Folate and healthy babies: Case Study

In 1989, Professors Carol Bower and Fiona Stanley published the results of a case-control study demonstrating the role of maternal dietary folate in reducing the risk of neural tube defects (NTDs) such as spina bifida. The data for this study came from what is now known as the Western Australian Register of Developmental Anomalies (WARDA) which was established in 1980. The study contributed evidence to support public health interventions, including mandatory fortification of bread flour, which since 2009 has helped lower NTD rates and removed the gap between NTD rates in non-Aboriginal and Aboriginal populations. In 2018, mandatory fortification of flour with folic acid was recognised by the Public Health Association of Australia as one of the top 10 public health successes of the past two decades in Australia.

Origin

Folate deficiency was first suspected as a cause of neural tube defects (NTDs) in the 1960s. In the United Kingdom, researchers Elizabeth Hibbard and Richard Smithells found that women who had given birth to children with serious birth defects - and specifically infants with central nervous system defects - were more likely to have an impaired folate status than mothers of infants with no birth defects.

In 1980, Smithells and others reported the results of a non-randomised clinical trial showing the possible prevention of recurrence of NTDs by providing women with folic acid and other vitamin supplements before and in early pregnancy. These researchers showed that giving supplements to mothers who previously had an infant with an NTD, reduced the incidence of NTDs in a subsequent pregnancy to less than 1% of cases. The figure was around 5% for unsupplemented mothers. Through the 1980s, such research spurred many studies investigating folate and NTDs.

Work on folate in Australia began within the NHMRC-supported Research Unit in Epidemiology and Preventive Medicine at The University of Western Australia (UWA), which later formed the nucleus of the Telethon Kids Institute.

Prompted by the thalidomide disaster and concerns about Agent Orange use in Vietnam, the Deputy Director of the unit, Professor Fiona Stanley, and her colleague Professor Carol Bower, established WARDA – the first register of its kind to be established in Australia. Their work guided the development of such registers in other states.

Grants and Investment

NHMRC supported the establishment of the Research Unit of Epidemiology and Preventive Medicine at UWA and also funded Stanley, Bower and Professor Heather D'Antoine with a number of grants between 1975 and 2010.

Professor Carol Bower
- Public Health Travelling Fellowship: 1982
- Research Fellowships: 2001, 2005

Professor Fiona Stanley
- Clinical Sciences Fellowship: 1975
- Research Unit Grant: 1989
- Project Grants: 1991, 1994
- Targeted Calls for Research (TCR): 1993, 1995
- Centre of Research Excellence (CRE): 2005
- Enabling Grants: 2005, 2006

Professors Carol Bower and Fiona Stanley
- Program Grants: 1996, 2000, 2005
- CRE: 2002

Professor Heather D'Antoine
- Postgraduate Scholarship (PGS): 2004
- TCR: 2005

The neural tube, which later becomes a baby's spinal cord, spine, brain and skull, develops very early in pregnancy.

Folic acid supplementation prior to conception helps prevent NTDs such as spina bifida, where the fetal spinal column doesn't close completely, leading to lifelong impairment.

Research

Bower and Stanley collected data from the mothers of case subjects with NTDs and two groups of control mothers: one whose infants had other birth defects (identified from the Register) and one whose infants had no birth defects (identified randomly from the Midwives data system). These data included information on diet, illness, drugs and alcohol intake, cooking methods and vitamin supplementation. They also collected blood samples to enable estimation of folate levels.

In 1989, they published the results of this research which showed that an increased intake of dietary folate in the first six weeks of pregnancy protected against the occurrence of isolated NTDs in infants. Many other observational cohort and case-control studies were published in the 1980s and early 1990s, also showing a protective effect of folic acid supplementation or dietary folate prior to conception.

In the early 1990s, two overseas randomised controlled trials were published, providing conclusive evidence that periconceptional folic acid supplementation prevented both recurrent and occurrent NTDs. Informed by this research, in 1993-94 NHMRC issued recommendations for use of periconceptional folic acid supplements, and the following year it considered fortification of foods with folic acid. Voluntary fortification of certain foods with folic acid began in 1997.

Folate is a B group vitamin especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folic acid is the manufactured version sold as supplements and added to fortified foods.

Translation

In 1992, Bower and Lynda Blum led a health promotion campaign in WA, the first of its kind in the world. The campaign promoted folate-rich foods and supplements and informed health professionals and women of childbearing age of the folate-NTD link. Similar programs were later undertaken in other parts of Australia.

Through such health promotion interventions, and also through voluntary fortification of selected foods with folate, NTDs were reduced by 30% in WA, and from 10%–30% in other states

However, many women of child-bearing age still had inadequate folic acid intakes, largely due to the considerable number of unplanned pregnancies, but also to a lack of knowledge regarding folic acid benefits and to barriers to supplement use, including cost and access.

Using data from WARDA, Bower, D'Antoine and colleagues found that Aboriginal infants had a higher rate of NTDs than non-Aboriginal infants, and that the decline in NTDs following health promotion was confined to non-Aboriginal infants. Mandatory fortification of bread was seen as a potential solution to this disparity.

In 2004, the Australia and New Zealand Food Regulation Ministerial Council requested that Food Standards Australia New Zealand (FSANZ) consider mandatory folic acid fortification to help reduce the incidence of NTDs.

The research and ongoing advocacy of Bower, Stanley, Blum and D'Antoine played a central role in the government reaching this decision.

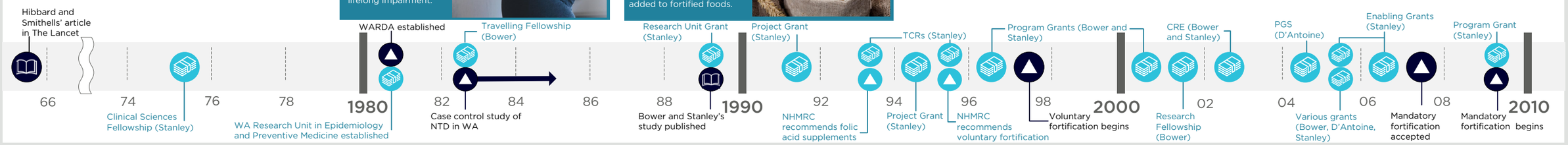
Outcomes and Impacts

After extensive consultation, mandatory fortification requirements were accepted in 2007 and from September 2009 became effective as part of *Standard 2.1.1 Cereals and cereal products* in the Australia New Zealand Food Standards Code. The Standard requires the addition of folic acid to wheat flour for making bread in Australia within the prescribed range of 200-300 micrograms per 100 grams of flour to bread (excluding bread represented as 'organic').

Following mandatory folic acid fortification, the rate of NTDs in Australia decreased significantly (by 14.4%). Among teenagers, the rate of NTDs decreased even more, by almost 55%, and for Aboriginal and Torres Strait Islander women, the rate of NTDs decreased by 74%.

A study by Bower, D'Antoine and colleagues, of Aboriginal people in WA before and after fortification, found that 10% of female participants and 26% of male participants were folate deficient before fortification, that fortification had resulted in additional 145-178 dietary folate equivalents in intake per day, and that no participant was folate-deficient post-fortification. NTD prevalence in Aboriginal infants in WA fell by 68% following fortification.

In 2017, a study - commissioned by the Australian Health Ministers' Advisory Council (AHMAC) - on the effectiveness and cost effectiveness of mandatory folic acid fortification, reported that this intervention yields approximately 500 additional quality-adjusted life years and saves $2 million per year, each year it is in place.



Professor Fiona Stanley AC

Professor Stanley has spent her career researching the causes of major childhood illnesses such as birth defects. She was Founding Director of the Telethon Kids Institute in Perth, WA, inaugural Chief Executive Officer of the Australian Research Alliance for Children and Youth, Professor of Paediatrics, UWA, and Vice-Chancellor's Fellow at The University of Melbourne. She is currently Distinguished Research Professor, School of Paediatrics and Child Health, UWA. Professor Stanley is a leading Australian epidemiologist and has been active in improving health conditions in Australia's Aboriginal populations by recruiting and training Aboriginal researchers and leaders. She was made a Companion (AC) in the General Division of the Order of Australia in 1996 and was named Australian of the Year in 2003.

Professor Carol Bower

Professor Bower is an epidemiologist and public health physician, and a Senior Principal Research Fellow at Telethon Kids Institute. She established the first birth defects registry in Australia in 1980 (WARDA) and served as its head from inception until 2016. She has undertaken extensive research on NTDs and Fetal Alcohol Spectrum Disorder, with a focus on translation and evaluation. She has used WARDA data for regular monitoring and surveillance of birth defects and supported use of the data for research into causes, outcomes, evaluation of prevention, screening, management and diagnosis of birth defects. Professor Bower was inducted into the Australian Academy of Health and Medical Sciences in 2017 and WA Science Hall of Fame in 2019.

Professor Heather D'Antoine

Professor D'Antoine is a Distinguished Honorary Fellow of Menzies School of Health Research (Menzies). She has 25 years of experience in health services as a registered nurse and midwife and as a health service manager in both Aboriginal health services and general health services across Western Australia. She transitioned into research in 2001 and served eight years at Telethon Kids Institute and 10 years at Menzies. She has clinical qualifications in general nursing and midwifery and academic qualifications in health economics. Professor D'Antoine's research interest is in maternal and child health with a focus on the area of Fetal Alcohol Spectrum Disorder and other birth defects.

Ms Lynda Blum

Ms Blum has a Master of Public Health (UWA) and has worked for the Department of Health in the Northern Territory and in Western Australia, and at Edith Cowan University. Over her career, she has worked on several high-profile health promotion campaigns including folate. Ms Blum has educated allied health professionals and worked to influence women of child-bearing age of the importance of folate to prevent NTDs.

WARDA

The Western Australian Register of Developmental Anomalies (WARDA) records and monitors developmental anomalies and keeps track of where and when they are occurring in Western Australia. This information guides research and is used to aid investigation into the causes, prevention and management of developmental anomalies.
WARDA has been central to the story of folate and the prevention of NTDs and its data have been used in case-control studies, population prevalence studies and monitoring of NTD trends over time. The data have provided the evidence to support public health interventions and to evaluate their effectiveness.