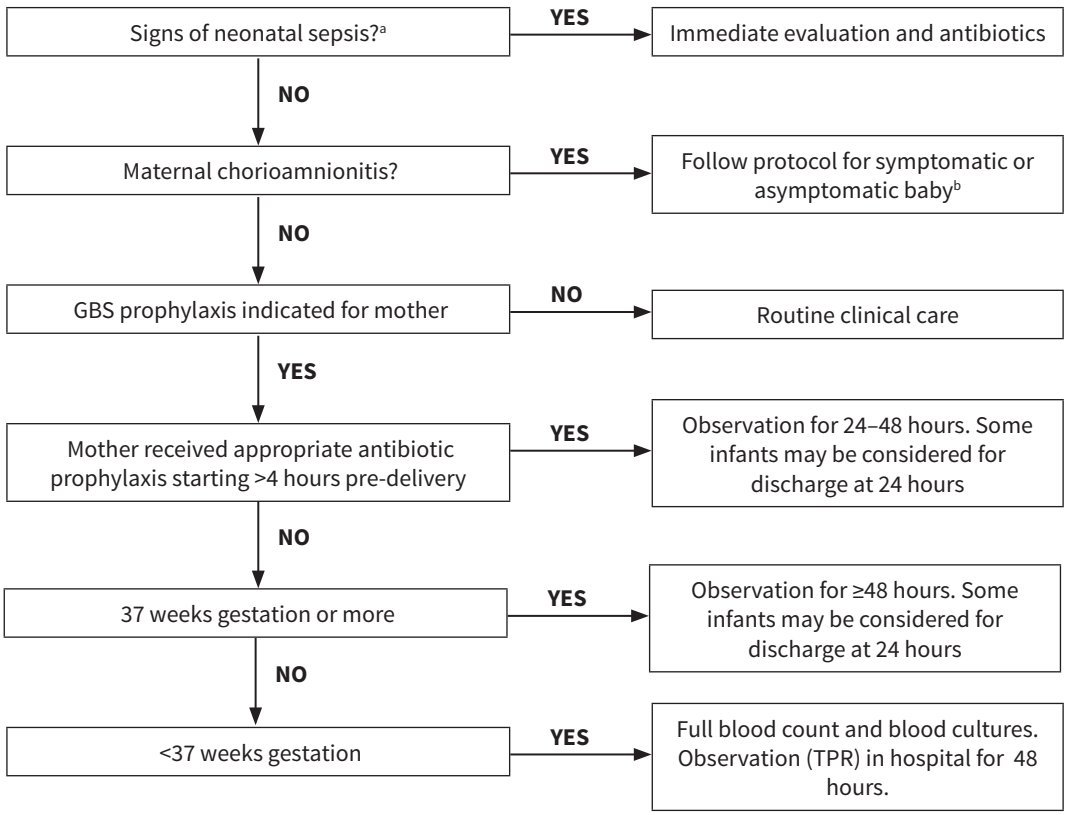
[b] Some local protocols advise more broad spectrum antibiotic regimens for preterm births.

[c] If chorioamnionitis is suspected, GBS chemoprophylaxis is insufficient and aggressive treatment with broad-spectrum antibiotics is required.

[d] A GBS screen includes a low vaginal and rectal swab and must state "GBS screen" so that the laboratory use the appropriate culture technique. If a correctly taken swab at 35–37 weeks is negative in a woman who then goes on to have preterm labour or ruptured membranes >18 hours, intrapartum antibiotics are not indicated.

[e] When there is an incidental finding of GBS on a vaginal swab from early in pregnancy the recommendation is that the swab is repeated at 35-37 weeks as above. If that has not been done at the time of labour, the woman should be considered to have a risk factor for EOGBS and IAP should be offered.

Figure 2: Management of newborn babies



[a] Signs of sepsis are often non-specific and can include tachypnoea, apnoea, fever or temperature instability, lethargy, or "unwell".

[b] Some authorities recommend that all babies of women with chorioamnionitis should receive immediate evaluation and empiric antibiotic therapy. However, as the risk of an asymptomatic baby having sepsis is still very low no additional recommendation has been made.

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Renal replacement therapy associated with lithium nephrotoxicity in New Zealand

J Elisabeth Wells, Nicholas B Cross, Ruth L Savage, Lianne Parkin, Simon Horsburgh, Ann K Richardson

ABSTRACT

AIM: To document the numbers and characteristics of New Zealand patients commencing renal replacement therapy because of end-stage kidney disease attributed to lithium treatment, and to calculate incidence rates.

METHOD: Data on such patients were provided by the Australia and New Zealand Dialysis and Transplant Registry from the start of the Registry in 1977 until 2013. Numbers of patients prescribed lithium in the community were provided by the Ministry of Health for 2009–2013; earlier years had fewer than 96% of prescriptions for lithium linked to individuals by their unique National Health Index number. Time trends were analysed by linear, logistic and Poisson regression. Incidence rates were also calculated for five-year periods.

RESULTS: Thirty-five new patients were located with 'lithium toxicity' as their primary renal disease, starting the year after 'lithium toxicity' was included in the standard list (1995). A broader search for lithium within 'other' causes and 'other' comorbidities did not yield further patients. The mean age at the start of renal replacement therapy was 61.1 years (SD 9.2). Twenty-five patients were female. For 1996 onwards, new patient numbers increased on average by 8% per year (95% CI 1 to 15%) and incidence rates increased by 7% per year (95% CI 0 to 14%), an approximate doubling per decade. Form 2007–2011, the average annual incidence per million population was 0.74 (95% CI 0.43 to 1.21) for New Zealand, similar to that reported elsewhere: 0.78 (95% CI 0.67 to 0.90) for Australia and 0.91 (95% CI 0.50 to 1.52) for southern Sweden. Prescription rates across the three countries were also similar. In New Zealand between 2009 and 2013, over 7,500 patients were prescribed lithium each year.

CONCLUSION: Dosing and monitoring of patients prescribed lithium should follow guidelines, not only to avoid future psychiatric episodes and acute toxicity but also because such adherence may reduce uncommon but serious outcomes of long-term treatment such as end-stage kidney disease.

In their 2012 review of the science and practice of lithium therapy, Mahli et al state that, "Its use in bipolar disorder is under-appreciated, particularly as it has the best evidence for prophylaxis, qualifying it perhaps as the only true mood stabilizer currently available".[1] Nonetheless, they acknowledge that in patients treated with lithium, renal function can become impaired and that even end-stage kidney disease (ESKD) can occur, although they point out that the increased occurrence of ESKD may in part be due to other risk factors associated with bipolar disorder. In 2014, a large UK retrospective cohort study of general practice patients with bipolar disorder[2] compared those ever treated with lithium with non-users and, after adjusting for age, gender, comorbidities and poly-pharmacy, found the relative hazard for ESKD for patients treated with lithium was 2.7 (estimate using validated lithium exposure). The absolute increase in risk varied by age and by time since first diagnosis (a proxy for time on lithium). The absolute increase in risk of ESKD was low at 0.15% in those under 50 years of age, but 2.3% in those over 50. The increase in risk of renal impairment was 0.95% in those under 50 and 8% in those over 50. Swedish studies[3,4] indicate that patients on renal replacement therapy whose ESKD is attributed to lithium treatment have been treated with lithium for at least a decade and have reached ESKD twenty to thirty years after lithium was started. The UK general practice study[2] had no patients followed for more

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than 20 years, suggesting that their estimates of absolute risk increases due to lithium will underestimate those for patients followed up for thirty or more years.

In Australia and New Zealand, every renal unit contributes data on all patients treated for ESKD to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) (www.anzdata.org.au/), which was set up in 1977. In April, 1995, 'lithium toxicity' (Code 019) was added to the standard list of options for primary renal disease.[5] Prior to that, lithium toxicity could have been listed under the 'other' category for primary renal disease. In addition, 'lithium toxicity' could at any time have been recorded under 'other' comorbidity.

Roxanas et al have reported on all Australian patients commencing renal replacement therapy (dialysis or transplant) whose ESKD was attributed to treatment with lithium.[6] They found a total of 187 new patients with incidence rates increasing steadily over five-year periods, from 0.02 per million population per year in 1987–1991 to 0.78 in 2007–2011.

There have been no similar papers reporting the New Zealand experience. This paper reports numbers, characteristics, incidence and trends over time for New Zealand.

Method

A de-identified data extract of new patients commencing renal replacement therapy in New Zealand as a result of lithium treatment was provided by The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). An initial search was carried out only for those with lithium toxicity (code 019) listed under "Primary Renal Disease" (this code was added in April, 1995). A second broader search looked for mention of lithium under 'other' disorders and 'other' comorbidity and covered the whole period since the start of the Registry in 1977 until 2013, the last year for which data collection was complete and checked. ANZDATA also provided annual estimates of the total New Zealand population so that crude incidence rates could be calculated.

The Ministry of Health (personal communication) provided annual numbers of patients who had Pharmaceutical Management Agency (PHARMAC)-subsidised, community-dispensed lithium for the period 2009–2013. In this period the proportion of lithium dispensing records which included a unique National Health Index (NHI) number increased from 96% to 98% which meant that the number of individuals dispensed lithium in the community could be ascertained with a high degree of accuracy. The NHI is a unique patient identifier number assigned to all people accessing universally available health care in New Zealand. Note that all available forms of lithium prescribed are eligible for PHARMAC subsidy.

Analyses were carried out in SAS/STAT 12.1 (www.sas.com), apart from calculation of confidence intervals for some proportions for which OpenEPI (http://www.openepi.com/Proportion/Proportion.htm) was used with mid-P exact values. Descriptive statistics were calculated and some 95% confidence intervals. All p values were two-tailed. Poisson regression was used to investigate trends over time with the number of new patients in each year as the dependent variable and the year as the predictor. For analysis of incidence rates the population for each year was added as an offset. Trends over time were also investigated using linear regression with the age of each new patient as the dependent variable and using logistic regression with sex (female) as the dependent variable. Crude incidence rates were calculated annually and also averaged over five years by using the number of new patients over that period divided by the middle year population (the population increase was approximately linear). Given the small numbers of new patients within a five year period, age-standardised incidences were not calculated.

Results

Thirty-five new patients were found with lithium toxicity as the Primary Renal Disease. The broader search including 'other' disorders and 'other' comorbidity did not yield any additional patients. Initial treatment for 20 of these patients was Continuous Ambulatory Peritoneal Dialysis (CAPD), Hospital Haemodialysis (HD) for 12, and three patients received a pre-emptive transplant.

The mean age at the start of renal replacement therapy was 61.1 years (SD = 9.2) with the median at 63 (IQR 55-68). The number under 65 was 19 (54%) with a further four aged 65. Twenty-five patients were female: 71% (95% CI 55 to 84). While significantly different from a 50/50 distribution (p=.01) the New Zealand sex distribution did not differ significantly (p=.18) from that for Australian incident cases with lithium toxicity (111/187, 59% female, 95% CI 52 to 66%, p=.01 for comparison with 50/50).[6] The mean age for New Zealand female patients was 62.4 (SD 9.1) and 57.8 (SD 9.2) for males, a non-significant difference of 4.6 years (95% CI -2.3 to 11.5; p=.19). Age at commencement of renal replacement therapy did not increase over time (slope per year of 0.22, SE=0.34, p=.45) nor did the proportion of females change (slope per year of log odds of -0.06, SE=0.09, p=.47).

Late referral, being referred to a renal unit less than three months before the start of renal replacement therapy, occurred only early in the series. The Registry records 'racial origin': 33 patients were 'caucasoid' and two were Māori. Only three patients were born outside New Zealand, all in the UK.

Including only the period 1996-2013, for which lithium toxicity was one of the listed options for Primary Renal Disease, numbers of new patients, which varied from 0-4 per year, increased on average by 8% per year (95% CI 1 to 15%, p=.03). The crude incidence rate per million population in New Zealand, which took account of population changes, increased by 7% per year (95% CI 0 to 14%, p=.057). Over a decade this corresponded to approximately a doubling of the numbers of new patients (ratio=2.11, 95% CI 1.08 to 4.12) and just under that for incidence (ratio=1.90, 95% CI 0.97 to 3.71). Over the whole period of the Registry since 1977 the increase was highly significant (p<.0001) for new patient numbers and for the incidence rate with a four-fold increase per decade for new patient numbers and 3.6 fold increase for incidence. However the absence of any lithium toxicity cases before 1996 may be because lithium toxicity was not listed under Primary Renal Disease, not because there were no such patients. From the data available it is not possible to distinguish these explanations, although the absence of additional patients from the broader search including 'other' disorders and 'other' comorbidity does suggest that there may not have been any missed from earlier years. Nonetheless the clinical awareness of lithium nephrotoxicity may have been low historically. Another possible factor is that there appear to have been changes over time in the ages accepted for Renal Replacement Therapy, regardless of Primary Renal Disease. In New Zealand no-one over 64 years was accepted until 1975, no-one over 74 years was accepted until 1987 and no-one over 84 years was accepted until 1997.[7] Numbers for older age groups have been more stable from 2007–2012.[8]

Incidence rates in New Zealand can be compared with those for Australia,[6] and two regions in Sweden,[3,4] although for the Swedish studies it is necessary to infer incidence from prevalence by comparing the numbers prevalent at the two time points plus any who died in between those times. Because of changes in incidence rates over time in Australia and in New Zealand it is important to ensure comparable time periods are used. For Australia over the period 2007-2011 the average annual incidence per million population was 0.78 (95% CI 0.67 to 0.90) and for New Zealand it was 0.74 (95% CI 0.43 to 1.21). For Sweden the estimate was 0.91 (95% CI 0.50 to 1.52) for the period 31/03/2005 to 1/12/2010. These are all very similar although rather imprecise for New Zealand and Sweden because of the small numbers of cases (16 and 14 respectively). The proportion of the population currently prescribed lithium also is not markedly different in the three countries. For New Zealand the numbers of patients prescribed lithium declined from 7,913 in 2009 to 7,641 in 2013 (personal communication, Ministry of Health), which corresponds to rates per million population of 1,846 down to 1,727, all under 0.2%. In 2011 in Australia the rate per million was calculated to be 1,150.[9] In southern Sweden the rate was 1,2554 in 2005 and 1,3593 in 2010. Given the time from the start of lithium therapy until ESKD develops historical prescription data would be of interest, but is not available.

Discussion

This paper supplements a 2010 New Zealand Medsafe (Ministry of Health) prescriber alert about the renal dangers associated with long-term lithium use.[10] That alert was based on voluntary reporting to the Centre for Adverse Reactions Monitoring (CARM) of nine cases of serious renal disease attributed to lithium, whether or not patients had commenced renal replacement therapy. In contrast this paper is based on all New Zealand patients who commenced renal replacement therapy with lithium toxicity listed as the Primary Renal Disease. A total of 35 new cases from 1996 to 2013 is not a large number. Nonetheless it is important to remember the burden each case imposes on the patient, family and on society. Just over half the patients were under 65 at the start of dialysis or the time of transplantation so that the tiredness and lack of energy which characterize very poor kidney function will have interfered with patients' ability to work, as well as other aspects of their function over the years before as well as after renal replacement therapy was necessary. Furthermore dialysis is time-consuming and, particularly for home dialysis, dedication is required to carry it out correctly. The costs to society are not just reduction in employment. The annual cost to the health system of each dialysis patient is $30,000 to $60,000.[11]

The increase over time in numbers of new patients (incident patients) and in incidence rates are similar to those reported for Australia.[6] The increase may result from changes in lithium prescribing patterns since the 1970s such as the numbers of patients prescribed, the duration of treatment, the doses used and the monitoring regimes for both lithium levels and for kidney function. There also appears to have been increasing willingness over time to provide renal replacement therapy for older patients. An Australian study comparing deaths due to renal failure in 2003-2007 with ANZDATA enrolment indicated that about half of those who died of renal failure had never had renal replacement therapy.[12] Of this untreated half, 20% were under 70 years of age. The likelihood of renal replacement was about 90% up to age 60 but declined sharply at older ages down to 4% for those aged 85 years and above.[13]

Epidemiological studies across a number of countries including New Zealand have found similar rates of bipolar disorder for males and females, in contrast to the higher female rates for depression,[14-18] although a more recent cross-national study found that the male:female ratio depended on the type of bipolar disorder (BPI/BPII/subthreshold).[19] Nonetheless a large UK general practice study[2] found approximately a 60:40 female:male ratio for patients diagnosed with bipolar disorder regardless of treatment, and a 60:40 female:male ratio was also found among patients on lithium in Sweden.[3] These ratios are close to those found among patients starting renal replacement therapy as a consequence of lithium treatment in New Zealand and also in Australia[6] and in Sweden.[20]

The strength of this study is that it contains complete national data from New Zealand. One weakness, however, is that the diagnosis of lithium toxicity is a clinical one with no pre-specified criteria and no means of checking this diagnosis. Moreover there is no information on the course of lithium treatment and whether or not there had been any episodes of acute lithium toxicity. This study is also limited for an understanding of the risk of ESKD following lithium treatment in that not all patients with ESKD do start renal replacement therapy.

Lithium is widely used to treat patients with bipolar disorder and there is much known about its efficacy, particularly for prophylaxis.[1,21] In contrast, less is known about how to prevent renal damage from long-term treatment with lithium.[1,2] Some Swedish psychiatrists are optimistic that the treatment and monitoring regime in place in Sweden for lithium since the early 1980s has been effective in preventing ESKD.[20] None of the patients with ESKD that they located through their registry of patients on renal replacement therapy had commenced lithium treatment after 1980, although there were other renal replacement patients who had started lithium earlier. They do admit, however, that the time period covered and the size of the population studied

(population 2.8 million) may have been inadequate. Furthermore there may have been patients who did not go on to renal replacement therapy even though this is unusual for patients with ESKD in Sweden.

Stopping lithium treatment is one option if kidney function begins to decline at more than the usual age-related rate: eGFR declines 1 mL/min/1.73m^2 per year after age 40. Such a decision requires careful consideration of how well the patient has been on lithium, potential suicide risk, and experience with other mood stabilisers. Nonetheless it is not known at what point stopping lithium prevents or at least slows the progression towards ESKD. Some patients who have stopped lithium have gone on to ESKD.[3,4,23] Roxanas et al.[6] recommend considering stopping lithium and switching to another mood stabiliser if two successive test results indicate declining renal function or if eGFR is < 45mL/min/1.73m^2. Sabiosky[24] and Roxanas[25] recommend referral to a nephrologist as soon as kidney function is of concern. This will prevent late referrals to renal units and provides patients with more time to adjust to the possible future need for renal replacement therapy. However it is not clear that early referral can markedly influence the continuing decline in renal function.

Another issue is the extent of variation in creatinine from blood test to blood test,[9] which can make it difficult to ascertain trends in renal function. Psychiatrists and clinicians already stress to patients on lithium the need to avoid marked dehydration to prevent episodes of acute lithium toxicity, which may harm renal function. Nonetheless mild dehydration may often occur in these patients as duration of lithium treatment is associated with loss of renal concentrating ability.[22,26] Therefore another practical recommendation is to instruct patients to make sure they are well hydrated before they present for blood tests, in order to remove one source of fluctuation in measurement of kidney function.

This paper documents the numbers of patients in New Zealand who have commenced renal replacement therapy following ESKD attributed to lithium treatment. Because of the decades required from the start of treatment to ESKD, the consequences of modern approaches to treatment with lithium will not be seen for many years. There are a number of guidelines about dose and monitoring[1,20,27] to avoid or minimise acute toxicity and, while these are mainly based on consensus decisions, they represent the best advice currently available. Although the influence of dose and episodes of acute toxicity on the development of end-stage renal disease is not known it would be wise for these guidelines to be followed and future studies should elucidate the long term outcomes of their use. Little is known in New Zealand about current dosing, duration of treatment, and monitoring. One study based in the Canterbury District Health Board in 2009/2010[28] showed that the 2006 UK National Institute for Health and Clinical Excellence (NICE) recommendations for lithium levels and monitoring were often not met. This is of concern given that over 7,500 patients are treated with lithium annually in New Zealand.

Competing interests: Nil

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Is the statement that if a person is off work for 70 days the chance of ever getting back to work is 35% justified?

Gordon Purdie

ABSTRACT

The Australasian Faculty of Occupational and Environmental Medicine released a position statement which included statements about the chance of ever getting back to work if a person is off work for 20, 45 and 70 days. These statements are being repeated by government and non-government agencies in New Zealand and Australia. They have been presented with the intent to influence public policy. They are presented to general practitioners in the context of certifying people as unfit for work. The statements are based on an incorrect interpretation of the referenced study, are not justified and should be corrected.

The 2010 Australasian Faculty of Occupational and Environmental Medicine (AFOEM) position statement, *Realising the Health Benefits of Work*[1] contains the following statements:

Work absence tends to perpetuate itself: that is, the longer someone is off work, the less likely they become ever to return.

If the person is off work for:

- 20 days the chance of ever getting back to work is 70%;
- 45 days the chance of ever getting back to work is 50%; and
- 70 days the chance of ever getting back to work is 35%.

The statements are referenced to a study for the Victorian WorkCover Authority by Johnson and Fry published in 2002.[2] However, the reference does not contain the statements or results that could support them.

The statements are being repeated by New Zealand[3] and Australian[4,5] government agencies, in the explanatory memorandum for a bill to amend the Safety, Rehabilitation and Compensation Act in Australia,[6] non-government organisations[7] and the commercial sector, including insurance.[8] They were presented to the New Zealand Government's Welfare Working Group Forum in the context of influencing government policy.[3] The statements are frequently referenced to Johnson and Fry.[2] They have appeared in international literature,[9] also referenced to Johnson and Fry.[2]

Misinterpretation of survival curves

The conclusions appear to be based on the misinterpretation of survival curves. A presentation by Dr Robin Chase (President AFOEM) and Dr Mary Wyatt (Chair Policy and Advocacy Committee AFOEM, Co-chair and Australian lead of the working group which contributing substantially to the position statement) shows the statements associated with a figure that looks like figure 5.3 (Survivor Functions: Males, Timeliness) from the position statement's referenced study.[10] A webpage by Dr Mary Wyatt shows what appears to be same figure and states, "This graph shows that the likelihood of return to work goes down the longer the person is off work", together with the same statements about the chance of ever getting back to work, as the statements quoted above from the position statement.[11]

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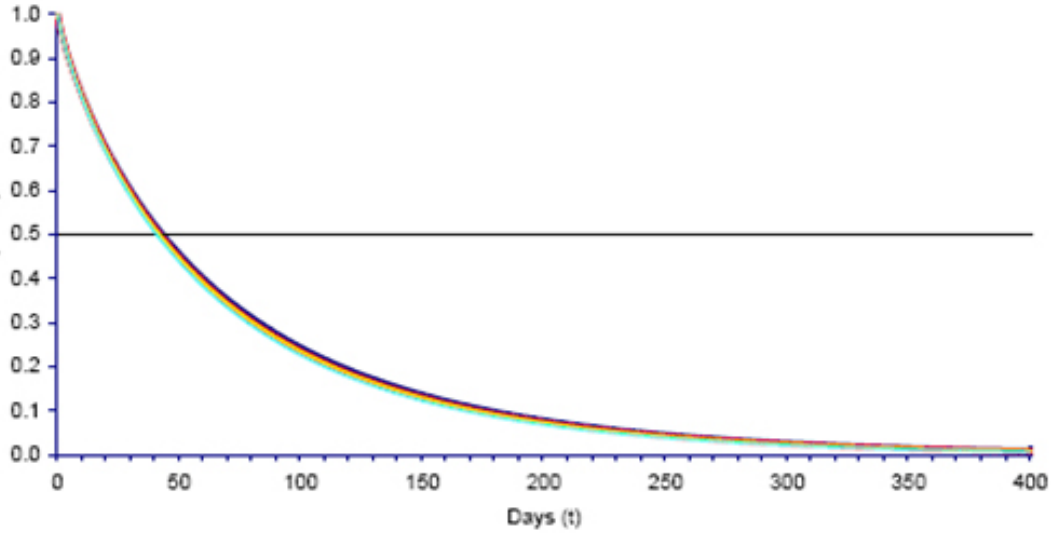
Figure 1: Graph from Chase and Wyatt presentation[10]



All of the other occurrences of these statements appear to postdate the AFOEM Position Statement, which seems likely to be their source.

Figure 1 is the graph from Chase and Wyatt presentation[10] and appears the same as the graph on Wyatt's web page.[11] What the graph shows is that if the person is off work for 20, 45 or 70 days, the chance of ever getting back to work is close to 100%. The graph is the fitted survival distribution from a Weibull model which, as time becomes infinite, has this property. The graph does not show "the longer someone is off work, the less likely they become ever to return".

In figure 5.3 of the Johnson and Fry publication, the vertical axis of the graph was labelled Pr(T>=t).[2] This is the probability that the time to the event is greater than or equal to the time on the horizontal axis. The event is the cessation of weekly payments, treated synonymously as return to work. Time is the number of days off work, after an initial 10 days. The data comes from the Victorian WorkCover Authority's administrative database of injured workers. Only those off work for more than 10 days are included, 100% of those have a time to return to work greater than 10 days, the Pr(T>=t) = 1.0 (the vertical axis) at 0 days. About 70% have a time to return to work greater than 20 days, about 50% greater than 45 days, and about 35% greater than 70 days. Only about one or two percent have, from the model fitted, a time to return to work greater than one year.

The curves in the figure are for males with sets of characteristics, rather than an overall curve for all males. Males with different characteristics—and females—will have different curves. Those seriously injured have, not surprisingly, much lower probabilities of having returned to work within a year (see figure 5.5 in Johnson and Fry[2]). The figures were presented in the publication to illustrate the differences in probabilities under a range of circumstances and are not suitable for estimating the overall chance of ever getting back to work.

The graph does show that the longer someone is off work the less likely they are to return in the next time period; however, this aspect of the shape of the curve is hard to see.

When I read the statements I thought them unlikely to be true, so I looked for their source, the position statement,[1] and checked the referenced study,[2] which shows them to be without foundation. Presumably the authors and repeaters have found them believable, for example Dr David Bratt, Principal Health Advisor, Ministry of Social Development, New Zealand, said at the Welfare Working Group Forum, that the figures come from Australia, but that he knows that figures would show exactly the same thing happens here.[12]

The statements have been presented in non-injury contexts, for example being out of work[12] or mental illness.[7]

The statements use

The statements are being used to support statements like: "Urgent action is required if a person is not back at work within a matter of weeks. If a person is not back at work within three weeks urgent attention is needed"[11] even though the data is for time after an initial 10 days off work.

The incorrect statements about the chance of ever getting back to work are being presented to general practitioners (GPs) continuing medical education conferences in the context certifying people as unfit for work, together with statements like the 'benefit' is "an addictive debilitating drug with significant adverse effects to both the patient and their family (whānau)".[13] They are being presented to GPs in the context of assisting patients to safely stay at work or return to work early.[4] These appear to be encouraging GPs to assess injured and unwell patients as having capacity for work and not issuing medical certificates for work incapacity. This could result in the cessation of welfare benefits or injury compensation. When these patients lack the capacity to work, they could experience increased financial hardship. For example, people might move from injury compensation to an unemployment benefit, and those without benefit entitlements to no income. There are also consequential beneficiaries of these income shifts. For example, reductions in government expenditure have been associated with reductions in taxation. Reductions in injury compensation for work-related injuries could result in reductions of employer levies/premiums for workers' compensation and consequential increases in dividends to the owners of businesses.

The statements have also been presented with the intent to influence public policy.[3,6,14]

Others have critically noticed the statements—describing them as surprising and most ludicrous—noting they are claiming that time off work causes time off work.[15] They point out that association is not causation, but did not note the statement's erroneous nature.

Not only are the statements an incorrect interpretation of a graph, the data in the graphs are also being generalised to all persons off work, whereas the graph was for a subset of males who have had more than 10 days off work after an injury. The data are censored at 520 days, and hence extrapolation beyond one year five months to ever getting back to work would be unlikely to be reasonable. The data came from 1993–1998 and due to changing circumstances may not be applicable to inform today's policies.

Conclusion

The statement that, if a person is off work for 70 days, the chance of ever getting back to work is 35%, is not justified by the study the position statement references. The statements appear to be based on an incorrect interpretation of a graph in the referenced study.

A reasonable summary of the graph would be that after more than two weeks off work due to an injury, most people return to work within a year. However, even that summary only applies to males with certain sets of characteristics, at a certain time.

It is not known what effect the statements are having, but they are based on an incorrect interpretation of the referenced study and should be corrected.

Competing interests: Nil

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Potential new regulatory options for e-cigarettes in New Zealand

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ABSTRACT

While e-cigarette usage has grown rapidly in New Zealand and around the world, the scientific evidence base regarding the net benefits and risks of these types of products at the population level remains uncertain. The health-based policy experience is also minimal. Here, we analyse plausible future regulatory options for e-cigarettes that the New Zealand Government could explore, and that further research could help clarify. These options include: (1) a full free market (an option we doubt is desirable for multiple reasons); (2) controlled increased access through: (a) pharmacy only, (b) pharmacy only plus sales by prescription/ to licensed vapers; (c) additional controls through non-profit supply/distribution (eg, public hospital pharmacies); (3) increased restrictions compared with current (eg, adopting a complete ban on self-imports and use). In addition, we consider mechanisms to improve product quality and safety, and argue that policy makers should take great care when regulating e-cigarettes, given the scientific uncertainty and the role of commercial vested interests.

Globally, the market for e-cigarettes, or electronic nicotine delivery systems (ENDS), is highly dynamic and rapidly evolving. There are numerous different product types,[1] including non-electronic forms, and many of the new types look highly dissimilar to smoked cigarettes. However, in this article, for simplicity, we use the most familiar term: 'e-cigarettes'. Alongside dedicated independent producers of e-cigarettes, the tobacco industry has also been entering the market with its own heavily promoted e-cigarette products. Given the evolving situation, we aimed in this Viewpoint to explore a range of regulatory options that the New Zealand Government could consider further to ensure that e-cigarettes make a positive contribution to the achievement of the smokefree nation 2025 goal.

The current New Zealand situation

The current status of e-cigarettes in New Zealand parallels Australia and Canada.[2] That is, such products cannot be legally sold if they contain nicotine unless they meet regulatory standards for achieving a therapeutic purpose: ie, as a pharmaceutical-grade smoking cessation product as per Medsafe requirements.[3] Nevertheless, e-cigarettes with nicotine and nicotine-containing 'e-liquid' can be legally imported for personal use in New Zealand. Shops can sell the e-cigarette devices and e-liquids not containing nicotine, but some may have been selling e-liquids containing nicotine as well, albeit illegally.

At present, the extent of imports is unknown. Yet, the level of use by New Zealand youth suggests a considerable volume, with growth from 7% to 20% in ever-use of 'electronic cigarettes' during the 2012–14 period.[4] Among adult New Zealand smokers in 2013, e-cigarette usage in the last two weeks ranged from 8% (in non-quit attempters) to 15% (in serious quitters).[5] For 2014 data, the 'current use' amongst adults was reported at 0.8% overall and 0.9% in Māori.[6] Increasingly, there are advertisements for e-cigarettes in New Zealand (eg, the display of posters in shop windows, transit advertising, New Zealand-based websites, and a radio campaign by NZVapor.com in May 2015), some of which have features likely to encourage experimentation among youth and non-smokers.[7] Strong views in favour of liberalising

access to e-cigarettes are apparent in public responses to a blog post[8] detailing potential new options around regulating e-cigarettes in New Zealand (in a related forerunner piece to this Viewpoint article).

Potential benefits and harms of e-cigarettes

The published scientific literature on e-cigarettes/ENDS is now large and growing rapidly. For example, we identified 128 review articles in PubMed when searching for relevant terms ('review' and 'e-cigarette'/'electronic cigarette' in May 2015), and multiple systematic reviews exist (eg, six since January, 2014[9-14]). Recently, the United States Preventive Services Task Force concluded that there are insufficient data on the effectiveness of electronic cigarettes to determine whether the devices can help smokers quit.[15] The literature may also be influenced by authors with a 'conflict of interest' eg, one systematic review reported conflicts of interest in 34% of 76 included studies.[10] However, to briefly summarise this large literature, it is probably reasonable to say there is no scientific consensus on how the total potential benefits of e-cigarette availability compare to the total potential harms in the longer term.

A potential benefit of e-cigarettes is that they could offer smokers another therapeutic option to help them quit smoking, and may thus increase quit rates at a population level. E-cigarettes might be particularly important for smokers who have tried existing therapies without success. They also may be an appealing method that prompts smokers who have not tried to quit previously to do so. But, it is not clearly known how effective this approach to quitting is and the extent to which those who quit remain addicted to e-cigarettes (eg, high nicotine exposure from e-cigarettes may prevent 'nicotine cessation'). Another potential benefit of e-cigarettes is that they may provide a possible substitute source of nicotine with much lower adverse health effects among those who cannot, or do not wish to, end their nicotine dependency. Nevertheless, the long-term safety of using e-cigarettes is not established and there are potential downsides to long-term dependency on them (eg, the financial costs, stigma of being 'drug dependent', and users having to go outside of any 'vaping-free zones' etc). Even so, given that the health impacts on users are likely to be much less than for tobacco cigarettes, for many users long-term dependency on e-cigarettes might not amount to being that different from the inconvenience of caffeine dependency.

E-cigarettes could also have important adverse effects, including reducing quit rates among smokers and increasing smoking uptake among youth. Examples of how e-cigarettes might potentially reduce quitting rates by smokers, or lead them to relapse, include: (i) the ability to use e-cigarettes to cope with withdrawal symptoms in smokefree environments might remove the impact of such environments to motivate people to quit smoking (and thus result in long term 'dual use'); (ii) smokers may try to quit unassisted using e-cigarettes, rather than seeking support from quitlines or other cessation services, resulting in reduced quit success; or (iii) seeing people using e-cigarettes may provoke urges to smoke in smokers, resulting in increased smoking or relapse among ex-smokers.[16] Furthermore, the novelty of e-cigarettes may be attractive to youth and to curious non-smoking adults. Thus e-cigarettes may potentially form a gateway to (or 'back to' for ex-smokers) tobacco smoking, or could result in new nicotine addiction that would not otherwise have occurred, particularly among youth and young adults. In addition, the use of e-cigarettes (especially those that are 'cigarette-like' in appearance) could potentially 'renormalise' smoking behaviour in general. There are also concerns about nuisance and potential health impacts from 'second-hand' exposure to the aerosol from e-cigarettes for non-users. Less directly, there is also the risk that discussions about the regulation of e-cigarettes may give the tobacco industry a formal place at the policy table where they could do more to undermine tobacco control policy more generally.

Plausible regulatory options for New Zealand

In the face of the issues and uncertainties around the net benefits and harms of

Table 1: A list of plausible options for changing the regulation around nicotine-containing e-cigarettes in New Zealand.

Policy goal/s		Direction of policy (restrain/liberalise)
1	To increase access to e-cigarettes (full free market).	Liberalise fully
2a	To increase access to e-cigarettes as a quitting aid or long-term nicotine maintenance product in those who cannot quit nicotine eg, pharmacy-only sales.	Liberalise—but still controlled
2b	As above for pharmacy-only sales, but with tighter access requirements (eg, 'licensed vapers' or as 'prescribed' by a registered health professional).	Liberalise—but tighter controls than above
2c	As above but for very tight control on e-cigarettes to minimise profit-driven risks eg, only public hospital pharmacy as the outlet.	Liberalise—but even tighter controls than above
3	Fully minimise any risk of harm from e-cigarettes to everyone (ie, assuming no net benefit from e-cigarettes) via a complete ban on importation and use.	Increased restraint (vs existing New Zealand law)

e-cigarettes at a population level, we provide a list of plausible regulatory options for nicotine-containing e-cigarettes in New Zealand in Table 1 and follow this with more detailed comments. To inform this list, we reviewed recent literature on regulatory options for e-cigarettes, including an expert survey,[17] an ethical analysis,[18] a New Zealand-specific policy analysis,[19] and other international work.[1,2,20-22] Nevertheless, much of the international literature is of limited value when considering e-cigarettes in the context of a country: (i) which is an island nation with strong border controls; (ii) in which nicotine-containing e-cigarettes cannot currently be legally sold (in contrast to many other jurisdictions considering regulatory frameworks where such e-cigarettes are already widely available); and (iii) where the Government has a smokefree nation goal for 2025.[23]

Option 1: Policy goal of maximising access to e-cigarettes (full free market)

This option would involve a change in existing New Zealand law to allow e-cigarettes with nicotine to be made widely available with no regulatory oversight (eg, towards the situation as currently largely exists in the US and various European countries). However, this seems to be an undesirable option in the New Zealand setting at present, for the following reasons:

- It seems fundamentally problematic for society to allow a highly addictive drug (such as nicotine) to be sold in unregulated environments without health professional advice and support for quitting. The existence of widespread tobacco outlets (dairies, supermarkets and petrol stations) can be considered a historical anomaly in New Zealand that needs urgently to be fixed by other measures, such as licencing and a phase-down process for retail outlets.[24]
- Existing tobacco outlets (especially dairies) appear to chronically break the law around tobacco sales (eg, 64% breaching regulations in one survey and extensive evidence of sales to underage youth[25-28]). The current New Zealand regulatory machinery seems to take a relatively low key approach to enforcement around tobacco sales to youth and progress on developing a retail licensing system has been extremely slow. In contrast, a more controlled potential outlet (such as pharmacies) are probably much less likely to break the law and monitoring compliance would be easier, given the smaller numbers of pharmacies compared to other outlets (for example, there are around 980 pharmacies compared to an estimated 5,000 plus tobacco retail outlets[29]).
- In the wake of the recent sale of synthetic cannabis and 'party pills' from outlets on New Zealand high streets (albeit now discontinued in 2014), it seems likely that some policy-makers could be risk averse around any further liberalisation of 'drugs' (which is how e-cigarettes may be perceived if sold in outlets such as dairies or more specialist stores selling recreational drug paraphernalia).

Option 2a: Policy goal of increasing access to e-cigarettes as a quitting aid or long-term nicotine maintenance product in those who cannot quit nicotine (eg, pharmacy-only sales)

This option would permit nicotine-containing e-cigarettes to be sold, but in a relatively controlled and medicalised way. For example, this product could be sold only by health-focused outlets such as pharmacies, alongside pharmaceutical-grade smoking cessation products (such as nicotine replacement therapy) and only for those e-cigarette products that met specified quality and marketing standards (Table 2). This option might require an amendment to the Smoke-free Environments (SFE) Act to permit sales and to remove e-cigarettes from Medsafe jurisdiction (as per fluoride when added to drinking water which is now specifically defined as not being a medicine and is therefore now clearly not under Medsafe jurisdiction[30]). At the same time the new SFE Act amendment could include tight marketing restrictions and restrictions on sales to youth for e-cigarettes; eg, under 18 years (Table 2). If careful monitoring showed this approach did not advance public health and the smokefree nation 2025 goal, then it would be politically much easier to discontinue pharmacy sales than to manage product withdrawals from a wider variety of retailers as in Option 1 (given that pharmacists are health professionals with specified ethical standards). Nevertheless, for some policy-makers this option might pose risks of over-liberal uptake of e-cigarettes relative to Option 2b, below.

Option 2b: Policy goal as above but with tighter access requirements (eg, 'licensed vapers' or as 'prescribed' by a registered health professional)

The goal of this option would be as per Option 2a above, except with a requirement for a vaper's licence[22] or as 'prescribed' by a registered health professional or registered QuitCard provider. This would better target e-cigarette usage to those wanting to use them to help quit tobacco or to those who have failed to quit after multiple attempts and need to use e-cigarettes as a long-term nicotine maintenance product. Aspects of the proposed 'smokers' licence' system[31] could also be used for vapers. Pharmacists selling e-cigarettes could also be required to deliver brief cessation advice at the same time as selling e-cigarettes; this approach could help to more fully medicalise e-cigarettes (as a quitting aid or maintenance treatment for chronic nicotine dependency). Tighter controls on marketing could mean that all marketing is banned, or limited to government 'approved' informational brochures attached to each package of e-cigarette products sold (Table 2).

Option 2c: Policy goal to have very tight control on e-cigarettes to minimise profit-driven risks

By excluding any profit motive from the retail sector, there may be less chance of any commercial interest undermining the intent of any new law on e-cigarettes (eg, via viral marketing on the internet). To minimise this risk, a government purchaser and distributor (eg, Pharmac or a new organisation) could purchase e-cigarette products internationally and then supply them through government-owned settings (eg, pharmacies in public hospitals). However, the latter approach would require changes as these pharmacies are not currently set up for retailing to the public. Internet sales and self-imports could also be banned with this option. The brand/s of e-cigarettes supplied could be of the highest quality currently on the market and could meet all other quality criteria (Table 2).

Option 3: Policy goal to fully minimise any risk of harm from e-cigarettes via a complete ban on importation and use

This option would not only involve maintaining current New Zealand restrictions that ban the sales of e-cigarettes containing nicotine, but it could also ban the self-importation of e-cigarettes and their use in public places. Furthermore, it could potentially enhance enforcement around illegal sales of nicotine cartridges and e-liquid (eg, increased monitoring and penalties). This option might be favoured by those who suspect that

Table 2: Supplementary policy measures around non-user protection, product quality and pricing if nicotine-containing e-cigarettes were to become legally available in New Zealand.

Policy goal/s	Brief details and comments
Reducing potential harm and nuisance to others from vaping (and to limit normalisation of vaping)	Amendments to the SFE Act could ensure that there is complete consistency with restrictions on vaping ie, making it illegal to use e-cigarettes in any designated smokefree environment. This measure may reduce public confusion between vaping and smoking, reduce normalisation of vaping, and avoid nuisance impacts on those who simply dislike exposure to vaped aerosol. Such an amendment could provide an opportunity for a wider upgrade of the SFE Act, to build on the success of the ban on smoking in school grounds.[34] For example, it could include a nationwide ban on smoking and vaping: in cars with children, within 10m of children's playground equipment, in all stadiums, and on all sports fields. In contrast, the use of a nicotine-containing metered dose inhaler might still be permitted in such environments given that this would appear like a typical therapeutic inhaler in shape and function, and the aerosol delivered would be unlikely to disperse beyond the user to affect others.
Increased product quality	Quality controls (possibly under a revised SFE Act) to maximise effectiveness as a quitting aid/substitute (in terms of nicotine levels) and to minimise any health risks could ensure that there were no or minimal contaminants in those e-cigarettes allowed to be sold. Indeed, there are already brands that use pharmaceutical-grade manufacturing processes for their e-liquid with good manufacturing practices (GMP) certification. Furthermore, new regulations under the SFE Act could allow for the quality standards to be gradually tightened over time (eg, annually). Some informative New Zealand work on e-cigarette product testing has already been reported by Laugesen.[35] Such an incremental approach to quality improvement would probably improve access to e-cigarettes in the short-term, relative to the far more demanding options of manufacturers trying to: (i) meet the existing regulatory requirements under the Medicines Act as outlined by Medsafe;[3] or (ii) meet the requirements under the new Psychoactive Substances Act (as suggested elsewhere[19]) but probably only after nicotine was included into the scope of this relatively new and untested legislation. Nevertheless, this 'quality upgrade' option may not be a particularly feasible policy option in the sense that it would require the development and annual review of quite complex quality standards, testing of products and an enforcement regime. It is not clear if the New Zealand Government would put adequate resourcing into any of these measures.
Ensuring quality issues around legal sales	Quality criteria for legal sales of e-cigarettes could include use of age limits (18+ years, as is currently for tobacco in New Zealand), and the use of child-resistant packaging (as per New York State law[2]). Also, all manufacturers could be required to have warning labels (eg, that quitting smoking completely and then quitting e-cigarettes is best for health; that nicotine is highly addictive), to give information on levels of all ingredients, and to not make unproven health claims. No cross-branding practices could be allowed (eg, a ban on the use of tobacco industry logos on e-cigarettes[20]) and marketing could be tightly regulated, including a possible requirement for standardised (plain) packaging. We note the particular need for care with marketing controls given evidence of e-cigarette advertising that appeals to young people and glamorises use; and the experience that alcohol advertising in New Zealand has become very difficult to control again once it became liberalised in the late 1980s. We also note that optimal regulation around approved designs of e-cigarettes could be very difficult to achieve, as there are complex potential advantages and disadvantages of different products: eg, refillable 'tank' devices have the potential advantage of lowering costs for users (relative to tobacco smoking).
Encourage smokers to switch to e-cigarettes through price mechanisms	Price signals may help to achieve shifts in usage between tobacco products.[36] Therefore if the policy goal of shifting users from smoking to the use of e-cigarettes was favoured, it would seem desirable to have a large price gap between untaxed e-cigarettes (taxed with only the routine Goods and Services Tax (GST)) relative to smoked tobacco sold elsewhere. This gap could grow if the excise tax on the former kept increasing as part of a national endgame strategy[37] (and taxes on tobacco are a particularly important and cost-effective tobacco control strategy in themselves[38]).

adequate regulation of e-cigarettes is too hard for the New Zealand political and policy-making system (as discussed further below). But, if illegal sales of e-cigarettes became even more significant and hard to control, the viability of this approach could be eroded. Nevertheless, a large illegal market might be relatively unlikely, given the notable decline of the synthetic cannabis market after such products effectively became illegal in New Zealand.[32] Furthermore, the illegal tobacco market in New Zealand remains small,[33] despite high tobacco prices.

The best package of policy options for New Zealand?

Given the complexities around e-cigarettes, we have not attempted to reach any consensus, or even a majority view, on the 'most recommended' option/s for the New Zealand Government to consider. However, it seems logical for policy-makers to consider carefully the pros and cons of all the listed options, and to do so in the light of the smokefree nation 2025 goal.[23] The best long-term option for New Zealand should ideally be informed by on-going local research and careful monitoring of sales, use, product quality, and health effects. Hence the various surveys used in New Zealand should continue to collect data on e-cigarette usage.[5,6,39] There may also be potential lessons from the international experience with e-cigarettes and from other drug domains, such as international alcohol regulation and cannabis regulation (eg, as seen with various US states, Uruguay and Portugal). Indeed, the optimal evidence-based policy response may well change over time and so regulatory flexibility seems desirable. Furthermore, the goal of an e-cigarette regulatory regime should be to help end the current tobacco epidemic, and to help achieve the smokefree nation 2025 goal. The selected approach should therefore be implemented in tandem with enhanced tobacco control measures, eg, increasing tobacco taxes,[37,38] restricting access to tobacco sales,[24] and even reducing the nicotine content in tobacco.[40]

Additional reasons for caution when developing any new regulations

As we have outlined above, there is scientific uncertainty around e-cigarettes, therefore great care is required in crafting any new regulations. Other factors, which we outline below, should also make policy-makers cautious.

Firstly, policy-making around tobacco and nicotine seems very difficult, both internationally and in New Zealand. For example, New Zealand still has no licensing of retail tobacco outlets; no operationalised controls on tobacco product ingredients (including sugar, menthol, rum, and other flavours); no ban on duty-free sales of tobacco; and no restrictions on smoking in cars containing children. Furthermore, New Zealand is not moving quickly to implement standardised (plain) packaging;[41] and the legal situation around smoking in the 'outdoor' areas of hospitality settings remains problematic (eg, see this survey[42]). Other product-related examples of regulatory deficiencies in New Zealand include: still permitting advertising of prescription medicines;[43] the lack of virtually any controls on the sales of vitamins and supplements (though some new legislation is pending); the weak regulations around alcohol sales and marketing;[44] and the tortuous process of phasing out leaded petrol.[45] These examples collectively provide a warning on the suboptimal health-related policy-making processes in New Zealand.

Secondly, some of the options outlined assume quality standards may be developed, implemented and enforced. We are not sure whether New Zealand has adequate infrastructure to do this at present. If not, it might be necessary to piggy-back on European Union or US Food and Drug Administration (FDA) standards or similar (either of which may come with its own set of problems).

Thirdly, some participants in the e-cigarette domain have commercial vested interests. For example, e-cigarette companies and some tobacco companies that own e-cigarette brands. The tobacco industry continues to be

influential in New Zealand, has historically opposed effective tobacco control measures,[46] and, at an international level, continues to undermine evidence-based policy.[47,48] Irresponsible advertising of e-cigarettes in the US is also well described.[2] For these reasons, the tobacco industry should be excluded from discussions regarding e-cigarette regulation, and submissions from any tobacco company should be viewed by the Government with considerable scepticism.

Fourthly, any liberalisation of e-cigarette supply (with its risks) may reduce pressure on the Government to introduce and implement a comprehensive strategy to achieve the smokefree nation 2025 goal (with such elements outlined by the Māori Affairs Select Committee[49]). Such a comprehensive strategy is likely to be the most important step that the Government can take to end the epidemic of tobacco-use related deaths in New Zealand.

Conclusions

Any further regulation of e-cigarettes in New Zealand will require careful analysis and re-opening the regulatory toolkit is not risk-free (ie, increasing access to e-cigarettes may be a benefit, but may also generate new problems that outweigh the benefits). This is especially so given the genuine scientific uncertainties and the vested commercial interests involved. Nevertheless, policy-makers may wish to consider further the pros and cons of the regulatory options outlined in this article.

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A case of botulism in New Zealand

Duncan Smyth, Eamonn Deverall, Michelle Balm, Annette Nesdale, Ian Rosemergy

ABSTRACT

We describe the first case of food-borne botulism seen in New Zealand for 30 years. Botulism is an important diagnosis to consider in a patient with rapidly progressive descending paralysis and normal sensorium. Early recognition, timely institution of intensive care support and administration of botulism antitoxin are the most important aspects of management.

Botulism is a rare, toxin-mediated disease with high mortality. The clinical presentation can mimic other acute progressive neurological disorders. We present the first case of food-borne botulism in New Zealand since 1984.

Case report

A 55-year-old male was admitted to Wellington Hospital two days after returning from Japan. On arrival in New Zealand, he consumed a 'wet risotto' packet meal despite it tasting 'rancid'. Within 24 hours, he developed vomiting, followed by dizziness, diplopia and dysarthria.

His provisional diagnosis on admission was of a posterior circulation stroke; however, on review by the neurology service six hours later, the findings were of ophthalmoplegia with right lateral rectus palsy, lower motor neuron facial weakness, dysarthria, dysphonia and glossal paresis. He had subtle distal weakness in both hands. Reflexes were retained. The patient remained alert and afebrile.

An MRI was unremarkable and cerebrospinal fluid (CSF) collection showed white cell count, protein and glucose within normal limits.

A rapid clinical deterioration followed such that within 10 hours he had developed severe bilateral ptosis, marked bilateral facial weakness, complete anarthria, moderate upper limb weakness, and all reflexes were now absent. Forced vital capacity (FVC) was significantly reduced to 2.82 L (30 mL/kg). He was also tachypnoeic. Transfer to the Intensive Care Unit was facilitated due to continued respiratory deterioration and within hours he required intubation following a respiratory arrest.

Neurophysiology studies performed 48 hours after initial symptom onset showed markedly reduced compound muscle action potential (CMAP) amplitude with normal sensory studies. Of diagnostic significance, the abductor hallucis brevis CMAP amplitude increased 300% after tetanic stimulation.

While consideration was given to alternative diagnoses, such as Miller-Fisher variant of Guillain-Barre syndrome and acute neuromuscular junction disorders (myasthenia gravis), the speed of decline and combination of gastrointestinal symptoms followed by progressive cranial motor neuropathies, absent sensory features, normal sensorium and low CMAP amplitudes within hours of symptom onset all supported a probable diagnosis of botulism.

The patient was treated with botulinum antitoxin and required two weeks of intensive care support. Blood, stool and gastric washings were cultured, but no *Clostridium* species were isolated. *C. botulinum* toxin genes were not detected by PCR in gastric washings. Anti-GQ1B and acetylcholine receptor antibodies were

Table 1: Neurophysiology Studies

Motor Studies	Within first 3 days of symptom onset				10 weeks post symptom onset
	Distal Motor Latency (ms)	Conduction Velocity (m/s)	Pre tetanic stimulation CMAP Amplitude (mV)	Post tetanic stimulation CMAP Amplitude (mV)	CMAP Amplitude
Right AHB	5.0 (3.96±1)	43.8 (48.5±3.6)	0.4 (5.8±2)	1.2 (300% amplitude increase)	Not tested
Right APB	2.96 (3.49±0.3)	54.8 (58.7±5.1)	0.1 (7±3)	0.1	2.0
Right ADM	2.79 (2.95±0.4)	59.2 (57.7±5)	0.2 (5.7±2)	0.2	6.8
Sensory Studies (antidromic)	Sensory nerve action potential (SNAP) amplitude within first 3 days of symptom onset			10 weeks post symptom onset	
Median (digit II)	35.6 uV (38.5±15.6)			50.6 uV	
Ulnar (digit V)	20.8 uV (35.0±14.7)			28.5 uV	

AHB – Abductor hallucis brevis muscle, APB – Abductor pollicis brevis muscle, ADM – Abductor digiti minimi muscle
Compound muscle action potential (CMAP) is a summation of all underlying individual muscle fibre action potentials.[1] The table shows extremely low amplitude CMAPs on initial testing, which then normalised when retested 10 weeks later. Distal motor latencies and conduction velocities were essentially normal. The large increase in CMAP with tetanic (repetitive) stimulation of abductor hallucis brevis helped to localise the problem to the presynaptic part of the neuromuscular junction, and differentiated it from other neuromuscular junction disorders such as myasthenia gravis. The sensory nerve studies were normal at disease onset and during follow-up studies.

negative. His course was complicated with *Klebsiella pneumoniae* bacteraemia and ventilator associated pneumonia and acute kidney injury requiring temporary dialysis; however, after motor function began to return, he made a rapid and full recovery. Convalescent neurophysiology testing 10 weeks after the initial symptom onset confirmed the reestablishment of normal CMAP amplitudes. The neurophysiologic findings are shown in Table 1, with normal ranges given in brackets.

Public Health Investigation

Regional Public Health staff interviewed the patient's travel companion (via interpreter) and family. There was no history of intravenous drug use or therapeutic or cosmetic botulinum toxin application. His companion reported that he had eaten something 'off' at a relative's house, and had been the only person to do so. His family reported that it was a packet risotto product. Further investigation revealed that the risotto was a wet, chilled product purchased by a family friend. It had not been refrigerated and would have been several months past its best-before date. Packaging was not available for testing. When later shown photos of packaging of the presumed brand, the patient felt very confident that this was the product he had eaten. He confirmed that the risotto had a 'blue cheese' taste to it, and was also 'very bitter'. Of concern was that instructions to keep chilled were in very small font on the back of the package, 'Ready to eat' was written on the front despite the need for thorough reheating, and there was a best-before as opposed to a use-by date.

Discussion

This case illustrates that while botulism is rare, it must be included in the differential diagnosis of a patient with rapidly progressive descending paralysis and normal sensorium. Normal CSF protein and

low amplitude CMAPs help determine the diagnosis. Mortality is greatly reduced by timely institution of intensive care support and administration of botulinum antitoxin.[2] Effectiveness of antitoxin is greatest when given early and should be given on clinical suspicion without waiting for results of diagnostic testing.[3]

Botulism is a toxin-mediated disease with high mortality. Botulinum toxins act presynaptically, preventing acetylcholine release at the neuromuscular junction, resulting in flaccid paralysis. These are the most potent toxins known, with an estimated oral lethal dose of 70 mcg in a 70 kg man.[4] *Clostridium botulinum*, *C. butyricum* and *C. baratii* may produce botulinum neurotoxins (BoNT), of which BoNT A, B, E, and F cause human botulism.[5] In adults, the commonest exposure to botulinum neurotoxins is through ingestion of pre-formed toxin in food which has been incorrectly preserved or stored, allowing growth of toxin-producing clostridia species. Gastrointestinal symptoms often develop within hours of ingesting the contaminated meal, with neurological symptoms evolving rapidly over subsequent hours to days.[3] Shorter incubation periods are associated with greater toxin doses, a more rapid progression of symptoms and more severe illness.[6]

Laboratory confirmation of botulism is difficult, particularly from samples with high levels of competitive bacterial flora or proteinases which may degrade the toxin.[5] The gold standard test is the mouse lethality assay which is not available in New Zealand. Detection of *C. botulinum* toxin genes in gastric washings was attempted by PCR at the Animal Health Laboratory, Ministry of Primary Industries. This assay does not detect all possible types of BoNT.

The last reported cases of botulism in New Zealand were two sisters who became ill after ingesting home-preserved watercress and mussels.[7]

There have been other cases from similar wet, chilled products. In France in 2008, two people developed severe botulism requiring ventilation after eating pre-cooked chicken enchiladas, which had been kept at room temperature for two weeks. French authorities recalled the product, requested the manufacturer improve packaging to make storage instructions more visible, and issued a reminder about respecting storage conditions.[8] Inappropriate storage also featured in two outbreaks in California in 1994, of vacuum packed clam chowder and black bean dip, both kept at room temperature for 1 month and 3 weeks respectively.[9] This reinforces the need for adequate labelling around storage and shelf-life and consumer adherence to these recommendations in New Zealand.

Competing interests:
During the time of the investigation, Regional Public Health (the employer of Dr Deverall and Dr Nesdale) was providing 'Food Safety and Suitability Services' under contract to the Ministry of Primary Industries.

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Bullous Mantoux reaction

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A 40-year-old gentleman, non-smoker, with history of 10 kg weight loss, underwent chest radiograph. He had no other symptoms. Chest radiograph showed widened right paratracheal stripe. Intradermal tuberculin test performed, using 5 tuberculin units, showed a strongly positive reaction with formation of bulla by 12 hours, and induration of 40 x 30 mm by 24 hours (Figure 1). Magnetic resonance imaging of thorax showed enlarged heterogeneous, necrotic lymph node in the right paratracheal location meausring 30 x 30 mm (Figure 2). The endobronchial ultrasound guided transbronchial needle aspiration from the right paratracheal lymph node revealed pus which showed acid fast bacilli, and he was started on anti-tubercular therapy.

Discussion

Mantoux test is an example for the delayed hypersensitivity reaction to the tuberculin test.[1,2] Most develop mild erythema and induration by 24 hours, which peaks at 48 to 72 hours. Our patient had massive bullous response following mantoux testing.This strong reaction is common in patients with active tuberculosis, having high mycobacterial antigen load as in our patient.[3] Although mantoux test is a sensitive but non-specific test, in the diagnosis of active tuberculosis, it needs to be correlated to the patient's clinical context for assisting the diagnosis.

Figure 1: Mantoux test administered over the left forearm showing bullous reaction

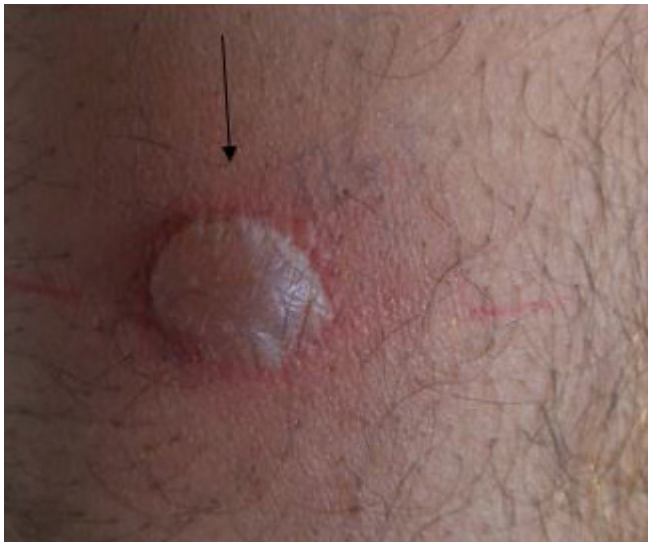
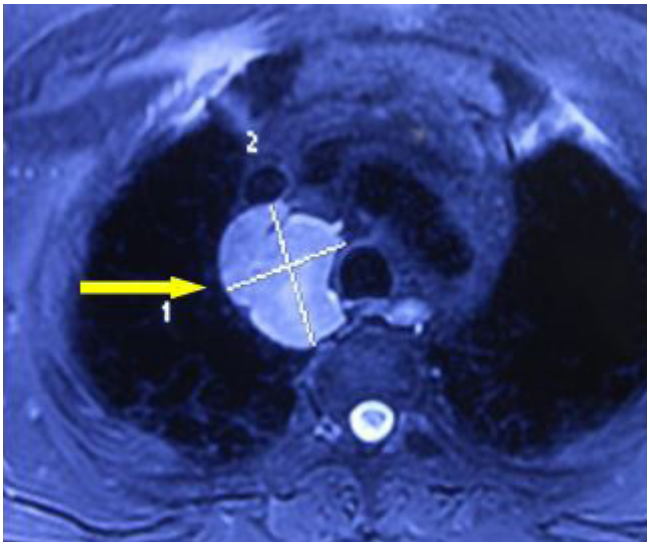


Figure 2: Magnetic resonance imaging of thorax showed enlarged heterogeneous, necrotic lymph node in the right paratracheal location



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Perioperative care in hip and knee arthroplasty—a survey of New Zealand orthopaedic surgeons

Marinus DJ Stowers, Andrew G Hill, Brendan Coleman, Jacob T Munro

BACKGROUND: Evidence for Enhanced Recovery After Surgery (ERAS) protocols continues to grow and is considered standard of care by many. ERAS coordinates evidence-based perioperative care interventions to hasten recovery. Pioneered by Prof Henrik Kehlet in colorectal surgery, ERAS principles have been adopted in many specialties, including bariatric, gastric, vascular, gynaecological and orthopaedic surgery.[1]

Specific to elective arthroplasty ERAS interventions include preoperative education, spinal anaesthesia/analgesia, local infiltrative analgesia, avoidance of surgical drains, tranexamic acid (TXA), early removal of catheters and early mobilisation.[2]

This survey aimed to characterise perioperative management among New Zealand orthopaedic surgeons across the private and public sectors, and compare this to the current literature.

METHODS: An online survey (www.surveymonkey.com) was sent to New Zealand hip and knee arthroplasty surgeons. It was composed of 10 multiple choice questions, including: surgeon's place of practice and experience (Q1 and Q2); routine perioperative surgical interventions used in hip and knee arthroplasty (THA and TKA, respectively) (Q3–9); and potential perceived barriers for ERAS implementation at their centres (Q10). The survey was designed by the authors and scrutinised for content and face validity by three arthroplasty surgeons (BC, JM and MD). The option of adding comments as free text after each question was made available.

After obtaining ethics approval from the University of Auckland Ethics Committee, the link to the survey was emailed to all current members of the New Zealand Orthopaedic Association (NZOA) for 2012–13, with an endorsement letter from the NZOA. The link to the questionnaire was sent on three separate occasions. The first was sent on 18 October, 2013, and then again one month and two months later. Patterns of perioperative care were characterised by level of experience (ie, fellow, consultant <5 years, consultant 5–10 years, consultant >10 years).

According to registry data for the period 2012–13, there were 198 surgeons who performed 10 or more THAs or TKAs.

RESULTS: Fifty-three (26.8%) surgeons responded to the online survey. One responder answered Q1 and Q2 only and therefore was excluded. Fifty-two surveys were therefore included in the final analysis.

Surgical approach

The majority of participants (62.5%) use a posterior approach to performing THA. In 19.6% and 14.3% lateral and anterolateral approaches were used. Only two surgeons used an anterior approach.

Among responders performing TKA, the surgical approach was unanimous in favour of the medial parapetallar approach (94.2%).

Tranexamic acid

Routine use of TXA in THA and TKA was 32.7% and 36.5% respectively. Ninteen percent of participants left this decision to the anaesthetist to decide. Despite the abundant evidence supporting the efficacy and safety of TXA in elective arthroplasty,[5,6] it is clear that TXA is not standard practice for many of our arthroplasty surgeons.

Surgical drains

Surgical drains were more commonly used for TKA (54.9%) than THA (39.2%). Twenty-four percent of surgeons were selective in their use of surgical drains. No use of surgical drains was reported by 23.5% of participants. Current evidence suggests closed drainage systems confer no additional benefit over no drain, with equivalent rates of infection.[7]

Mobilisation

All surgeons encouraged mobilisation by the first postoperative day, with 37.3% instructing patients to mobilise on the day of surgery. Four surgeons indicated that achieving this milestone was dependent on persisting regional and neuroaxial blockade.

Anaesthesia

There was a preference for spinal anaesthesia (SA) in combination with either regional blockade ± local anaesthesia (LA) for patients undergoing THA (n=34, 72.9%). A quarter of responding surgeons preferred to use general anaesthesia (GA) in combination with either SA ± regional blockade ± LA. Anaesthesia preference for TKA was similar to THA. The introduction of ERAS protocols have influenced choice of anaesthesia with centres encouraging same day mobilisation.[8,9] Such protocols may preclude the use of regional anaesthesia, as this may delay mobilisation via persistent motor blockade. Thus, local infiltrative anaesthetic is a more attractive means of providing adequate postoperative analgesia.

Indwelling catheter removal

When deciding to remove IDCs, removal is instructed for the first postoperative day in 34.0% and 31.9% of responders for THA and TKA, respectively. Ten (21.3%) surgeons indicated that the decision to insert an IDC was patient and anaesthesia dependent.

DVT pharmacological agent

Following THA and TKA, aspirin was the preferred chemoprophylactic agent in 70.6% of responders; clexane was preferred by 19.6% of surgeons; and rivaroxiban was preferred by 15.7% of surgeons. One responder each indicated that they used dabigatrin, or did not use any form of pharmacological prophylaxis. The choice of venous thromboembolic (VTE) chemoprophylaxis continues to perplex surgeons in this setting and the appropriate agent continues to be heavily debated.

Adopting ERAS

Of 51 responders, 13 (25.5%) stated that they already follow an ERAS approach. Forty-seven percent of responders indicated some form of barrier would be encountered when attempting to introduce an ERAS protocol for their arthroplasty units. The most common barrier likely to be encountered by surgeons was the lack of 'buy-in' from their colleagues (31.4%), followed by institutional barriers (25.5%). Kahokehr and colleagues state that "for successful implementation of ERAS the most vital ingredient is a surgeon willing to overcome traditional concepts of perioperative care".[10]

Conclusion

A nationwide survey was performed to describe several surgical practices among New Zealand arthroplasty surgeons and how these aligned or differed with the current literature and ERAS protocols. To the authors' knowledge, this is the first survey of perioperative care practices among arthroplasty surgeons. Although the response rate was low (26.8%), considerable variation in surgical practices among surgeons was identified and although many surgeons' practices aligned with the current literature, many did not. Based on these findings there is certainly scope to implement ERAS in arthroplasty units around the country, if they are not already established. The difficulty however, will be attaining sufficient 'buy-in' from key stakeholders and maintaining traction throughout this process. Implementing evidence-based care in a standardised manner can be challenging. Further research into addressing the potential barriers is required, including more robust studies on specific care interventions in ERAS for THA and TKA.

Competing interests: Nil

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Equitable care for those with rheumatic heart disease

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The editorial by Lennon and Stewart[1] summarises recent efforts in New Zealand to prevent acute rheumatic fever (ARF) by primary prevention of group A streptococcal pharyngitis in a widely publicised primary prevention programme.[2] We concur funding should continue till its evaluation in 2016–17, as a premature change may impact both programme delivery and outcomes. We all hope that this primary prevention programme is successful, like programmes in Cuba,[3] Costa Rica,[4] and inner-city Baltimore.[5]

The long lasting consequence of ARF is rheumatic heart disease (RHD) and that is the reason why preventing ARF is important. In New Zealand, RHD causes 600–800 hospital admissions per year, mainly in young adults, and 150–200 premature deaths per year.[6] RHD direct hospitalisation costs are conservatively estimated to be at least $12 million annually.[7] Globally, around 40% of adults with RHD do not recall a past history of ARF.[8,9] The recent study in Porirua suggested even higher rates of previously undiagnosed RHD, with 4 new cases for every known case of previous ARF. Mild or moderate carditis in the absence of arthritis, does not cause symptoms and hence these episodes of ARF go undetected. In the absence of secondary prophylaxis this can lead to permanent and worsening RHD. The WHO recommends active case finding for RHD[10] and echocardiography is more sensitive and specific compared to auscultation.[11,12] Over the past 8 years, the authors are among many involved in developing a model for detection of previously undetected RHD using portable echocardiography in high-ARF regions of New Zealand, mainly in schools targeting children aged 10–13 years. We have shown that such screening in the New Zealand setting is feasible,[12,13] and is highly acceptable by families.[14] We have identified 1–2% definite RHD in such high-incidence ARF populations,[12-14] and as we hypothesised, no definite RHD in regions without ARF,[15] so it is clear where to target the echocardiography. New Zealand researchers led international efforts to define the minimal criteria that constitute a diagnosis of RHD so that the threshold for diagnosis is appropriate.[16] Echocardiography studies have now taken place in the Counties Manukau, Tairawhiti, Bay of Plenty, Northland and Capital and Coast DHBs, with partnerships involving community paediatricians, public health physicians, cardiologists, community nursing in consultation with local communities. Counselling of those with positive tests has been by senior paediatricians. Funding to date has been by research grants, and local DHB, PHO, Hauora (Māori-led health providers) and community initiatives. Follow-up of individuals with borderline RHD category[15] is currently in progress to better understand the natural history. The accuracy of the test and threshold for treatment has been recently clarified by a case-control study from Australia.[17] Those with borderline RHD had an 8.8 times relative risk of ARF and a 1 in 6 chance of progression to Definite RHD at follow-up compared to controls. However, as a proportion of individuals with isolated mitral regurgitation graded as borderline RHD may represent upper limit of physiological regurgitation,[15,18] we currently recommend active surveillance with interval

follow-up and enhanced primary prevention for this group at first diagnosis. Secondary prophylaxis with penicillin is recommended for those with Definite RHD.

Screening programmes can cause harm, especially if inappropriate management or distress to patients results from a false positive result.[19] Led by University of Otago researchers, and with HRC funding support, we are currently investigating the potential harm of echocardiographic screening. With a 1 in 150 chance of a child living in the most deprived regions of New Zealand having an ARF episode,[20] another 1–2% having undetected RHD,[12-14] and the high cost of RHD mainly due to cardiac surgery,[7] the economic analysis of case detection using echocardiography is predicted to be favourable. Two recent modelling studies support this contention.[21,22]

Thus, the four broad key components of a public health programme[23] are in place: there is a condition (latent RHD) that can best be detected by a test (portable echocardiography) and there is a treatment (penicillin) that prevents disease progression. Fourthly, the New Zealand health service has sufficient resources and infrastructure for such RHD case detection.[12-14]

Future funding for ARF/RHD control in New Zealand, as raised by Lennon and Stewart,[1] should be equitable for all, and in addition to primary prevention, should include funding for those with RHD, both detected and undetected. We have shown that there is a significant group of children with RHD in New Zealand who are unaware of their diagnosis who would be identified by echocardiography. Primary prevention efforts will not benefit people with already established RHD. Both primary prevention and active case finding using echocardiography are logical ways to minimise overall RHD disease burden.

Establishing an echocardiography screening programme in high-risk ARF areas will also provide data of the true burden of RHD in New Zealand. This would be another robust measure to monitor the effects of the primary RF prevention strategies.[1]

A novel strategy to combine the health promotion messages of primary prevention and echocardiographic detection of unknown RHD in the future would be the implementation of a New Zealand ‘rheumatic fever bus’ similar to current mobile dental and ORL services. This could travel to high-incidence RF regions, visibly continuing a variety of primary prevention activities, and have the capability to perform echocardiography in local communities. This model is used in South Africa and is being implemented in Fiji.

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Ticagrelor in the real world: The Midland Regional Cardiac Network Experience

Marcus Lee, Sarah Green, Tina Cherian, Charles Heald, Gerard Devlin

Novel antiplatelet agents, like ticagrelor and prasugrel, have been developed in response to evidence that there are a subgroup of patients who are less responsive to clopidogrel and may predispose patients to recurrent ischaemic events and higher mortality in the setting of an acute coronary syndrome.[1,2] We report on a retrospective observational study assessing the experience and compliance of patients commenced on ticagrelor in the Midlands region.

133 patients were identified and interviewed for the purpose of the study. 69% were male with a mean patient age of 67. 10% identified as New Zealand Māori. 53% were Non-ST-segment elevation MI (NSTEMI) and 97% were on aspirin in addition to ticagrelor. Two-thirds (67%) were treated with percutaneous revascularisation and 20% with medical therapy. The remainder were elective patients commenced on ticagrelor post angioplasty.

42% (56/133) of patients had completed the 12 month duration of dual-antiplatelet therapy at the time of the telephone interview and 30% (40/133) were still taking ticagrelor. Self-reported compliance was excellent, with 97 % (129/133) reporting missing a dose less than once a month, or not at all. Overall satisfaction with ticagrelor treatment was positive. 65% (87/133) of patients reported satisfaction with ticagrelor. 8% (10/133) were ambivalent. Patients who had previous experience with clopidogrel expressed a preference for this agent.

Premature discontinuation of ticagrelor occurred in 25% (34/133) of patients, primarily due to dyspnoea 56% (19/34). Bleeding was responsible for stopping ticagrelor in 9% (3/34) of discontinuations.

This real world experience in discontinuation rates may in part be explained by inexperience in managing patients with dyspnoea on ticagrelor. These patients often present in primary care and other causes of dyspnoea, which include heart failure and bronchospasm need to be carefully excluded before concluding a likely relationship with ticagrelor.[3] On-going education of both patients and practitioners is essential in the management of anticipated side effects to ensure patients are not denied potential benefit, which includes a reduction in cardiovascular mortality with this agent.

Competing interests: Nil

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Children's positive attitudes towards the tobacco industry is associated with initiation of smoking

Anette Kira, Marewa Glover, Dudley Gentles, Judith McCool, Robert Scragg, Chris Bullen, Vili Nosa

Seventeen percent of New Zealand ever-smoking children smoked their first cigarette before 10 years old (Māori 26%, Pacific Island 20%, European 10%.)[1] Eighteen percent of Māori and 11% of Pacific Island 14–15 year olds are regular smokers children (vs 6% for European youth).[2]

Cross-sectional research has found that teenagers who hold tolerant attitudes, for example that the tobacco industry is truthful and does not target young people, are more susceptible to smoking uptake than those who consider the tobacco industry to be manipulative or who agree that the tobacco industry targets adolescents.[3-5] New Zealand cross-sectional research with 14–15 year olds found a significant association between tolerant attitudes of tobacco industry trustworthiness, the tobacco industry's rights and the tobacco industry's responsibility for youth smoking uptake and susceptibility (absence of a definite commitment not to smoke) and having ever smoked (initiation).[5]

We were interested to see if tolerant attitudes towards the tobacco industry was associated with smoking initiation for 10–13 year old pre-adolescents from predominantly Māori and Pacific Islander populations.

Methods

Students from year 7 (10–11 years old) and 8 (11–12 years old) from the control groups of the Keeping Kids Smokefree (KKS) study participated. Ever-smoking students (answered "yes" to the question, "Have you ever smoked a cigarette, even just a few puffs") at baseline and students who had less than one follow-up measure were excluded.

Students were surveyed at baseline and when they reached year 9 (12–13 years old). Ever-smoking was measured both times. Demographic variables and susceptibility to smoking initiation (without a definite commitment not to smoke), was collected at baseline. The students were asked if they "agree, disagree or don't know" to nine statements relating to attitudes towards smoking and the tobacco industry.

Data were analysed using SAS v 9.2 (SAS Institute., Cary, NC, US) with all tests being two-sided; $p<0.05$ deemed statistically significant. We produced logistic regression models with outcome smoking initiation (represented by ever-smoking) at follow-up. Smoking at follow- up (Table 1) was adjusted by attitude, age, gender, ethnicity (Māori, Pacific, European, Indian and Asian) and parental smoking at home, friends smoking at home and time to follow-up (1 or 2 years). Ethics approval was obtained from the University of Auckland Human Participants Ethics Committee (Ref. 2006/416).

Results

The overall response rate for KKS was 83% (4,688 of 5,648 students approached at baseline participated). Analysis was restricted to the 1,505 children at baseline who completed all the relevant questions and had a follow-up measurement. Most were 10 and 11 years old (91%); 60% were Māori and Pacific. At the end of two years follow-up, 134 students (9%) had tried smoking for the first time. Table 1 shows the

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Table 1: Demographics at baseline according to whether they subsequently smoked during follow-up (n=1,505)

	Smoked counts N=134 (row%)	**Did not smoke** counts N=1,371 (row%)
Age at baseline		
10–11	122 (8.5%)	1,311 (91.5%)
12–13	12 (16.7%)	60 (83.3%)
Gender		
Boys	61 (8.5%)	659 (91.5%)
Girls	73 (9.3%)	712 (90.7%)
Ethnicity		
Māori	41 (16.4%)	209 (83.6%)
Pacific	70 (10.8%)	576 (89.2%)
European	4 (4.7%)	81 (95.3%)
Indian	16 (4.1%)	378 (95.9%)
Asian	3 (2.3%)	127 (97.7%)
Susceptible		
Yes	38 (21.1%)	142 (78.9%)
No	96 (7.2%)	1,229 (92.8%)
Parental smoking at home		
Yes	46 (14.4%)	273 (85.6%)
No	88 (7.4%)	1,098 (92.6%)
Friends smoking at home		
Yes	6 (17.1%)	29 (82.9%)
No	128 (8.7%)	1342 (91.3%)

odds ratios of children's attitudes toward smoking and subsequent smoking initiation at follow-up, with all models adjusted for age, gender, ethnicity parental smoking in the home, friends smoking at home and time to follow- up. The attitudes "I would believe it if a tobacco company said they had made a safer cigarette", and "Tobacco companies should have the same right to sell cigarettes as other companies have to sell their products", was associated with initiation of smoking (Table 2).

Discussion

In this first longitudinal study of children's attitudes towards the tobacco industry and subsequent smoking uptake, two attitudes were found to predict smoking initiation, both sympathetic to the tobacco industry. McCool et al[5] found a significant association between susceptibility to smoking initiation and attitudes towards whether the tobacco industry is trying to get young people to start smoking and the trustworthiness of the industry. However, the current study found that only attitudes relating to trustworthiness of the industry were associated with smoking initiation.

Tobacco industry denormalisation campaigns have been found to reduce smoking prevalence among youth, reduce smoking initiation, and reduce perceived peer smoking prevalence,[6] but there has been little focus on this in

Table 2: Children's attitudes toward smoking and the Tobacco Industry at baseline and subsequent smoking initiation at follow-up–showing multivariate† odds ratios and 2 x 2 tables with counts (row %).

	Response	Ever-smoker	Never-smoker	OR	95% CI
Do you think cigarette smoking could make you unwell?	Yes No	124 (9%) 10 (10%)	1,281 (91%) 90 (90%)	1.1 1.0	0.53–2.17
Pregnant women shouldn't smoke.	Agree Disagree	122 (9%) 12 (9%)	1,245 (91%) 126 (91%)	0.9 1.0	0.49–1.79
People under the age of 16 should not smoke.	Agree Disagree	129 (9%) 5 (6%)	1,288 (91%) 83 (94%)	0.6 1.0	0.24–1.58
My parents or caregivers would be upset if they knew I smoked.	Agree Disagree	130 (9%) 4 (12%)	1,342 (91%) 29 (88%)	1.4 1.0	0.47–4.40
Tobacco companies are responsible for people starting to smoke.	Agree Disagree	97 (8%) 37 (11%)	1,078 (92%) 293 (89%)	1.4 1.0	0.89–2.06
Tobacco companies try to get young people to start smoking.	Agree Disagree	95 (8%) 39 (10%)	1,021 (92%) 350 (90%)	1.1 1.0	0.73–1.67
I would believe it if a tobacco company said they had made a safer cigarette.	Agree Disagree	30 (15%) 104 (8%)	164 (85%) 1,207 (92%)	2.2 1.0	1.39–3.53*
Tobacco companies should have the same right to sell cigarettes as other companies have to sell their products.	Agree Disagree	27 (13%) 107 (8%)	173 (87%) 1,198 (92%)	1.6 1.0	1.01–2.65*

*p<0.05

New Zealand campaigns. The predominant focus recently in New Zealand has been on promoting quitting by annually increasing tobacco excise tax and extending smokefree environments. Since July, 2012, tobacco products were no longer allowed to be displayed at point of sale. In February, 2013, the Government announced it would bring in standardised packaging, following Australia's lead (though this hasn't happened yet). In response to the announcement, the tobacco industry ran several campaigns to bolster sympathy towards them. To protect children from being influenced by tobacco industry communications it may necessary to run tobacco industry denormalisation campaigns that raise awareness of deceitful behaviours and build critical media-use skills.

A strength of this study is the use of a longitudinal design, enabling analysis that shows susceptibility and certain attitudes both preceded smoking initiation. A limitation was that students were predominantly Māori and Pacific Island, limiting generalisability to non-Māori and non-Pacific pre-adolescents.

Competing interests: Nil

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Trends and patterns in medical student research and publishing in New Zealand

Ibrahim S Al-Busaidi

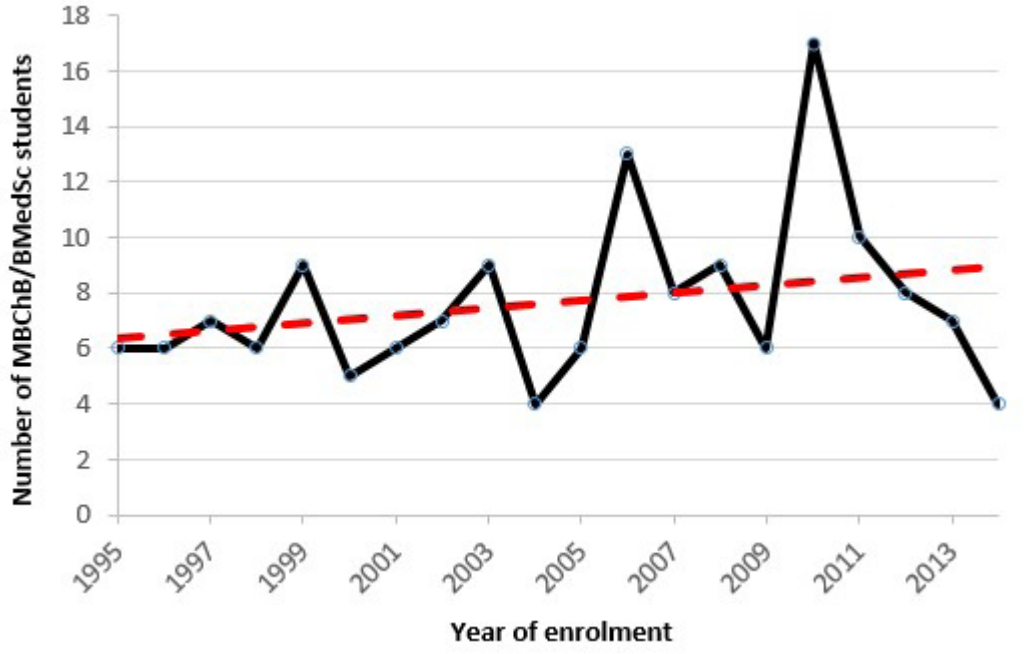
The letter by Alamri[1] discussing some of the current international trends in medical student research and publishing raised unanswered questions about our own trends in New Zealand.

Medical student-led research dates back to the mid-17th century; a contribution that resulted in major scientific discoveries and breakthroughs.[2] Since then, medical institutions have continued to encourage student research and publishing through the introduction of mandatory and extra-curricular research activities to their medical programmes (such as intercalated degrees, summer studentships, and research electives/selectives).[3] Preliminary research from New Zealand found that students have contributed significantly to the scientific and medical literature;[4] an encouraging finding that might reflect the increased participation and interest in undergraduate medical research.[4,5]

Worldwide, several trends in medical student research and publishing have been explored recently. In line with the overall growth in medical publications over the past few decades,[6] an upward trend of student-authored articles has been observed in New Zealand[4] and globally.[3] This could be attributed to the increase in undergraduate research opportunities provided by medical schools. For example, the number of Otago medical students who enrolled in the MBChB/BMedSc(Hons) intercalated programme has gradually increased over the past 20 years (Figure 1).

Despite the witnessed growth in the student-led literature, a number of worrying trends have recently been

Figure 1: Number of students enrolled in MBChB/BMedSc(Hons) intercalated programme at the University of Otago (1995–2014).



reported. These include a gradual decline in the number of physician-scientists,[7] a decrease in the ratio of student authors to total authors per publication, and a low citation rate of student-authored publications.[3] To be able to staunch, if not reverse, the above trends, characteristics of research conducted by medical students need to be regularly explored.

Despite the acknowledged importance of student medical publishing,[3-5] little attention has been paid to the study of student publishing patterns in New Zealand. The only available data on the characteristics of student-led research in New Zealand come from a retrospective review[4] that investigated students' contributions to the *NZMJ*. To explore some of the trends in student research and publishing in New Zealand, a further analysis of the study's data was conducted (a detailed description of the methods used has been published elsewhere).[4] Data from this study showed that the number of authors per publication has increased throughout the study period (mean±SD; 2000–2004 = 3.4±1.9, 2005–2009 = 3.5±2.3, 2010–2014 = 4.4±3.2, Kruskal-Wallis chi-squared = 6.8, df = 2, p=0.03). However, the number of student authors per publication has relatively remained the same (mean ± SD; 2000–2004 = 1.2±0.8, 2005–2009 = 1.2±1.0, 2010–2014 = 1.6±2.3, Kruskal-Wallis chi-squared = 2.3, df = 2, p=0.32).

Findings from this study suggest that although a gradual increase in the number of student-authored publications has been observed in New Zealand,[4] the ratio of student authors to total authors per publication has decreased; a finding which echoes international research.[3] A number of reasons could explain this observed trend. The expanding number of authors per article could be ascribed to (1) an increase in collaborative and multicentre research,[6] (2) a rise in the number of academic staff supervising students, (3) or may represent an extension of the phenomenon of 'honorary authors' (naming a person as an author without meeting authorship criteria).[8]

To conclude, studies into student research and publishing are generally lacking in New Zealand. Future studies are needed to better explain the observed trends and characterise the impact (ie, citation rates) and scientific validity of student-led research in New Zealand and worldwide.

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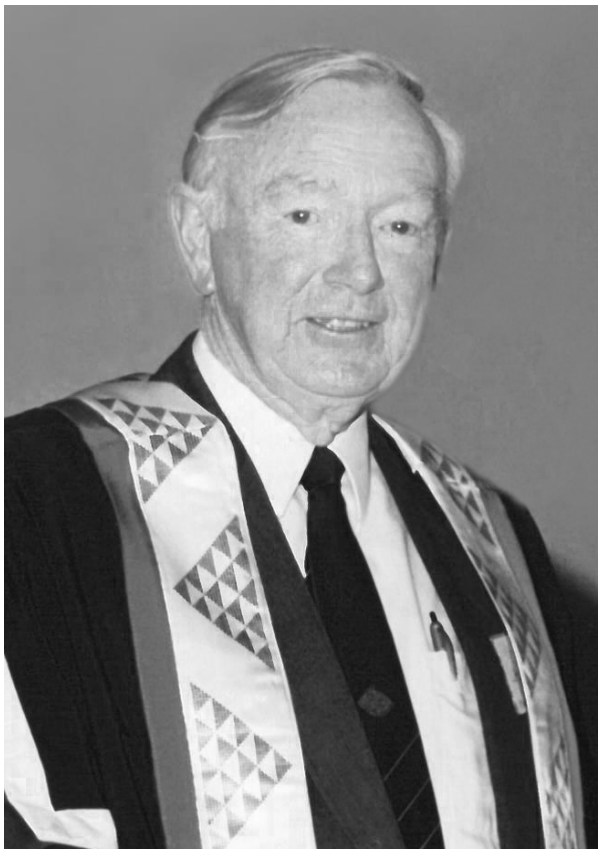
Sydney Rae West

11 December 1925 –25 April 2015

MBChB, Dip Obst., Dip Prof Ethics, FRCGP, FRNZCGP(Hons), FAFPHM



It is with great sadness that I write this account of the career of Associate Professor Rae West, general practitioner, researcher, epidemiologist, co-worker, mentor and friend, who died on 25 April, 2015.

Rae was a leader in what might be termed the 'Family Practice Movement'—doctors who aligned themselves with this concept think not just of the individual as requiring medical care at a time of illness, but to think of the family as a *whole* as 'unwell', and endeavours to treat *each* member who may require a different approach, even if not overtly 'sick'.

At an even higher level, this care may extend into the community where, in a similar way, every member of the family, including the nominated patient, plays a part in the care of the member who is 'unwell'; thus hopefully providing outstanding care of patients.

Rae was the epitome of good general (or family) practice, seeking to provide the best possible treatment for his patients and marshalling community cooperation and care of a high order when that seemed appropriate.

Rae qualified in 1948 and became first a House Officer in Christchurch and Masterton hospitals, and then worked as a family doctor in rural Waiuku, where he remained for 22 years. During this time, he coordinated the health-related services in that area. This included, from time-to-time, supervising final-year medical students during their 4–6 weeks apprenticeship to selected doctors. Students valued and enjoyed the opportunities for 'hands-on' work and many considered it 'a mind changing' experience.

In 1971, Rae was awarded a Nuffield Travelling Fellowship and visited a number of countries, in particular the US, UK, Europe

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and Australia. He used these studies to produce a report on Post Graduate studies for family practitioners (*Continuing Medical Education*, SR West, 1971).

Shortly after this, he accepted the position of Senior Lecturer in the Department of Preventative & Social Medicine at Otago University Medical School, followed by an appointment at Auckland Medical School in 1977, where he was appointed an Associate Professor in the Department of General Practice.

Among many research projects conducted by Rae were several of international significance. An example of this was his interest in, and study of, health indicators and disease coding— thereby facilitating research into disease incidence and exploring comparisons of different countries, climates, and diets.

Rae's interest in epidemiology was wide and one of the more fascinating involved an analysis of the cries of infants. Ever observant, he conducted a study of baby cries in the hope of establishing patterns occurring as an infant, which if developed, had the potential to aid in the diagnosis of deafness, earlier than before.

Outside of medicine, his innovation was seen in the production of a small, written, AH Reed's *Guide to Trees of New Zealand* for lay people, using simple and easy methods of differentiation.

Rae gave much time to helping establish the College of General Practitioners, later to become the Royal College. He served 6 years as the College representative on the Medical Education Committee of the New Zealand Medical Council. A year as President of the College was another example of an onerous and challenging job well done. It had always been the practice that the name of the President of the College should be nominated by the faculties in succession, but not so with Rae. He was nominated by a faculty to which he did *not* belong: a great tribute to his competence and popularity.

As might be expected, with such a background, he served for some years on the Medical Research Council of the day. In addition to all this, he was Editor of the "New Zealand Family Physician".

In his retirement, Rae studied for, and passed, the Diploma of Medical Ethics examination. Family has always been very important for Rae. Over the years, he and Lilian worked together and had a fine reputation for their hospitality. They have 4 living children. We extend to the family the sincere condolences of the profession at the passing of this remarkable doctor.

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www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1425-20-november-2015/6737

Idarucizumab for dabigatran reversal

Dabigatran is an oral thrombin inhibitor which has been shown to be an effective anti-coagulant and, unlike warfarin, does not need frequent blood tests to make it effective and safe. However, until now there has been no way to rapidly reverse its effects.

Idarucizumab, a monoclonal antibody fragment, binds dabigatran with an affinity that is 350 times as high as that observed with thrombin. This report concerns a prospective study which evaluates its effectiveness in the clinical setting. 90 patients being treated with dabigatran were involved. 51 of them has serious bleeding and 39 required an urgent surgical procedure.

Apparently, 5g of intravenous idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. There were no toxic or rebound hypercoagulable effects.

N Eng J Med 2015;373:511-20

Birth weight and later life adherence to unhealthy lifestyles predicting type 2 diabetes

Both unhealthy lifestyles and early development have been implicated in the rapid rise of type 2 diabetes, but very few studies have explored potential interaction between prenatal and postnatal factors.

This prospective cohort study reviews this matter by evaluating data obtained from approximately 150,000 male and female health professionals in the US. The subjects did not have diabetes, cardiovascular disease or cancer at baseline and were followed for 20–30 years. The researchers defined unhealthy lifestyle on the basis of body mass index, smoking, physical activity, alcohol consumption and the alternate healthy eating index.

The conclusions reached were that both low birth weight and unhealthy lifestyle are associated with a significantly higher risk of type 2 diabetes and the joint effects of low birth rate and unhealthy lifestyle score are greater than the addition of risks associated with each individual factor, indicating significant interaction on an additive scale.

BMJ 2015;351:h3673

Induction of labour vs expectant management for large-for-date fetuses

Macrosomic fetuses are at increased risk of shoulder dystocia. This randomised trial aimed to compare induction of labour with expectant management for large-for-date fetuses for prevention of shoulder dystocia and other neonatal and maternal morbidity associated with macrosomia.

Nineteen tertiary-care centres in France, Switzerland and Belgium were involved. Women with singleton fetuses whose estimated weight exceeded the 95th percentile, were randomly assigned to receive induction of labour within 3 days between 37^{+0} weeks and 38^{+6} weeks of gestation, or expectant management. There were 407 women in the induction group and 411 in the expectant management group.

The conclusions reached were that induction of labour for suspected large-for-date fetuses is associated with a reduced risk of shoulder dystocia and associated morbidity compared with expectant management. Induction of labour does not increase the risk of caesarean delivery and improves the likelihood of spontaneous vaginal delivery. These benefits should be balanced with the effects pf early-term induction of labour.

Lancet 2015;385:2600-05

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www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1425-20-november-2015/6738

Book review: Scheme for dealing with tuberculous persons

By Dr Barty King, M.D. Edin., M.R.C.P., London and Edin.

THE WHITE PLAGUE. There is one thing that is always with us, and that is consumption. Whatever the colour of our skins there is one King—King Tubercle—who is great and powerful over us all.—*Dr. Mason at Maori Conference*. **The Doctor**: Look here, Hone, whatever you do, keep clear of this fellow— he is sure death. **Hone**: He is a bad fellow all right, but who introduced him to me? (*New Zealand Free Lance*, 18 July 1908).
Alexander Turnbull Library, Wellington, New Zealand. http://natlib.govt.nz/records/3580831

Dr. Barty King's scheme for dealing with tuberculous persons details an elaborate organisation for dealing with all suffering from tuberculosis in the County of London. It shows an extremely complicated piece of machinery with a central bureau, consisting of medical referees with clerical assistance. The whole question is too elaborate for anything which might be done in New Zealand, and is further complicated by dealing separately with "insured" and "uninsured" persons, a division which does not obtain in the Dominion. He suggests leaving "domiciliary treatment" in the hands of the panel doctors, which work is far better performed with the help of trained visitors, working in connection with the medical authority. The section dealing with the duties of the tuberculosis officer is excellent, and sums up all the many forms of activity in connection with this post. The paragraph on the national organisation opens up the question of a Government department being established to organise all the work in the country under the Minister of Public Health, and really touches the root of the whole question of the eradication of tuberculosis.

The charts at the end of the book show evidence of much thought and trouble, but they were spoiled by the bad printing which caused a double impression to be made when they were folded, and in consequence they are bewilderingly complicated. The short foreword by Sir William Osler sums up the whole problem under consideration in a few words, but even he recognises that Dr Barty King's elaborate piece of machinery will need to be "oiled by mutual good feeling" to run smoothly and efficiently.

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www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1425-20-november-2015/6739

Abstracts for the 218th Otago Medical School Research Society Scientific Meeting

Wednesday 23rd September, 2015

A systematic review and multiple treatments meta-analysis to evaluate preoperative carbohydrate loading for enhancing recovery after elective surgery.

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Surgical stress causes increased insulin resistance, which may lead to hyperglycaemia, which in turn may prolong post-operative recovery through delayed wound healing and impaired immune function. The administration of a carbohydrate load preoperatively is postulated to mitigate this. Many randomised controlled trials (RCTs) have examined this, and have been summarised in three recent meta-analyses. However, these could not use all available data, as it is not possible to account for the different doses of carbohydrate administered and the different controls used in the trials, with pairwise meta-analysis. We conducted a multiple treatments (network) meta-analysis to incorporate all available data, regardless of differences in the intervention and control treatments.

We systematically searched article databases for RCTs comparing preoperative carbohydrate treatment with water, a placebo drink, or fasting. We performed a four treatment network meta-analysis comparing two carbohydrate dose groups (low (10–44g); high (>45g)) with two control groups (fasting; water or placebo). Primary outcomes were length of hospital stay and post-operative complication rate. Secondary outcomes included post-operative insulin resistance, vomiting, fatigue and well-being.

We included 34 trials, involving 2,569 participants. Compared to fasting, preoperative low dose and high dose carbohydrate administration decreased post-operative length of stay by 0.6 days (95% confidence interval (CI) 0.1–1, P=0.01; back-transformed standardised mean difference) and 0.3 days (95% CI 0.1–0.5, P=0.005) respectively. There was no significant decrease in length of stay compared to water or placebo. We found no significant difference in post-operative complication rates, or any of the secondary outcomes, between the carbohydrate and control groups.

Carbohydrate administration before elective surgery conferred a small reduction in length of stay only when compared to fasting, but no significant difference when compared to water or placebo. No other significant effect on post-operative outcomes was found.

Supported by a Dunedin School of Medicine Dunbar Scholarship, a Royal Australasian College of Surgeons Foundation for Surgery New Zealand Scholarship, and the Health Research Council of New Zealand.

Cardiovascular microRNAs in diagnosis and therapeutic intervention of diabetic heart disease

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Diabetic heart disease (DHD) is often unrecognised in subclinical stage due to absence of pathognomonic signs, thereby restricting timeous diagnosis and management of disease. Recently, microRNAs (miRs) are gaining popularity as diagnostics and key regulators in the pathophysiology of several diseases including cardiovascular diseases. However, the diagnostic potential and pathophysiological role of miRs in DHD is still unknown.

RNA was extracted from plasma (n=14) of people with diabetes and age- matched non-diabetic volunteers with no history of heart disease. QPCR analyses revealed marked dysregulation of target-miRs (miR-1,-126,-132,-133 and -499) in diabetic plasma which was also dependent on duration of diabetes (P<0.05, unpaired student *t* test). To further answer, whether modulation of circulating miRs has a correlation with etiology of DHD, miR expressions were studied in cardiac tissues (n=10) of 8–32 weeks old type 2 diabetic (Db/db) and non-diabetic mice. Remarkably, all investigated miRs and their target proteins were dysregulated in diabetic myocardium, starting from 8-weeks of age (P<0.05). Importantly, echocardiography and immunohistochemical analyses did not reveal any noticeable changes in diabetic mice until 20-weeks of age (P<0.001). These findings suggest that miRs are early modulators of

DHD and can be explored as therapeutic interventions for prompt management of DHD. In line with these results, we elicited *in vitro* modulation of two target-miRs (miR-126,-132) to explore their therapeutic potential in diabetic state. It was demonstrated that restoration in expression of both miRs in HUVECs abrogated the deleterious effects against high-glucose-induced impaired angiogenesis, proliferation and cell survival (P<0.05). Current studies aim to determine the therapeutic potential of other miRs using HL-1 cardiomyocytes.

Overall, these findings provide the first evidence that miRs can be used as a novel diagnostic tool for early detection of DHD. It also opens up intriguing ways to develop miR-based therapies for management of DHD.

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Influence of obesity on energy expenditure during brisk walking in adults.

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The twentieth anniversary of the physical activity guidelines of 150 minutes each week of moderate intensity activity was marked in 2015. The guidelines represent the time required for a 70 kg man to expend 1,000 kcal. With the global growth in obesity, the average man is now 90 kg. As energy expenditure increases with body mass, obese adults could be expending significantly more than the recommended 1,000 kcal/week. This increased exposure to activity could contribute to the poor outcomes and compliance experienced by this population. The purpose of this observational study was to quantify how indices of obesity, primarily body mass; BMI; waist circumference; and, body composition influence energy expenditure during brisk walking in adults.

A sample of 62 adults (males=18, females=44) was purposively recruited to populate five subgroups of 10 to 13 participants each, sorted by BMI to facilitate equal distribution of BMIs: healthy-weight (BMI 19.5–24.9 kg/m^2); overweight (BMI 25–29.9 kg/m^2); obese I (BMI 30–34.9 kg/m^2); obese II (BMI 35–39.9 kg/m^2); obese III (BMI > 40 kg/m^2). The energy cost of walking (kcal/minute) was determined using indirect calorimetry whilst walking on a treadmill at 4.8 km/h for 15 minutes. Bivariate Pearson's correlation tests and linear regression analysis ($P \leq 0.05$) were used to establish whether indices of obesity are associated with energy expenditure.

Preliminary results show energy cost of walking was strongly correlated with body mass, BMI, waist circumference and fat mass (R=0.77 to 0.86, P <0.001). Moderate correlation was observed with body fat percentage and fat-free mass. Backward multiple regression indicates that energy expenditure can be accurately predicted using fat mass, fat-free mass, heart rate and body mass (R2=0.93, P < 0.001).

The energy cost of walking increases as obesity level rises. As physical activity prescription is based on expending 1,000 kcal/wk, obese adults are potentially significantly overdosing on activity. This data could be used to accurately prescribe a safe and effective individualised dose of exercise for obese adults.

Supported by a grant from the Physiotherapy New Zealand Scholarship Trust Fund.

Two heads are better than one: Dendritic cells and B cells enhance the anti-tumour immune response compared with dendritic cells alone

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The dendritic cell (DC) is well established as the key professional antigen-presenting cell (APC) for priming naïve T cells and, in theory, should be the APC of choice in T cell adoptive cell therapy (ACT). However robust clinical results using T cells primed by DC for ACT remain elusive. Varying methodologies and conditions between groups studying the anti-tumor response of various APCs makes meta-analysis difficult.

In this study the *in vitro* anti-tumor response (proliferation, cytokine profile, cytotoxicity) of T cells primed by one, two or three tumour-lysate-pulsed APCs (DCs, macrophages and B cells) were compared using flow cytometry, ELISA, VITAL and ELISPOT assays. The OVA transgenic (OT) mouse system with the T cell receptor (OT-I CD8+ and OT-II CD4+) responding to specific peptides of the model antigen ovalbumin was employed as the read out.

Granulocyte macrophage-colony stimulating factor (GM-CSF)-differentiated bone marrow fraction of B16OVA tumor lysate (sFTL) was superior to macrophages at stimulating OT-I CD8+ T cell proliferation ($P < 0.05$, unpaired t-tests). A synergistic proliferation response was achieved when GMDCs and B cells were used in combination to present sFTL to CD8+ OT-I T cells ($P < 0.05$, unpaired t-tests). This synergistic response was not seen seen in OT-II CD4+ T cells. The IFN-γ response to antigen presentation by a GMDC+B cell

was also superior to that of GMDCs alone in both CD4+ and CD8+ T cell co-cultures ($P < 0.05$, unpaired t-tests). The in vitro cytotoxicity assay to test the T cells' tumor cell killing ability showed a trend approaching significance, suggesting that the combination of two or more APCs yields more cytotoxic T cells than GMDCs alone.

The literature has multiple studies demonstrating in vivo cooperation between DC and macrophages and DC and B cells. Given that in vivo DC do not present tumor antigen in isolation, these results suggest that a single APC approach may be unnecessarily limiting the potential of ex-vivo APC adoptive cell therapy.

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Impact on glycaemia of walking after eating and standard physical activity advice in type 2 diabetes: a randomised crossover trial.

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Advice regarding physical activity is an accepted component of treatment for type 2 diabetes (T2DM). Physical activity has been shown to reduce blood glucose levels, may reduce cardiovascular disease and may help reduce body fatness in overweight or obese people with T2DM. Current T2DM physical activity guidelines recommend walking 30 minutes each day, but do not specify when physical activity should be taken within the day.

To determine the effects of a postprandial physical activity prescription on glycaemic control we recruited 41 T2DM adults (mean ± SD, age 59.9 ± 9.81 years, hbA1c 58.9 ± 15.50 mmol/mol) into a randomised cross-over trial.

Interventions were walking 10 minutes after each meal compared with walking continuously for 30 minutes at any time of the day, for periods of two weeks.

Continuous glucose monitors were used to calculate the incremental area under the curve (iAUC) for each meal and the sum of total meals. Biochemical and anthropometric measures were taken pre and post interventions. After adjustment for intervention order, iAUC (mmol/L. min) was significantly lower when walking after eating (RR 0.87; 95% CI 0.78, 0.99; P = 0.03), driven by a highly significant difference in the evening meal (RR 0.78; 95% CI 0.67, 0.91; P < 0.001). Changes in biochemical markers and anthropometric markers of body weight and body fatness did not differ between the two-week interventions. Compliance with walking prescriptions between interventions did not differ with 49% of walks undertaken.

Glycaemic improvements were observed when walking after eating compared with current physical activity guidelines that do not specify when in the day to walk. Walking after eating appears a practical means of interpreting physical activity guidelines for those wishing to improve glycaemic control with physical activity.

This trial is registered in the Australian New Zealand Clinical Trials Registry: ACTRN12613000832774, and was funded by the The New Zealand Artificial Limbs Service and a Department of Human Nutrition PBRF grant.

Disruption of NPY neuron developmental mechanisms by maternal obesity and IL-6

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A correlation has been shown, in humans and animal models, between maternal obesity during pregnancy, and obesity in the offspring. Furthermore, the ability of body weight regulating neurons in the arcuate nucleus of the hypothalamus (ARC) to innervate their targets is disrupted in the offspring of obese mothers. The mechanism behind this is unknown. Maternal obesity is associated with increases in inflammatory cytokines, including interleukin-6 (IL-6), in both the maternal and fetal circulation. We hypothesise that an increase in cytokine exposure disrupts the ability of ARC neurons to innervate their targets.

We first investigated a role for the axon guidance factor Netrin-1 in the fetal development of ARC weight regulating Neuropeptide Y (NPY) neurons under normal circumstances. In mice, using *in situ* hybridisation, we have shown that in late gestation Netrin-1 is expressed in a pattern consistent with guiding NPY axons to their targets. Additionally, using a primary culture model we found NPY neurons respond to Netrin-1 by increased elaboration of their growth cones (118 ± 12.75μm^2 surface area, mean ± SEM) when compared to controls (74 ± 9.92 μm^2 surface area, P < 0.05, two-tailed t-test, n=9).

Secondly, we used both *in vivo* and *in vitro* methods to evaluate whether changes in Netrin-1 signaling might account for altered NPY target innervation in maternal obesity. We used a mouse model of maternal obesity to show that fetal ARC expression of the Netrin-1 receptor Dcc was significantly increased in vivo (1.45 fold ± 0.18, P < 0.05, n=6) when compared with controls. We then replicated this finding *in vitro* by exposure of mouse fetal ARC to 100 ng/mL IL-6 (n=4, Dcc fold increase 2.1 ± 0.5, P < 0.05).

These data support a mechanism by which increased IL-6 during maternal obesity can disrupt the normal fetal development of neural feeding circuitry via Netrin-1 signaling.

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