
NATURAL
PRODUCTS NZ®

Treatment gaps, innovation and redefining evidence – a growing role for CM?

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NICM
THE NATIONAL INSTITUTE OF COMPLEMENTARY MEDICINE

MAPrc
We mend minds

TheAlfred

BLACKMORES INSTITUTE
RESEARCH | EDUCATION | INNOVATION


Alfred Hospital
Melbourne Australia

Healthcare spectrum

Wellbeing
Enhanced health

Occasional non-serious health issues

Chronic health condition

Everyday significant disability

Looking for enhanced physical and mental performance

Looking for cures and safe, effective symptom relief

Preventative health – looking to avoid disease

Looking to reduce frequency, severity or progression of disease

Complementary and integrative medicine

Pharmaceutical treatments and surgery

Enormous challenges in healthcare

- Increase in population
  - NZ 4.5 million people in 2013
    - Increase to 6 million by 2061
    - Australia –> 50 million within 20 years
- The projections indicate: population growth will slow as NZ's population ages

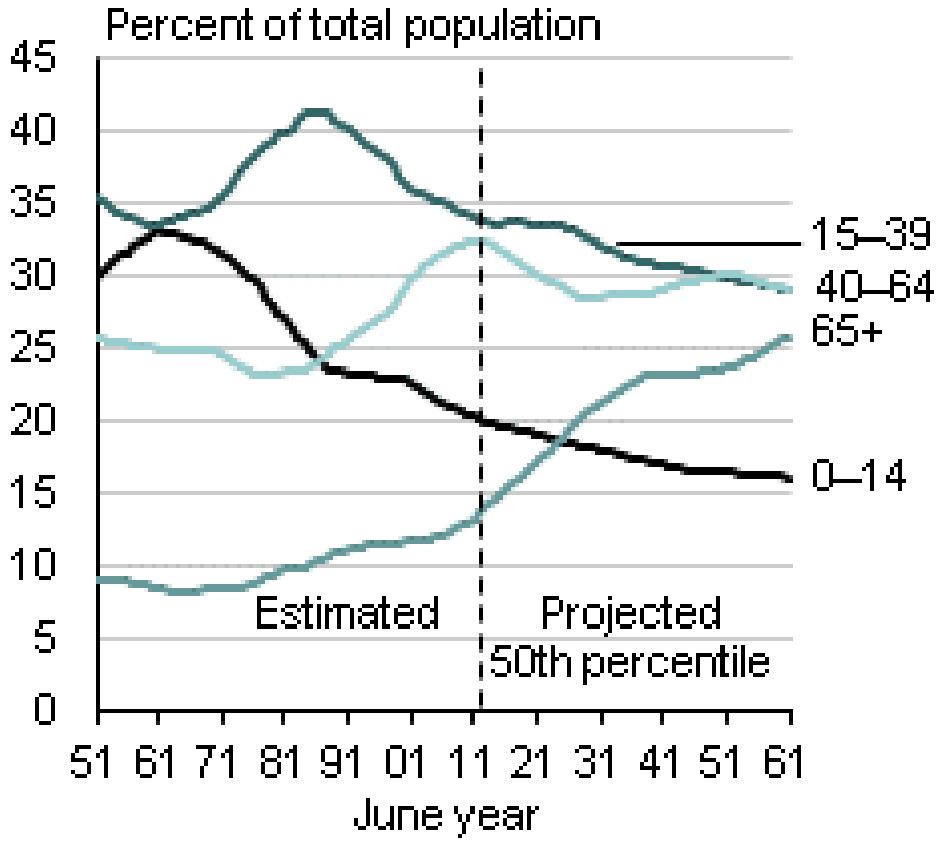
  -> more people with disease

  -> disease pattern changing

  -> sufficient healthcare workforce ? hospital beds?

Age distribution of population

1951–2061



Source: Statistics New Zealand

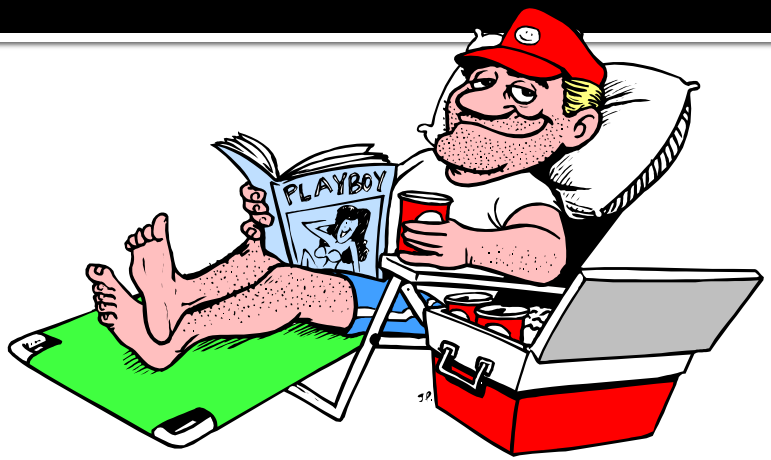
Enormous challenges in healthcare

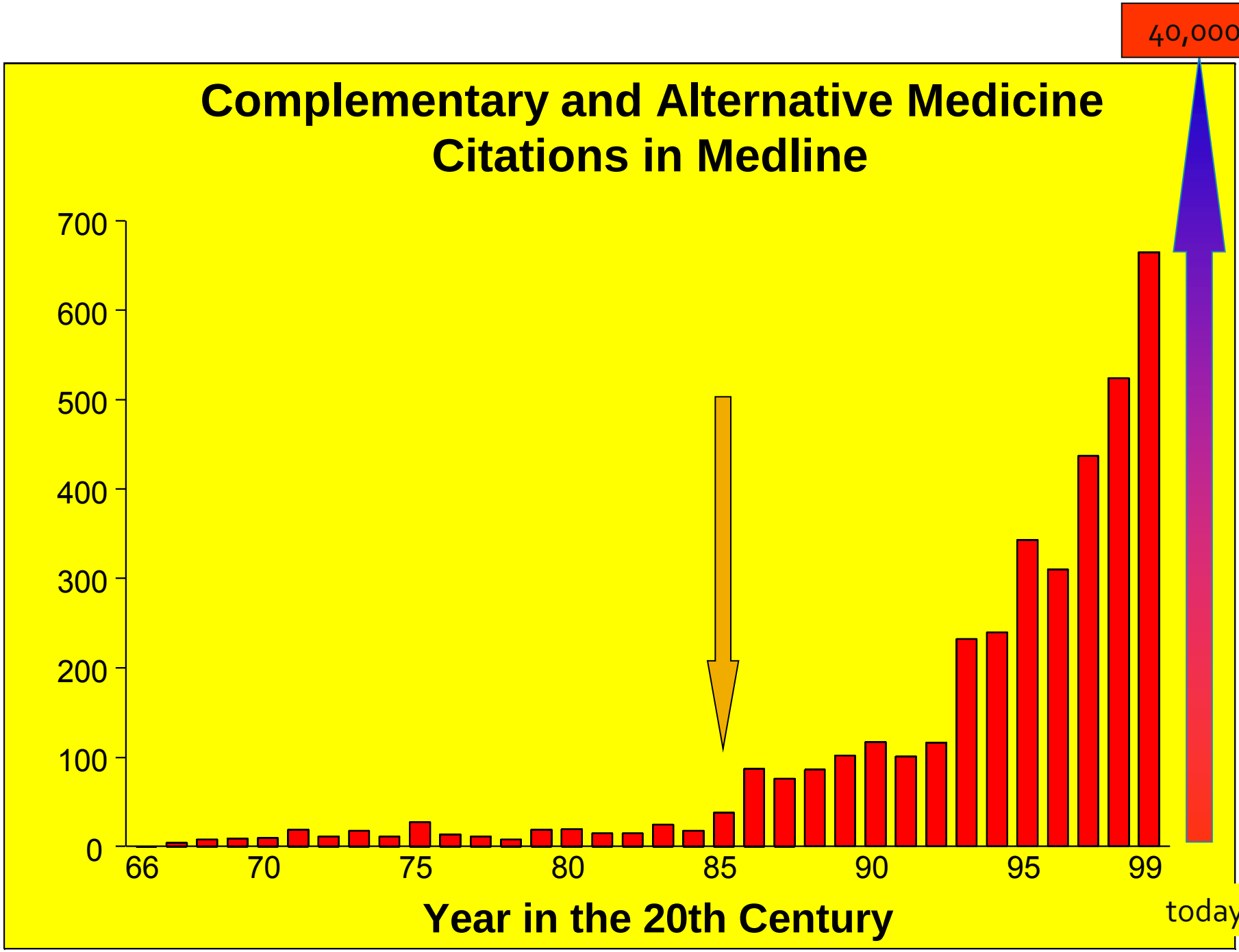
- Lack of change in the way h/care is delivered
  - Practice of medicine has not really changed over the last 30 years
    - Specialties and sub-specialties remain
    - The elderly often require medication for multiple chronic conditions but research and treatment guidelines tend to be more disease-driven than patient-centered
      - -> don't take into account multiple comorbidities, physical / psychological / practical and social needs

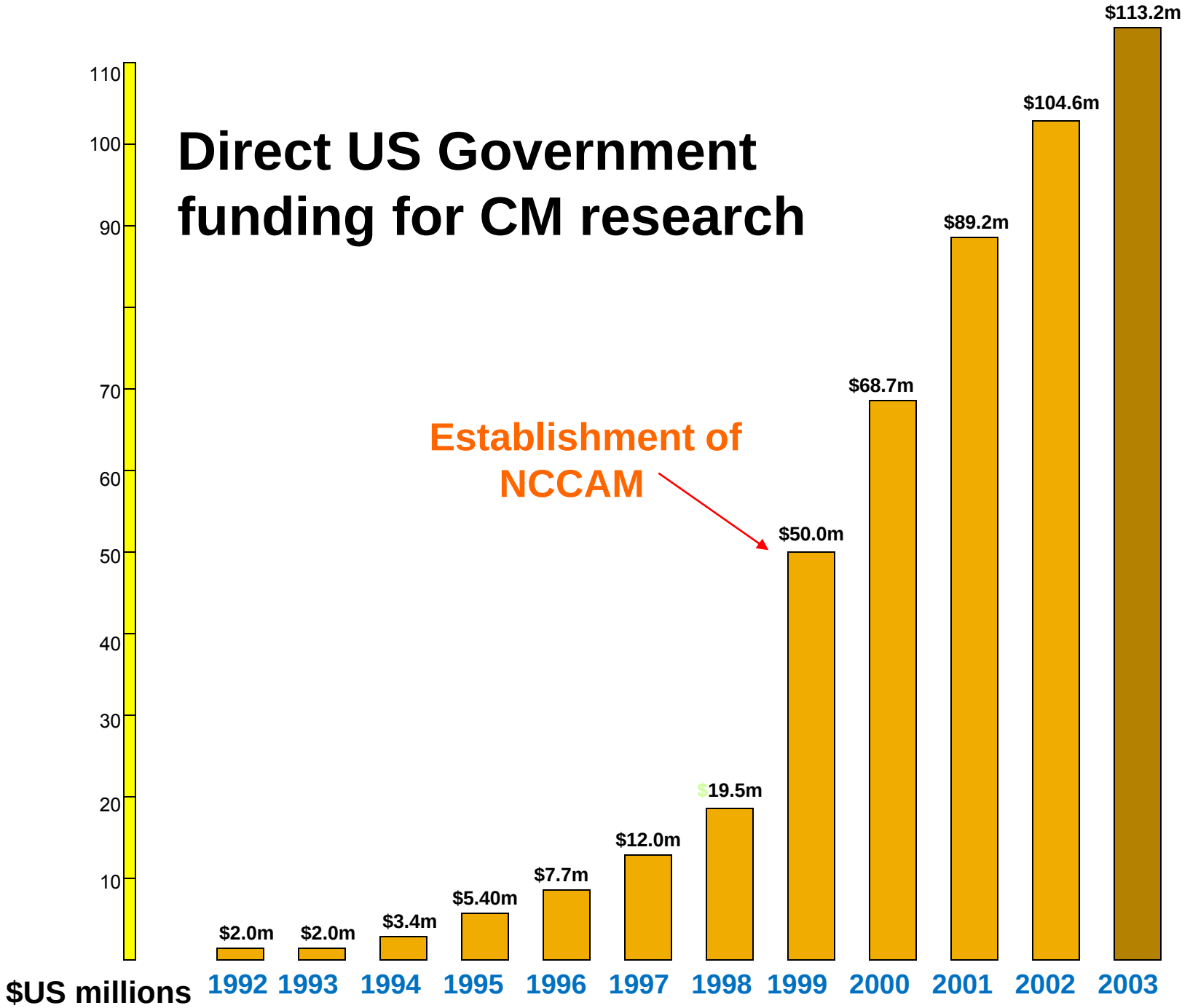
Enormous challenges in healthcare

- Enormous increases in healthcare costs
  - Drug costs, staff costs, transport costs, infrastructure costs
    - How will h/care delivery change?
- Some existing important treatments may no longer be effective enough
  - Antibiotic resistance
- Amount of published health information is increasing
  - How to keep up ? How to evaluate ? Implement in practice ?

Where's the evidence?




40,000
Complementary and Alternative Medicine
Citations in Medline
700
600
500
400
300
200
100
0
66
70
75
80
85
90
95
99
Year in the 20th Century
today


Direct US Government funding for CM research
$US millions
110
100
90
70
60
50
40
30
20
10
$2.0m
$2.0m
$3.4m
$5.40m
$7.7m
$12.0m
$19.5m
$50.0m
$68.7m
$89.2m
$104.6m
$113.2m
Establishment of NCCAM
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003

Producing the evidence in CM

- Problems
  - Scarce funding
    - Lack of government funding
    - Lack of patent protection for CM products/services/processes
  - Infra-structure
    - More researchers with CM expertise+/- understanding required
    - More specialised research centres required
  - RCT model not always relevant or suitable
    - E.G. placebo massage?

Stress reduction study on the cardiothoracic ward; RCT, n=152

Massage therapy for cardiac surgery patients—a randomized trial

Lesley A. Braun, PhD,[a,b] Catherine Stanguts, BNurs, BHSc,[a] Lisa Casanelia, BHSc, Grad Cert Ed,[c] Ondine Spitzer, MSocHlth,[a] Eldho Paul, MSc,[d] Nicholas J. Vardaxis, PhD,[c] and Franklin Rosenfeldt, MBBS, FRACS[a]

Objectives: To determine whether massage significantly reduces anxiety, pain, and muscular tension and enhances relaxation compared with an equivalent period of rest time after cardiac surgery. The feasibility of delivering the treatment, effects on heart rate, blood pressure, and respiratory rate, and patient satisfaction were also assessed.

Methods: Elective cardiac surgery patients were randomized to receive massage or rest time at 2 points after surgery. Visual analog scales were used to measure pain, anxiety, relaxation, muscular tension, and satisfaction. Heart rate, respiratory rate, and blood pressure were measured before and after treatment. Focus groups and feedback were used to collect qualitative data about clinical significance and feasibility.

Results: A total of 152 patients (99% response rate) participated. Massage therapy produced a significantly greater reduction in pain ($P = .001$), anxiety ($P < .0001$), and muscular tension ($P = .002$) and increases in relaxation ($P < .0001$) and satisfaction ($P = .016$) compared to the rest time. No significant differences were seen for heart rate, respiratory rate, and blood pressure. Pain was significantly reduced after massage on day 3 or 4 ($P < .0001$) and day 5 or 6 ($P = .003$). The control group experienced no significant change at either time. Anxiety ($P < .0001$) and muscular tension ($P < .0001$) were also significantly reduced in the massage group at both points. Relaxation was significantly improved on day 3 or 4 for both groups (massage, $P < .0001$; rest time, $P = .006$), but only massage was effective on day 5 or 6 ($P < .0001$). Nurses and physiotherapists observed patient improvements and helped facilitate delivery of the treatment by the massage therapists on the ward.

Conclusions: Massage therapy significantly reduced the pain, anxiety, and muscular tension and improves relaxation and satisfaction after cardiac surgery. (J Thorac Cardiovasc Surg 2012;144:1453-9)

Global health

Global population is getting bigger and it's ageing with more people (especially women) living beyond the age of 80 yrs

Global Burden of Disease (GBD) study 2010

- Collaborative project – nearly 500 researchers in 50 countries
  - led by the Institute for Health Metrics and Evaluation (IHME) at the Uni of Washington
  - largest systematic scientific effort in history to quantify levels and trends of health loss due to diseases, injuries, and risk factors
- GBD serves to inform evidence-based policymaking and health systems design

Global – high burden diseases whereby current treatment is inadequate in reversing or halting the progression of disease

Stroke, osteoarthritis, Alzheimer's disease, hearing loss, low back pain, chronic obstructive pulmonary disease (COPD) and alcoholic liver disease

- data from WHO, GBD Database in Geneva and the Institute of Health Metrics in USA were used to identify the most relevant diseases with the highest burden of disease, as well as the most relevant risk factors in the world.
- Information on predicted public health threats was obtained from the WHO, the EU and other official sources.

Global – high burden diseases whereby current treatment is inadequate in reversing or halting the progression of disease

Depression is a large and increasing contributor to the current and future global burden of disease.

- Priority areas – adolescents, the elderly, reducing side-effects and producing well tolerated treatments

Diabetes is among the leading causes of mortality and disease burden in Western countries

Major problem – **lack of adequate biomarkers to detect disease, track progression and use in research**

NZ Disease patterns

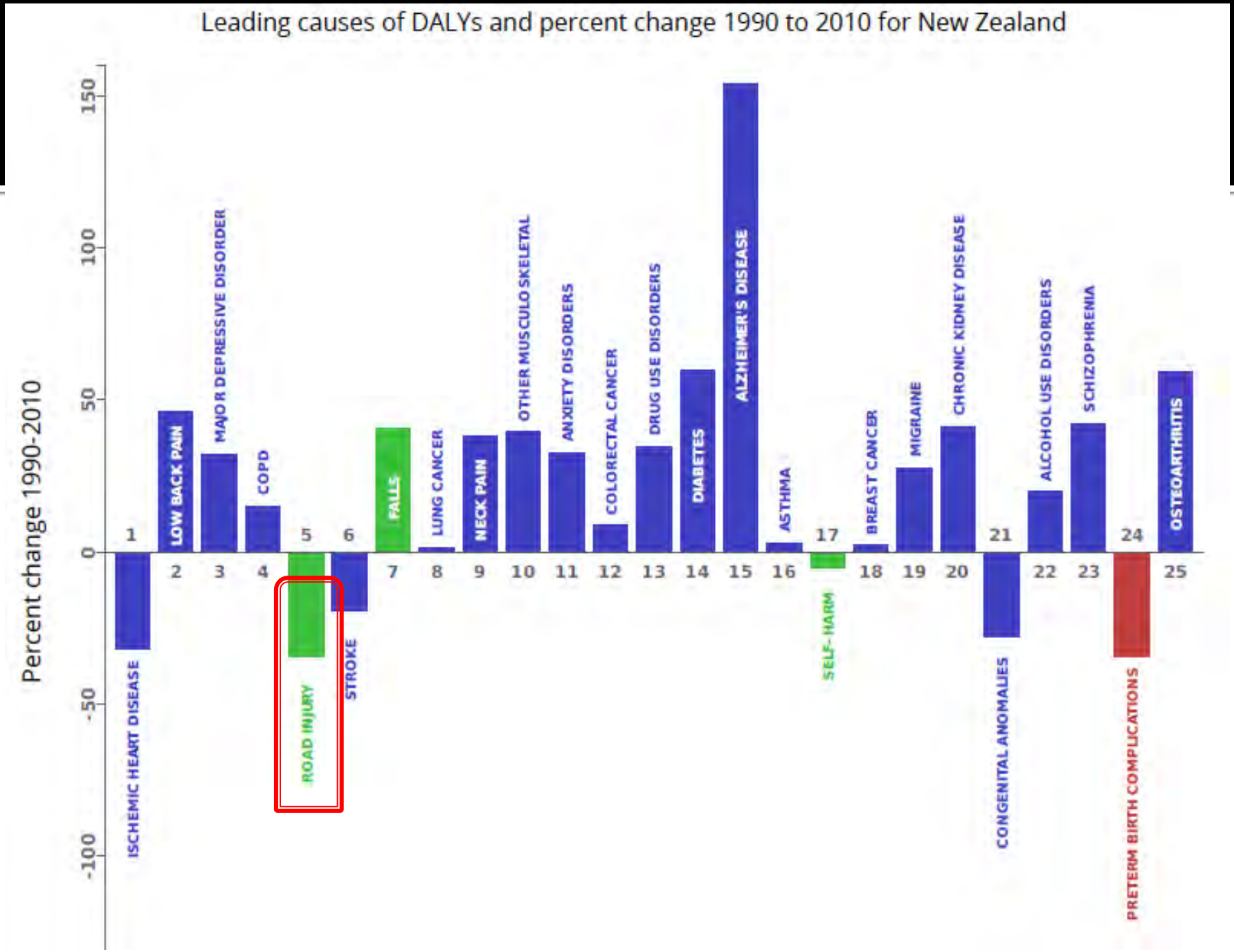
Disease patterns

In terms of the number of years of life lost (YLLs) due to premature death in New Zealand

- ischemic heart disease,
- trachea, bronchus, and lung cancers
- and cerebrovascular disease were the highest ranking causes in 2010.

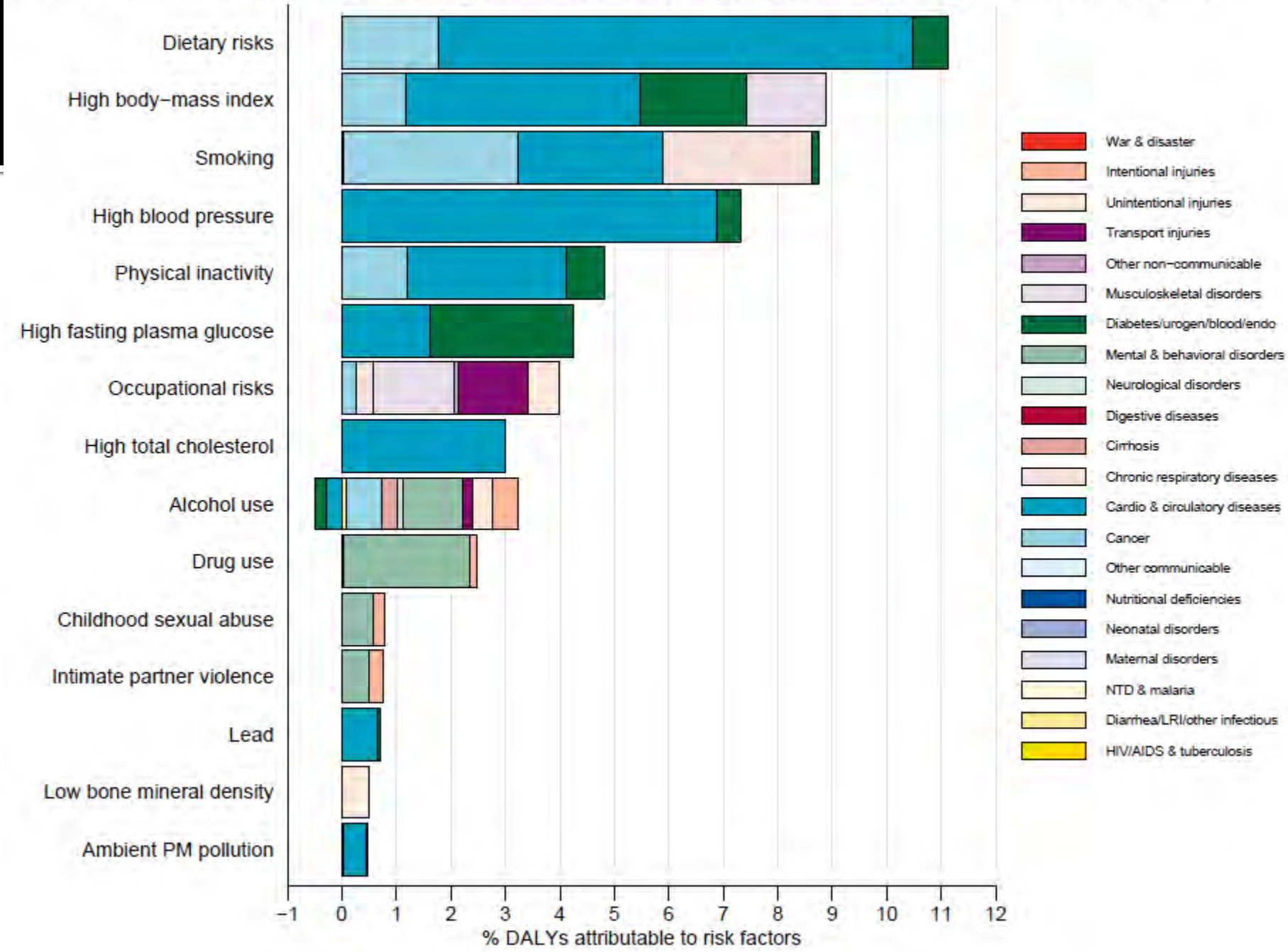
Of the 25 most important causes of burden, as measured by disability-adjusted life years (DALYs), road injury showed the largest decrease, falling by 34% from 1990 to 2010

The leading risk factor in New Zealand is dietary risks

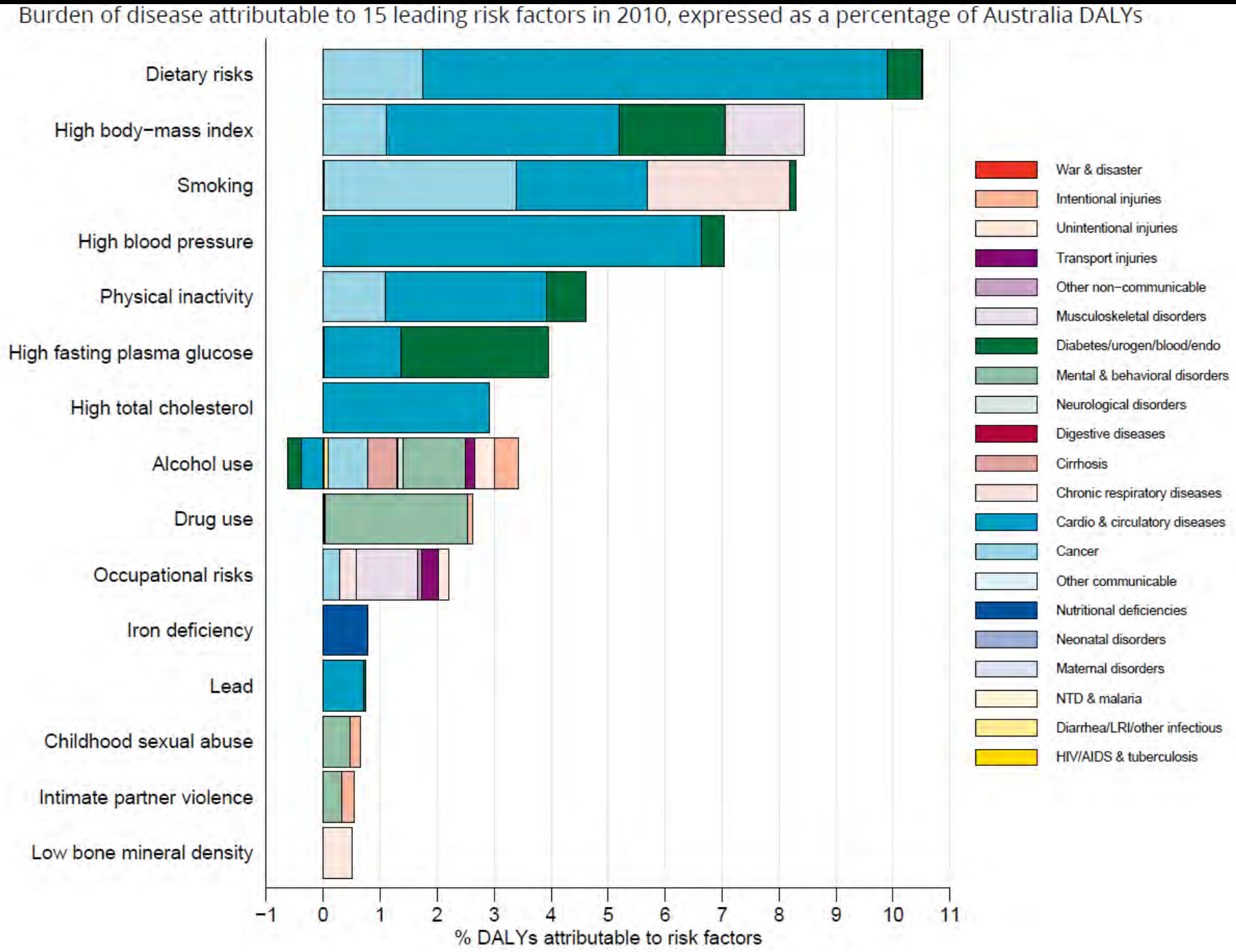

Leading causes of DALYs and percent change 1990 to 2010 for New Zealand
Percent change 1990-2010
150
100
50
0
-50
-100
1 ISCHEMIC HEART DISEASE
2 LOW BACK PAIN
3 MAJOR DEPRESSIVE DISORDER
4 COPD
5 ROAD INJURY
6 STROKE
7 FALLS
8 LUNG CANCER
9 NECK PAIN
10 OTHER MUSCULOSKELETAL
11 ANXIETY DISORDERS
12 COLORECTAL CANCER
13 DRUG USE DISORDERS
14 DIABETES
15 ALZHEIMER'S DISEASE
16 ASTHMA
17 SELF-HARM
18 BREAST CANCER
19 MIGRAINE
20 CHRONIC KIDNEY DISEASE
21 CONGENITAL ANOMALIES
22 ALCOHOL USE DISORDERS
23 SCHIZOPHRENIA
24 PRETERM BIRTH COMPLICATIONS
25 OSTEOARTHRITIS

The leading risk factor in NZ is related to dietary risks

Burden of disease attributable to 15 leading risk factors in 2010, expressed as a percentage of New Zealand DALYs



Australian disease patterns


Burden of disease attributable to 15 leading risk factors in 2010, expressed as a percentage of Australia DALYs
Dietary risks
High body−mass index
Smoking
High blood pressure
Physical inactivity
High fasting plasma glucose
High total cholesterol
Alcohol use
Drug use
Occupational risks
Iron deficiency
Lead
Childhood sexual abuse
Intimate partner violence
Low bone mineral density
−1
0
1
2
3
4
5
6
7
8
9
10
11
% DALYs attributable to risk factors
War & disaster
Intentional injuries
Unintentional injuries
Transport injuries
Other non−communicable
Musculoskeletal disorders
Diabetes/urogen/blood/endo
Mental & behavioral disorders
Neurological disorders
Digestive diseases
Cirrhosis
Chronic respiratory diseases
Cardio & circulatory diseases
Cancer
Other communicable
Nutritional deficiencies
Neonatal disorders
Maternal disorders
NTD & malaria
Diarrhea/LRI/other infectious
HIV/AIDS & tuberculosis

Treatment gaps – an opportunity

Treatment gaps

- A gap exists for a disease or condition when:
  - pharmaceutical treatments for that condition will soon become ineffective (e.g. due to resistance)
  - the delivery mechanism or formulation is not appropriate for the target patient group
  - or when an effective medicine either does not exist or is not sufficiently effective (e.g. lack of basic scientific knowledge or lack of financial incentive)

- WHO report

Treatment gaps
Opportunities for CM

- Common conditions with no/poor treatments
  - Changing population characteristics & needs
- Improving current treatments
  - Less tolerance, less side effects, less resistance, better response
- Producing better treatments
  - Safer, more accessible, cheaper, easier to use, more effective
- Preventative medicine and wellness promotion
  - Primary and secondary prevention

Some gaps to be filled

- More effective meds
  - eg anti-depressants and mild depression, pain treatment
- High risk and low benefit ?
  - eg some migraine prevention Rxs, acne treatment in young adults
- Resistance? & tolerance ?
  - eg antibiotics, benzodiazepines, opiates
- Safety issues
  - NSAIDs
- Poor adherence ?
  - eg statins, antidepressants
- Expensive ?
  - eg statins
- Improve usability ?
  - Eg need for refrigeration, multiple daily doses ?
- Not good enough ?
  - eg opiates and pain relief, NSAIDs and OA, benzodiazepines and insomnia, treatments for infection control ? menopausal symptoms ?

Treatment delivery

- Healthcare delivery changing
  - Workforce shortage in some areas
    - Specialties and geographic locations
  - Changes to location of service delivery
    - eg hospital vs community vs home based
  - Greater reliance on non-medical h/care providers ?
    - Greater role for CM practitioners ?
    - Pharmacists ? No fee for service and accessible
    - Nurse practitioners
    - Self-care?

Innovation

Define, discover, develop, demonstrate, DISCUSS & disseminate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xhkong.com


Our
Get Along
Shirt

innovation – 2 methods

1. Experimental

- Defined problem – letting solution unfold through discovery
  - Proceeds gradually through trial and error
  - exploring and uncovering parts of the solution
- Deferring judgement to allow creativity – within boundaries
- You have to deal with some uncertainty

Pharma companies do this all the time

Problem with granting bodies – is this type of innovation encouraged ?

2. Conceptual

- big, bold, revolutionary idea that you can define
- Still doesn't mean it will happen easily or quickly or even work

- Define
  - What do people want/need ?
  - What isn't being provided well & could be done better ?
    - Safer, effective, easy to use, fill the gap
    - Prevent, treat, improves quality of life
- Discover
  - Traditional evidence, phytopharmacology, novel mechanisms
- Develop
  - Characterisation, quality, stability, safety, deliverable
- Demonstrate
  - Testing – various models
- Discuss & disseminate
  - Publish, promote, let people know

Innovation in CM

- Novel/better delivery mechanisms
  - To increase bioavailability of key active components
  - To increase stability of product
  - To improve adherence to treatment
- Developing new or better treatments
  - With novel mechanisms
  - Based on known pharmacology of the herb
  - Based on traditional evidence + preclinical research + understanding of disease pathology
  - To address 'pharma treatment gaps'

Examples

Evidence of the involvement of the monoaminergic systems in the antidepressant-like effect of Aloysia gratissima;
Journal of Ethnopharmacology , 24/7/2013

Improved lipid profile in hyperlipidemic patients taking vaccinium arctostaphylos fruit hydroalcoholic extract: a randomized double-blind placebo-controlled clinical trial ; Phytotherapy Research, 24/05/2013

A randomized, double-blind, controlled trial of a Chinese herbal formula (Er-Xian decoction) for menopausal symptoms in Hong Kong perimenopausal women ; Menopause, 28/06/2013

Alkaloids as a source of potential anticholinesterase inhibitors for the treatment of Alzheimers disease
Journal of Pharmacy and Pharmacology, 25/06/2013

Comparison Between the Efficacy of Ginger and Sumatriptan in the Ablative Treatment of the Common Migraine
Phytotherapy Research, 13/05/ 2013

Innovation in CM

- **Integration**
  - **With existing treatments**
    - drug boosters using natural CYP inhibitors
    - reducing drug side effects
    - Improved drug or surgery response
    - Reducing AB resistance
  - **With service provision**
    - CM specialty services
      - Integrative oncology
    - CM preventative health specialists
      - Integrative cardiac wellness
    - In hospitals, clinics, home

Evidence

The days of the RCT standing alone at the summit of the hierarchy of evidence are numbered

Controversy over "Contradiction": Should Randomized Trials Always Trump Observational Studies?

ASTRID E. FLETCHER

386 AMERICAN JOURNAL OF OPHTHALMOLOGY MARCH 2009

Randomized controlled trials do not reflect reality: Real-world analyses are critical for treatment guidelines!

Martin T. R. Grapow, MD,[a] Robert von Wattenwyl, MD,[a] Ulrich Guller, MD,[b] Friedhelm Beyersdorf, MD, PhD,[c] and Hans-Reinhard Zerkowski, MD[a]

The Journal of Thoracic and Cardiovascular Surgery • Volume 132, Number 1 5

The RCT

- Sir Austin Bradford Hill - often credited for the modern RCT, not only warned about the "potentially dangerously misleading" nature of "poorly constructed trials," but also cautioned,

"any belief that the controlled trial is the only way would mean not that the pendulum has swung too far, but had come right off the hook."

Can J Neurol Sci 2013

Innovation and evidence

Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings

- Evidence with 'real life' relevance
  - 'field studies' , whole systems research, clinical audits
  - electronic health records (for efficacy and safety data)
- Comparative-effectiveness & cost-effectiveness
  - Does it present a benefit over std Rx? Eg safety, tolerance, cost, efficacy?

Circle of methods

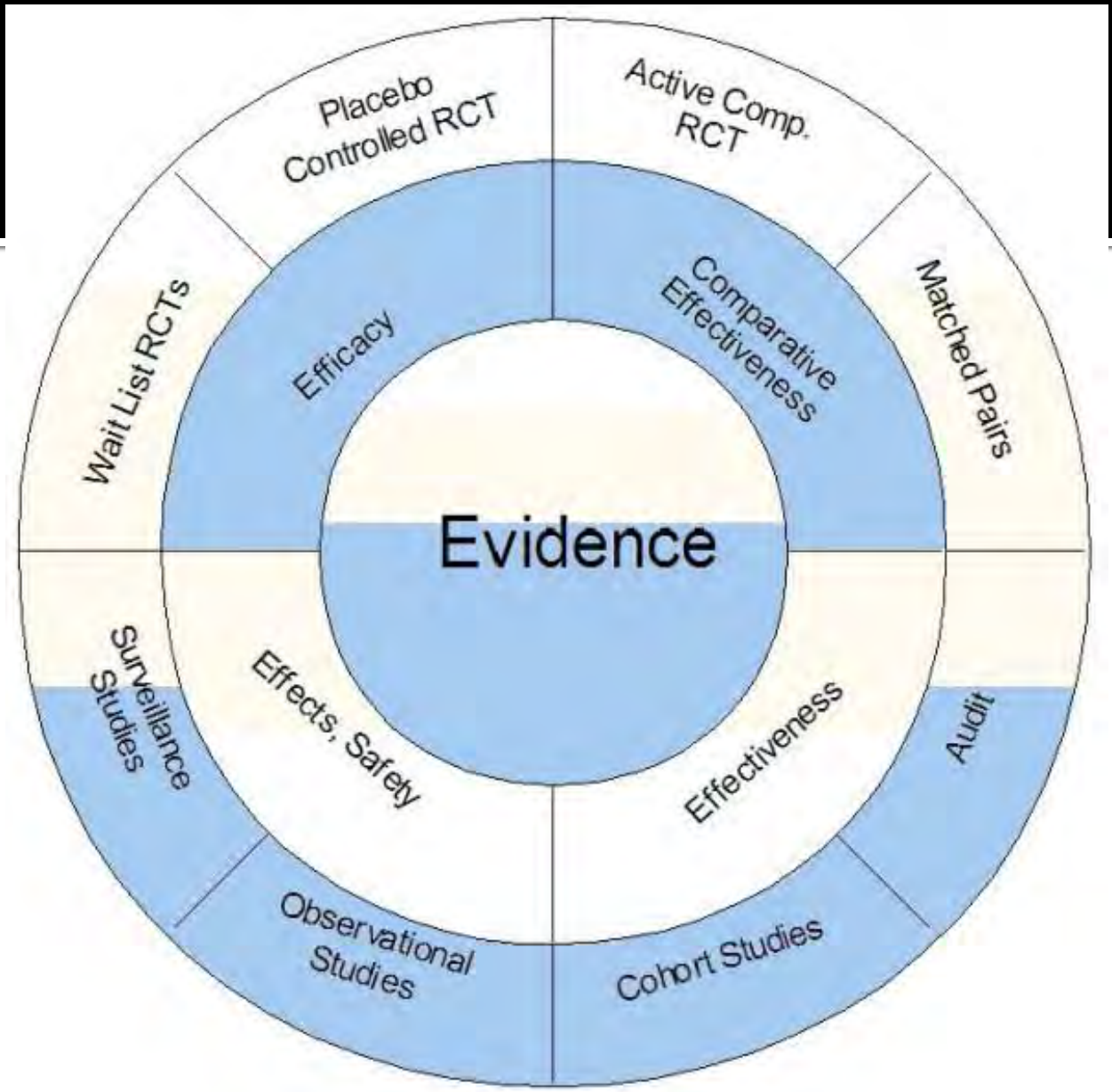
The whole essence of circularity is its ability to see the whole problem within a patient-centered and human therapeutic perspective, allowing rigorous evidence, individualized decision-making at the clinical interface.

Walach *et al. BMC Medical Research Methodology* 2006 **6**:29 doi:10.1186/1471-2288-6-29

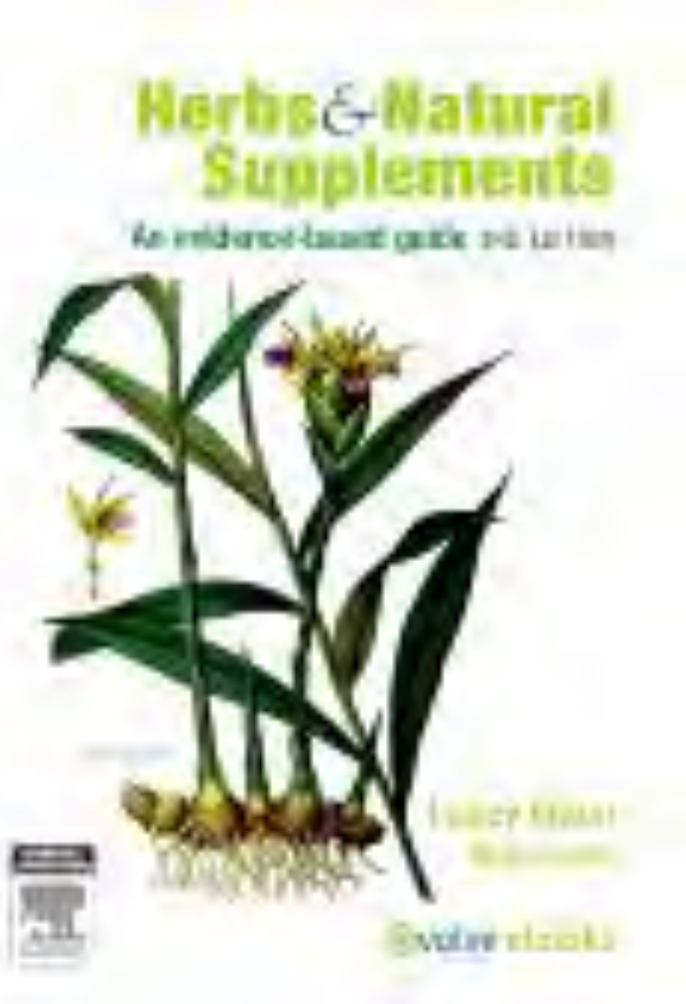
Experimental studies testing efficacy

Complemented by

Real life validity



Show me the evidence



Main actions – pharmacological activity based on in vitro and in vivo models

Main uses – based on clinical evidence and traditional use

Safety – based on mechanisms of action, case reports, post-market surveillance reports, traditional cautions and contra-indications

Snapshot of evidence

A body of evidence for a treatment built from multiple information sources using several models

Traditional evidence	Basic science	Pre-clinical	Case series Clinical audit	N=1 w rechallenges	RCT Waitlist Placebo Active	Obs study w large effect	Comparative effectiveness
Suggestive	Mechanism-based reasoning Biological plausibility		Proof-of-concept Real-life validity		Robust but not real	Suits some sit'ns when RCTs wont	Is it the same/better than std treatment ? Defining place in practice
I	II		III		IV		V

Greater role for the public

- "Despite an over three-fold rise in spending on pharmaceutical research and development in Europe since 1990, there is an increasing mismatch between people's real needs and pharmaceutical innovation'
  - Nina Sautenkova, WHO/Europe.

Validity and representativeness

- The public and patients should contribute to the relevance and quality of biomedical research and development based on their 'experiential knowledge

To what extent is a patients experiential knowledge representative ?

- And how best to consult ? Incorporate their knowledge into the scientific process?

To what extent is a public representative views valid and truly representative?

- What evidence is required to be sure ?

Communicating the evidence

- How do pharmacists, naturopaths and medical practitioners start incorporating evidence into practice ?

- Professional magazines and journals
- Conferences and continuing education
- Clinical guidelines
- Specific courses

Australian Journal of Pharmacy since 2000

- ACE-Inhibitors and zinc status
- Antibiotics and probiotics
- Statins and CoQ10
- PPIs and magnesium

COMPLEMENTARY MEDICINE

Individualised prescribing and nutrient–drug interactions

By Dr Lesley Braun, Senior Research Fellow, Department of Surgery, Monash University, Research pharmacist Alfred Hospital, Vice president of the National Herbalists Association of Australia

THIS IS THE FIRST IN A SERIES OF ARTICLES THAT CONSIDERS NUTRIENT–DRUG INTERACTIONS AND THEIR IMPLICATIONS TO PHARMACIST PRACTICE AND INDIVIDUALISED PRESCRIBING.

ANTIHYPERTENSIVES AND ZINC

Bearing this in mind, let's now consider the evidence surrounding the possible association between zinc and antihypertensive medication, an association recently brought into the media due to the launch of the new Blackmores range.

Back in 1988, Abu-Hamdan *et al* hypothesised that one of the side effects of ACE inhibitor use, hypogeusia (lack of taste acuity), may be due to medication induced zinc deficiency caused by increased urinary loss.[23] To test the theory, plasma zinc levels and urinary zinc

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1. To stimulate discussion and debate in the field of integrative medicine
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3. To encourage international and inter-disciplinary collaboration and networking between organisations, associations, institutions and practice based communities
4. To focus on rigorous clinical research, including both qualitative and quantitative, systematic and narrative reviews, case studies and surveys and other clinically relevant articles