

Growing up with GUSTO



Yap-Seng CHONG

Associate Professor, Dept of Obstetrics & Gynaecology, NUHS

*Executive Director, Singapore Institute for Clinical Sciences, A*STAR*

24 February 2016

Research

Clinical Care

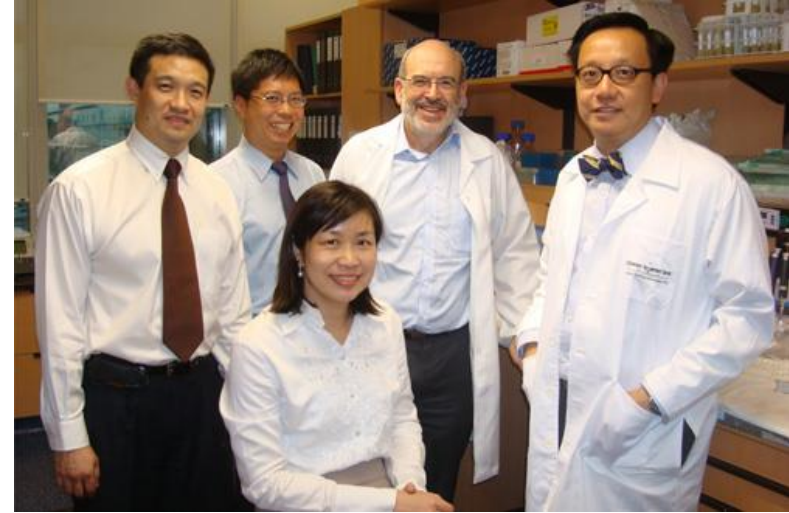
Education

DeVOS

Developmental Origins : Singapore

Translational and Clinical Research Flagship Programme

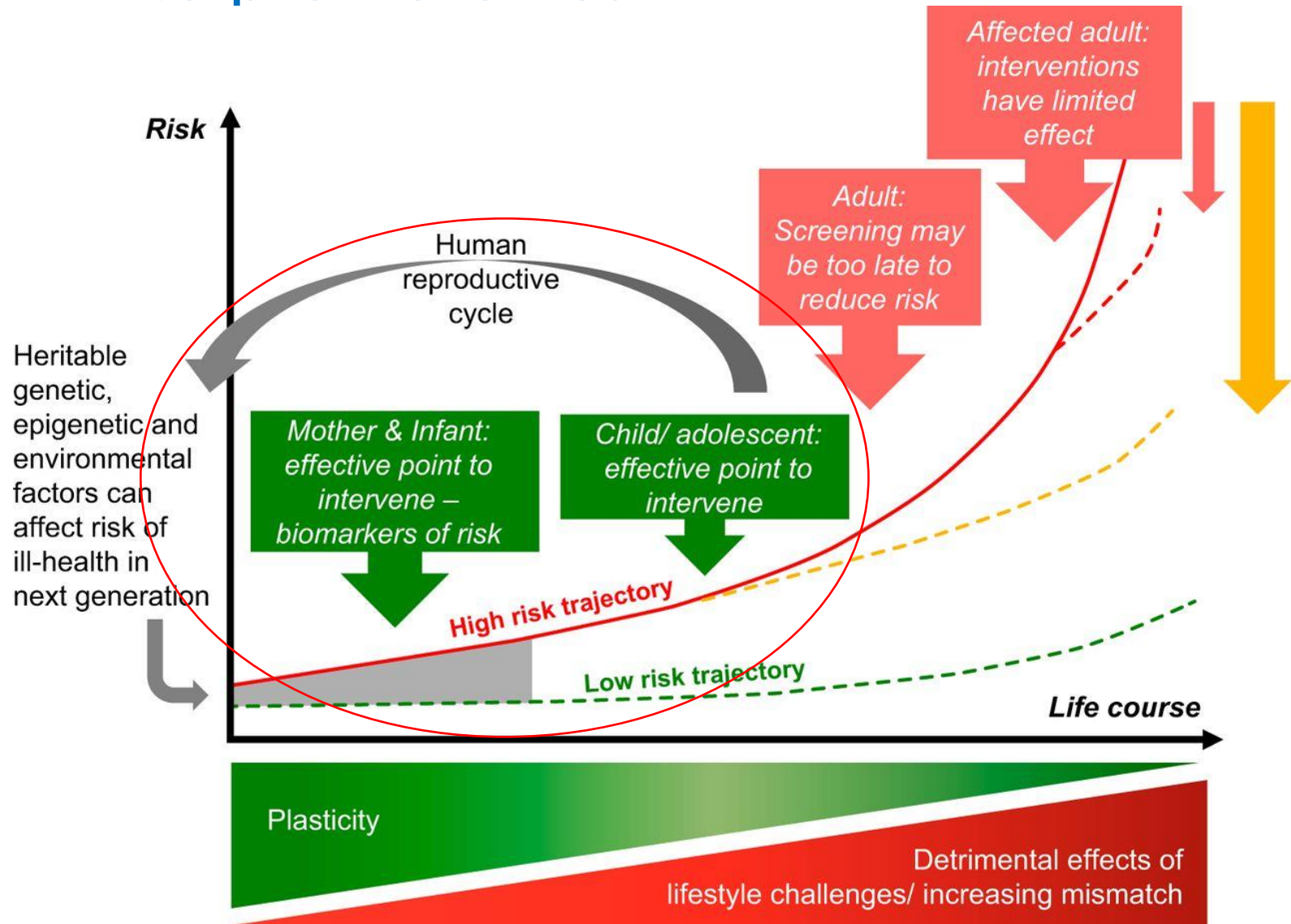
\$25 million over 5 years, awarded end 2008;
renewed end 2013



Developmental Pathways to Non-Communicable Diseases

- To study how **pregnancy** and **early childhood** conditions (development) influence the tendency of individuals to develop non-communicable diseases (obesity, diabetes, neurodevelopmental disorders) later on in life.
- To study how **ethnicity** influences the tendency of individuals to develop NCDs.
- Main aim is to find ways to **prevent** these chronic diseases rather than just treating them or preventing their complications.

Windows of opportunity to promote health



If you mess up
your children,
nothing else you
do really
matters.

Jacqueline Kennedy
Onassis, 1929-1994



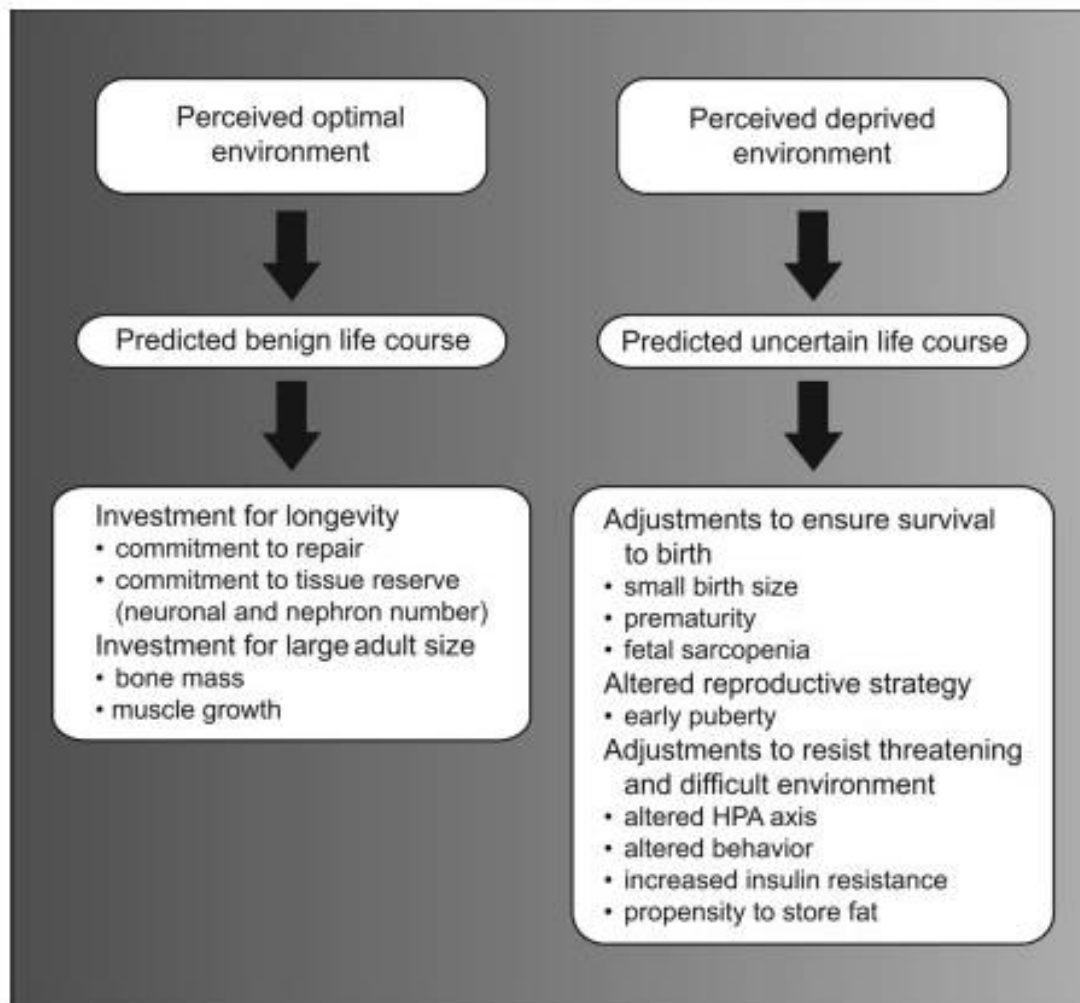
How does early life affect long term health?

Pregnancy

Early childhood

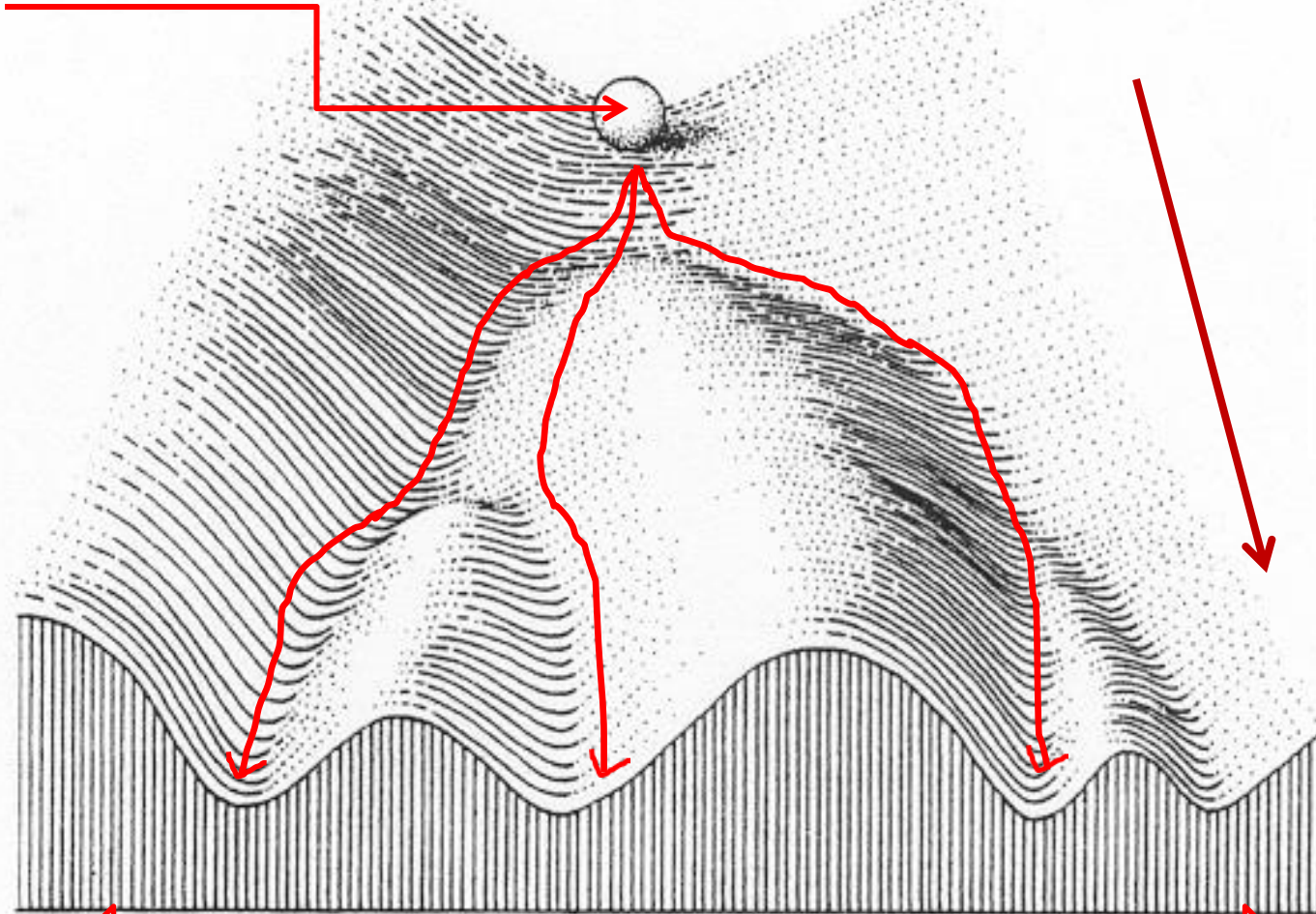
First 1000 days

How the pregnancy period affects the baby's future development



Development from a phenotypic perspective

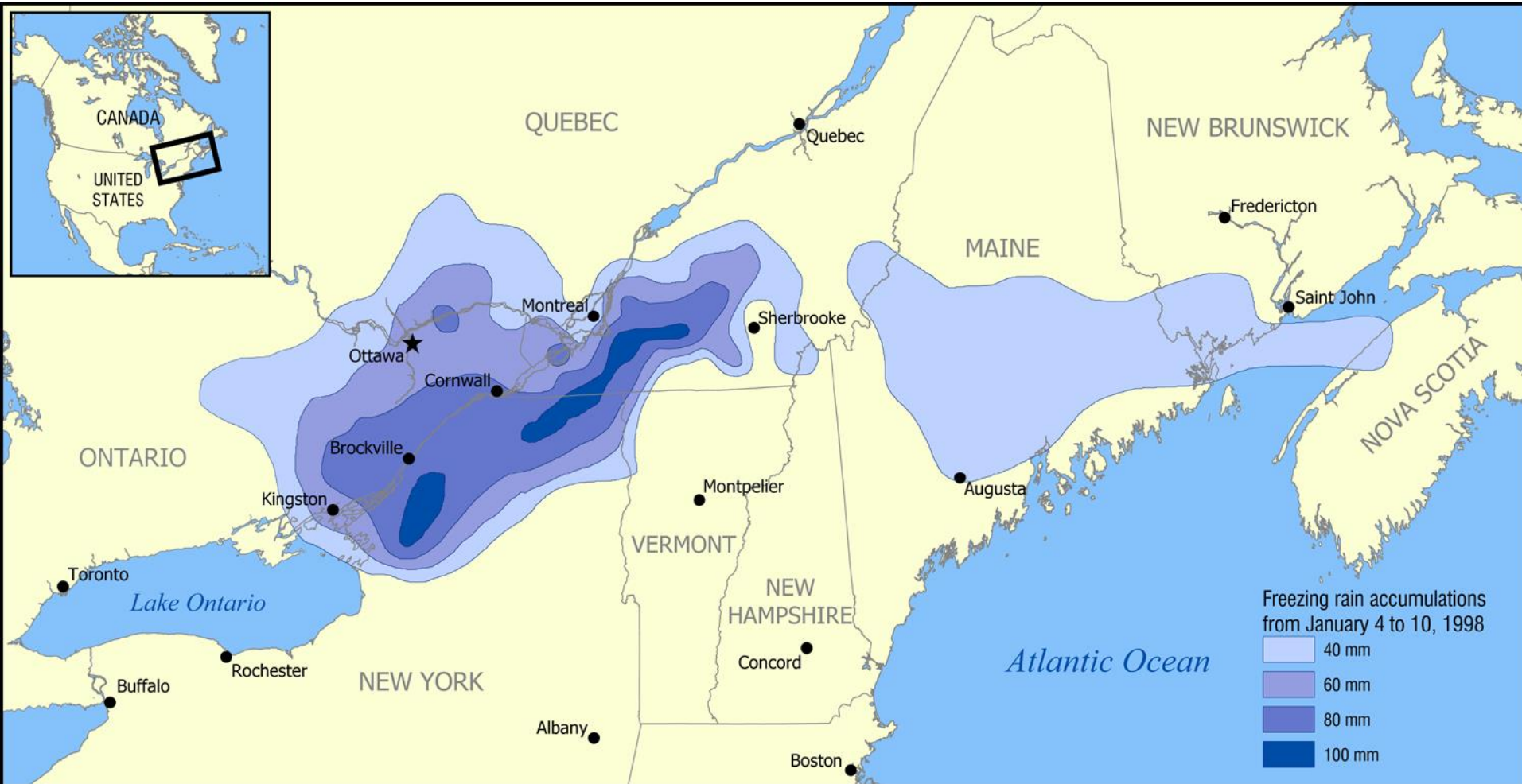
Genotype



**Development
(epigenetic
modification)**

Phenotype

Great Ice Storm of 1998



The **North American Ice Storm of 1998** was a massive combination of five smaller successive ice storms, which combined to strike a narrow swath of land in eastern Canada and northeastern USA in January 1998.

INSURANCE
BUREAU
OF CANADA



BUREAU
D'ASSURANCE
DU CANADA

January 1998



6 days of freezing rain
4.7 million Canadians without power
792,514 insurance claims
\$1.6 billion paid by insurers

Loyola High School Gym Shelter Closes its doors Jan 16th 1998 after serving Notre Dame De Grace area of Montreal for 9 days

Montreal Ice Storm Loyola Gym/shelter Kitchen ©Patrick McDonnell



Some of the volunteers and Emergency staff have time to talk Overview of the Shelter Dining Room



One of the many volunteers helps the refugees Montreal Downtown never closes during the Storm



Long term effects of antenatal maternal stress on their children

- The Great Ice Storm of 1998 caused **extensive infrastructural damage** to parts of Atlantic Canada and northeastern USA and left millions of people **without electricity for weeks**.
- Studies of **pregnant women exposed to this natural disaster** later found that their young **children's neurodevelopment were negatively affected**, reflected by lower general intellectual and language abilities.

Stress, March 2005; 8(1): 35–45



Taylor & Francis
Taylor & Francis Group

Psychiatry Research 219 (2014) 353–360

Contents lists available at ScienceDirect



ELSEVIER

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres



The effects of prenatal maternal stress on children's cognitive development: Project Ice Storm

SUZANNE KING^{1,2} & DAVID P. LAPLANTE²

¹Department of Psychiatry, McGill University, Québec, Canada, and ²Douglas Hospital Research Centre, Verdun, Québec, Canada

Prenatal maternal stress predicts autism traits in 6½ year-old children: Project Ice Storm



Deborah J. Walder^a, David P. Laplante^b, Alexandra Sousa-Pires^b, Franz Veru^{b,c}, Alain Brunet^{b,c}, Suzanne King^{b,c,*}

^a Department of Psychology, Brooklyn College and The Graduate Center of The City University of New York, 2900 Bedford Avenue, Brooklyn, NY 11210, USA

^b Psychosocial Research Division, Douglas Mental Health University Institute, 6875 LaSalle Boulevard, Verdun, Quebec, Canada H4H 1R3

^c Department of Psychiatry, McGill University, 1033 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1

“Truly World-class & Best-in-class” *Tachi Yamada*, A*STAR Board Meeting, June 2014.

“A study with great national impact - to prevent and manage diseases like diabetes and obesity.”
Minister Heng Swee Keat, MOE FY2015 Committee of Supply Debate-Speech, 6 Mar 2015.



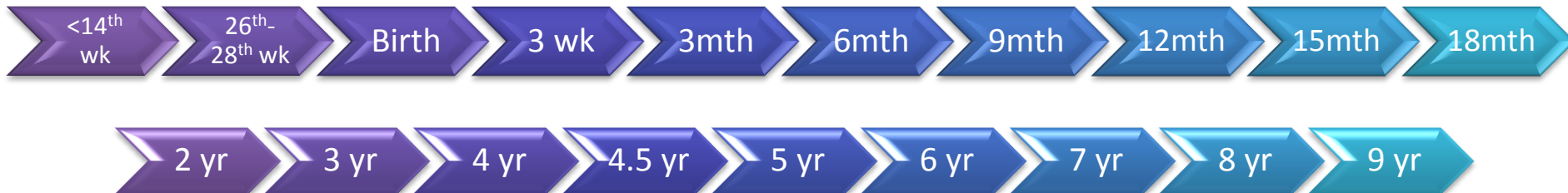
- Launched in 2009
- 1247 mother-child pairs
- 3 Asian ethnic groups
- Closest longitudinal follow-up ever
- Deepest phenotyping & biosampling



IN UTERO

BIRTH

INFANCY & CHILDHOOD



26-28wk clinic visit

Blood taking

Oral Glucose Tolerance Test

Biochemical markers (CRH, CRH binding protein, cortisol, leptin, alpha-feto protein etc)

Collection of hair sample

Non-mydiatic retinal photograph & autorefraction

Anthropometry (Ht, Wt, Skinfold thickness, MAC)

Pulse wave velocity (BP)

Questionnaires

Life style, family background and breastfeeding

Food diary (24 hour recall and 2 days food diary)

Self administered questionnaires

STAI, EPDS, BDI-II, LYDON & Question on domestic helper

Pittsburgh Sleep Quality Index (PSQI)



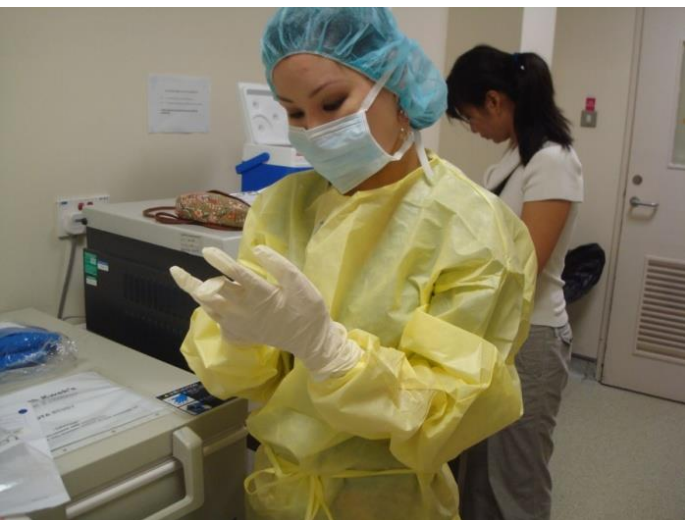
Deep phenotyping of mothers in mid-pregnancy



24/7 on-call team



Umbilical cord & placenta

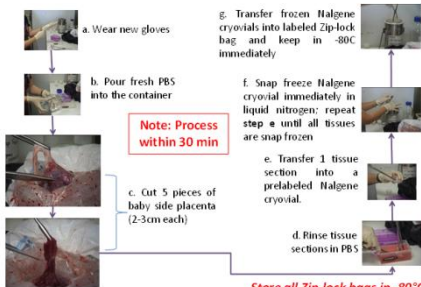


Collection of specimens at delivery



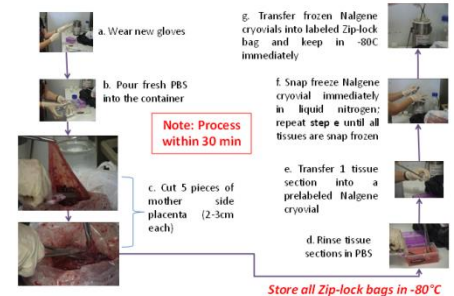
Preparation

Placenta (baby side) Processing



Snap freezing

Placenta (mother side) Processing



Maternal, Paternal, Cord blood, etc

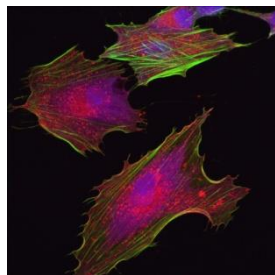
Interrogating the BioSamples

Umbilical cord
and placenta



Maternal and fetal blood

Longitudinal buccal swabs



Cord derived MSCs

Longitudinal microbiota
sampling



Blood chemistry

Including micronutrients, metabolomics

Genotyping

Omniexpress+ exome arrays
SNP and CNV

Methylome assessment

Infinium 450K arrays
RRBS
Methyl-capture-seq

Chromatin and histone assessment

TaCH / DNAase protection
Native ChIP-seq
Mnase-seq

Transcriptome assessment

Infinium HT12 v4 arrays
RNAseq
miRNAseq

Microbiome assessment

16S RNA sequencing
Metagenomics

Day 1 – Body Composition



Skinfold
measurement



Bioelectrical
impedance

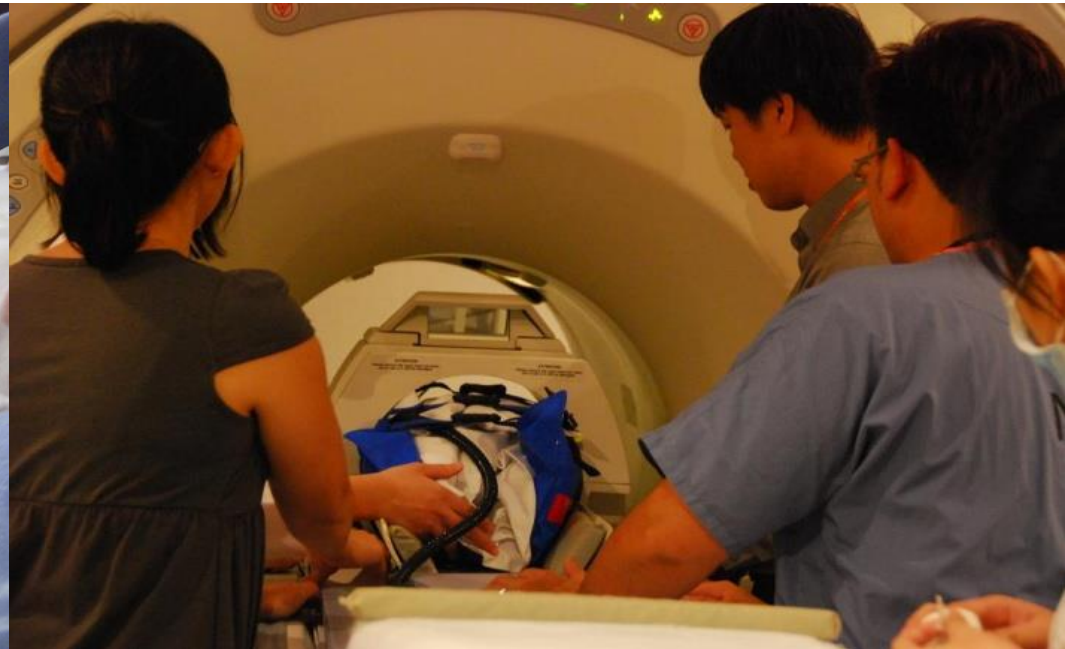


Air displacement
plethysmography

In GUSTO, we measured neonatal brain function right after birth



EEG on Day 1 of life



MRI on Day 7 of life

Reconsent



Preparation



Now used for sick infants in KKH



KK Women's and Children's Hospital
SingHealth

Skinfold & Anthropometry



386 MRIs done without sedation



For a subset, MRI is repeated at:
Week 6
Month 6

BIA



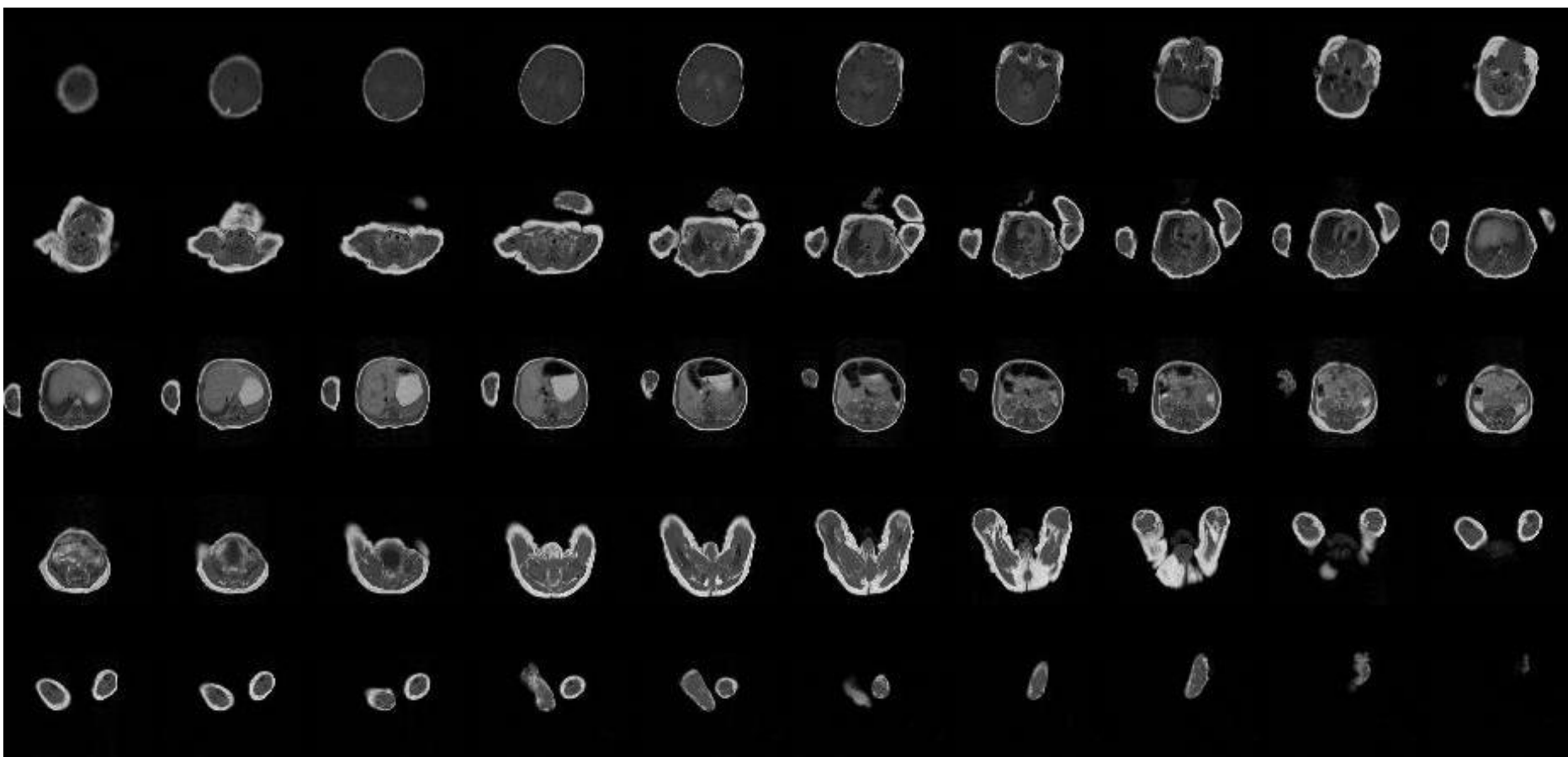
Into the MRI



MR Imaging



Whole Body Study: Head & Chest, Abdomen & Lower Limbs

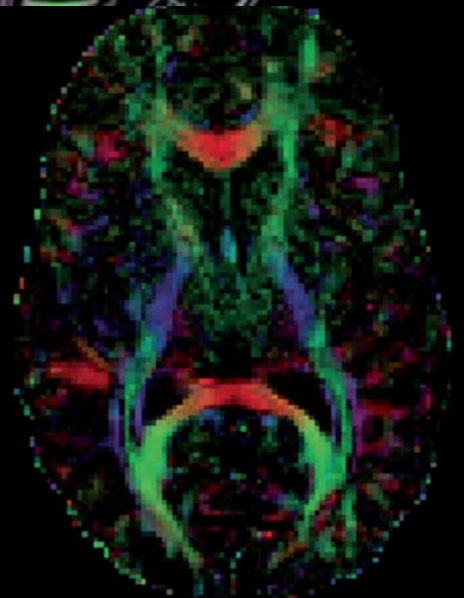
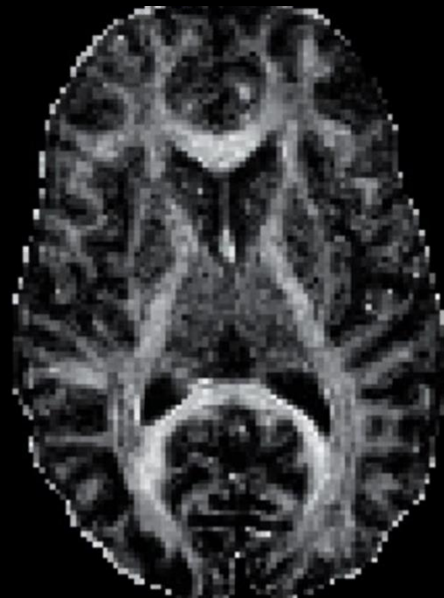
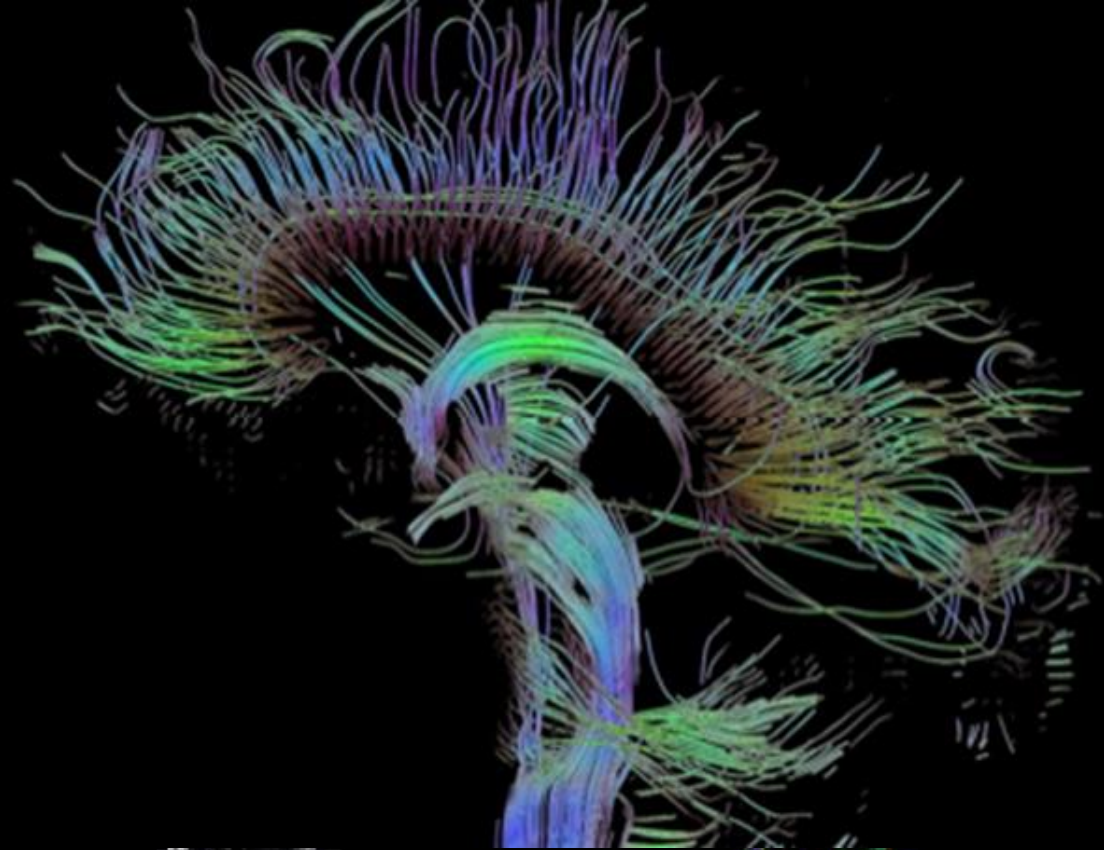


KK Women's and
Children's Hospital

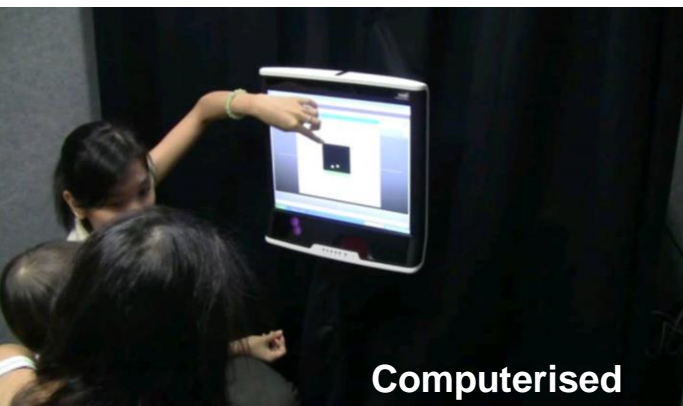
SingHealth



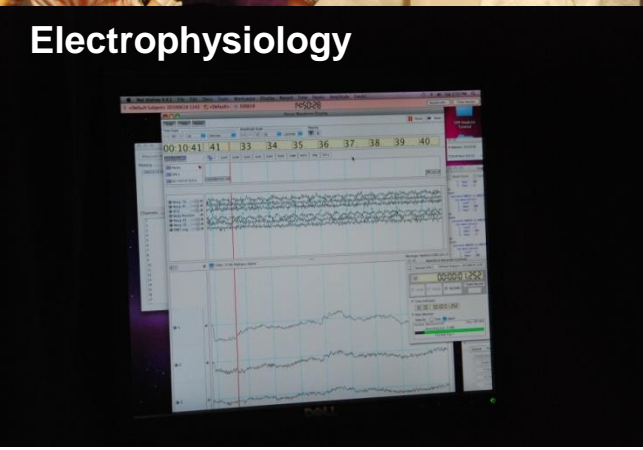
**FRACTIONAL
ANISOTROPY:**
INTEGRITY OF AXONS,
IMPORTANT IN
MEDIATING
NEUROLOGICAL
FUNCTIONS



Clinic Visits at 6, 18, 24, and 36 months: Neurodevelopmental and other detailed assessments



**Computerised
Eye Tracking**



Behavioural Observation



4 Years

School Readiness Test



Peabody Picture Vocabulary Test

This is a test of **receptive vocabulary** which assesses the child's vocabulary acquisition.

Lollipop Test

This test assesses the child's ability to **identify colours, shapes, numbers and letters**.

Number Knowledge Test

This test assesses the child's **intuitive knowledge of numbers**.

Visually Cued Recall Test

This test evaluates the child's **working memory** through visual images and verbal information.

Random Object Span Test

This test assesses the child's **visual working memory**.

Comprehensive Test of Phonological Processing- 2

This test evaluates the child's **phonological processing** as a prerequisite to reading fluency.



Panamath

This test measures the child's **number sense** and approximate number system (ANS) which underlies the ability to produce abstract number representation.



Child Behaviour Checklist

This checklist measures the child's **behavioural and socio-emotional functioning** as reported by parents.



These tasks carried out during the **48 Months Home Visit** help to assess the child's 'school readiness' in Singapore.

MRI: SAFARI ADVENTURE!



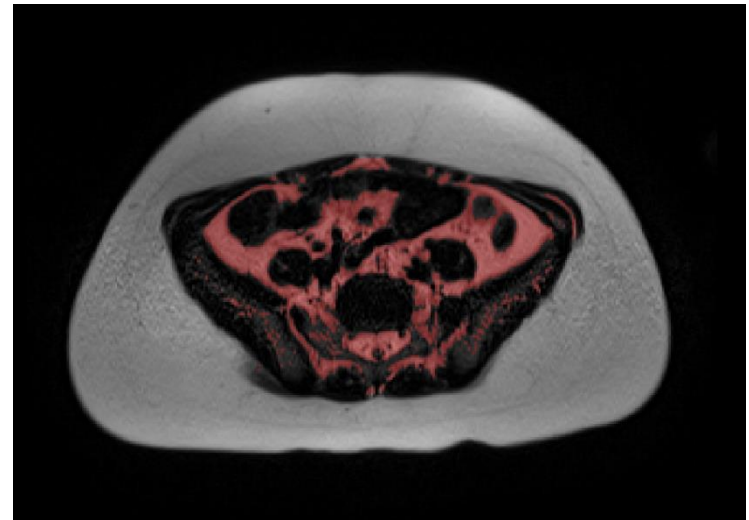
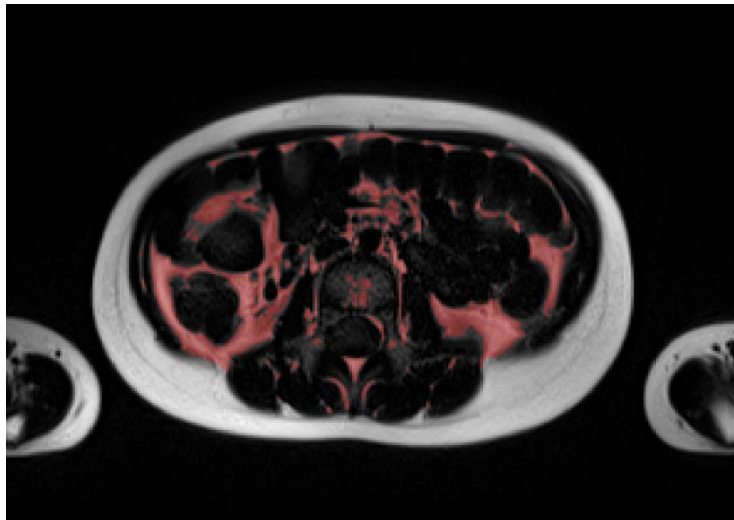
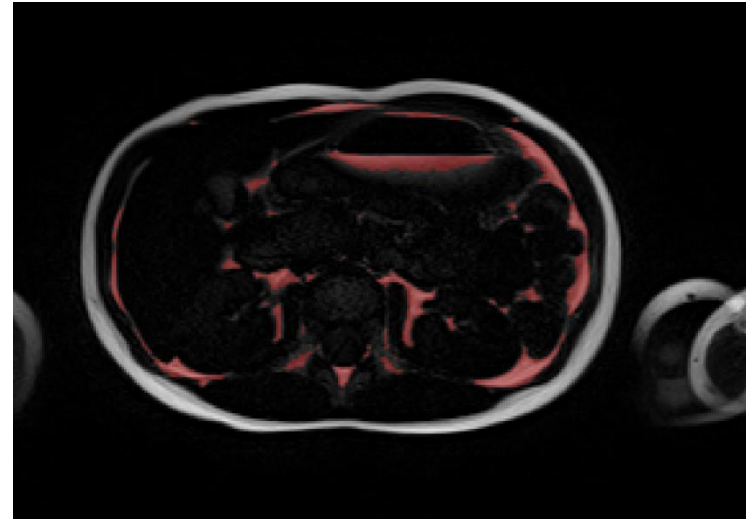
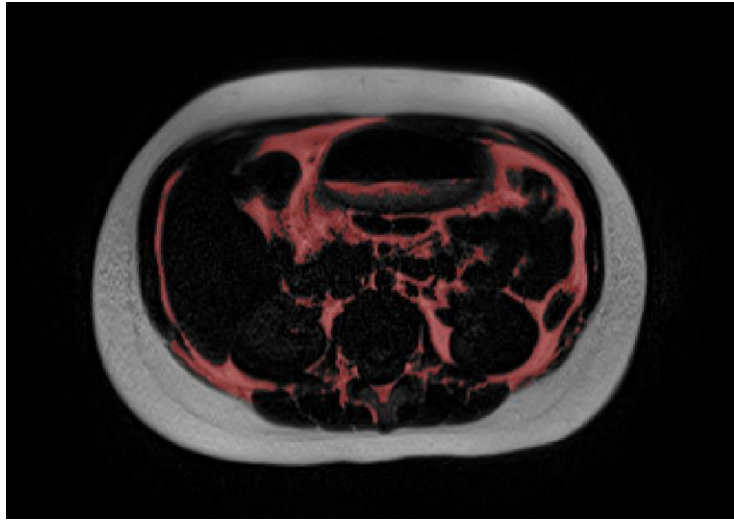
SIEMENS MAGNETOM Skyra syngo MR D13



KK Women's and
Children's Hospital
SingHealth

4.5 Years

MRI Abdominal Compartment at 4.5 years



BOD POD: *Spaceship adventure!*



Quantitative Magnetic Resonance Technology *QMR: Fun with sea animals!*



Visit	Status	Visit completed	BOD POD performed	QMR performed (KKH)
Year 5	Ongoing	647	329	193
Year 6	Just started	29	5	21

Translational impact

Turning research into action



Importance of Early Mental Health

Short-Term Memory, Working Memory, and Executive Functioning in Preschoolers: Longitudinal Predictors of Mathematical Achievement at Age 7 Years

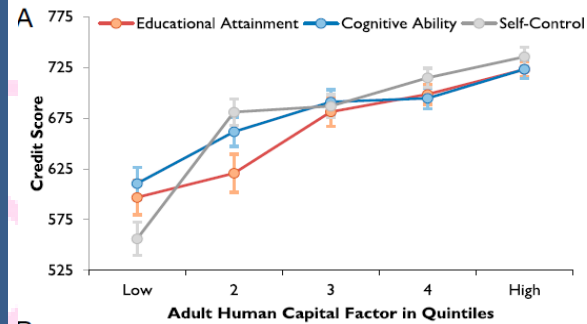
Rebecca Bull
School of Psychology, University of Aberdeen, Aberdeen, United Kingdom
Kimberly Andrews Espy and Sandra A. Wiebe
Office of Research & Department of Psychology, University of Nebraska-Lincoln

Correlations between Predictor Variables and PIPS Mathematics and Reading Scores

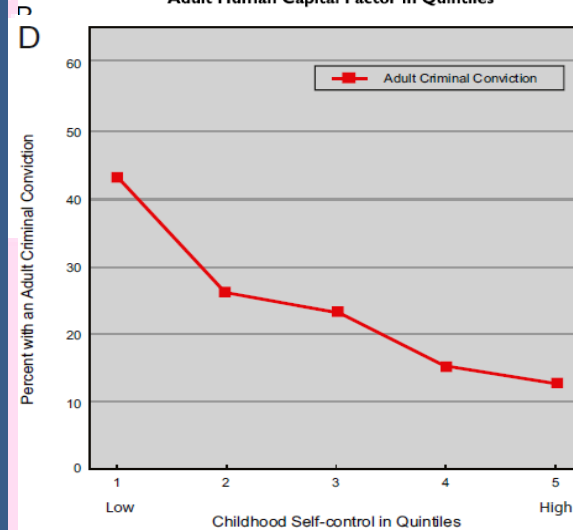
Predictor	PIPS Correlations Mathematics			PIPS Correlations Reading		
	Wave 1	Wave 2	Wave 3	Wave 1	Wave 2	Wave 3
<i>Short-term memory:</i>						
Cons Span Forward	.40**** (104)	.36**** (101)	.13 (82)	0.19* (104)	0.27*** (101)	0.28**** (83)
Digit Span Forward	.36**** (104)	.32**** (101)	.12 (82)	0.32**** (104)	0.35**** (101)	0.25** (83)
<i>Working memory:</i>						
Cons Span Backward	.34*** (78)	.36**** (75)	.39**** (58)	0.37**** (78)	0.55**** (75)	0.27** (58)
Digit Span Backward	.52**** (84)	.37**** (81)	.32*** (62)	0.45**** (84)	0.39**** (81)	0.23* (63)
<i>Executive functioning:</i>						
Shape School Inhibit (Efficiency)	.42**** (104)	.43**** (101)	.23** (82)	0.40**** (104)	0.46**** (101)	0.21* (83)
Shape School Switch (Efficiency)	.38**** (104)	.31*** (101)	.29*** (82)	0.45**** (104)	0.33**** (101)	0.29**** (83)
Tower of London	.46**** (104)	.30*** (101)	.26** (82)	0.41**** (104)	0.35**** (101)	0.17 (83)

Number of observations included in each correlation are provided in parentheses

* p ≤ .10
** p ≤ .05
*** p ≤ .01
**** p ≤ .001



Moffitt et al,
PNAS,
2010



Israel
et al, *PNAS*,
2014

For Education

For Financial
Responsibility and
Criminality

We are examining the influence of unique Singaporean factors on infant functioning

Cultural Differences in Mirror Self-Recognition in 18-month-old Singaporean Toddlers

Jun Pei Lim^{1,2}, Lidia Suárez², Litwee Sim¹, Birit F. P. Brokwek⁵, Peter Gluckman^{1,6}, Seang-Mei Saw^{1,7}, Michae

¹Singapore Institute for Clinical Sciences, Agency for Science, Tech University, ²Department of Psychological Medicine, Yong Loo Lin Sch National University Health System, ³Department of Obstetrics & Gynaec University of Singapore, National University Health System, ⁴KK Wor University of Auckland, ⁵Saw Swee Hock School of Public H Singapore

⁶Departments of Psychiatry and Neurology and Neurosurgery anne_rifkin@sics.a-star.edu

Abstract— Western societies put emphasis on the development of the individual in relation to social groups. In Western populations roughly 60% of 18-month themselves reflected in a mirror. Self-referential behavior has been used as a The aim of the current study was to investigate possible cultural difference themselves in a mirror. The current study involved 329 18-months-old Southe in a larger prospective mother-offspring birth cohort study GUSTO. In co toddlers showed mirror self-recognition behavior. However, rates significantly showing more self-referential behavior than Singaporean Malay and Chi differences in self-referential behavior and expression of self-recognition. We similarly across different cultures but that other variables, such as parenting st

Keywords—cultural differences; mirror self-recognition; toddlers

INTRODUCTION

A child's ability to show self-recognition is often viewed as a part of a larger suite language, symbolic play, planning, and object permanence. These abilities collect such as autobiographical memory and self-evaluation [1]. Self-recognition has also relations, social cognition, maturational, and affective growth [2]. Studies have f under-developed sense of self, which is crucial for development of empathy [1,3,4].

Self-recognition in toddlers is most frequently measured via the Rouge Mark t mark on an individual's face so that the mark cannot be seen directly. This is follow of the toddler towards his or her own reflection is observed [6]. Toddlers aged betw the rouge mark placed on his/her nose when placed in front of the mirror, showing recognition concept [1,7]. For example, Amsterdam (1972) observed a sample of and found that 42% showed self-recognition behavior. Nielson and Dissanayake (mirror self recognition (MSR) in a sample made of Australian-Caucasian toddlers. 67% of observed 18 months-old White toddlers exhibited MSR behavior.

Nevertheless, variations in the onset of MSR and expressivity of self-referential t

CHILD DEVELOPMENT

Child Development, xxxx 2014, Volume 00, Number 0, Page 0–0

Back to Basics: A Bilingual Advantage in Infant Visual Habituation

Leher Singh and Charlene S. L. Fu
National University of Singapore

Aishah A. Rahman ***
and Shami
Singapore Institute

AJCN First published ahead of print December 10, 2014 as doi: 10.3945/ajcn.114.095414.

Pratibha Agarwal
KK Women's and Children's Hospital

Jiang
Carnegie M

Chong Yap Seng
National University Hospital

Michael
Singapore Institute
and McG

Anne Rifkin-Graboi
Singapore Institute for Clinical Sciences

On behalf of the G

Infant feeding effects on early neurocognitive development in Asian children^{1–4}

Shirong Cai, Wei Wei Pang, Yen Ling Low, Lit Wee Sim, Suet Chian Sam, Michaela Bianka Braunstaeger, Eric Qindong Wong, Doris Kok, Birt P. Brokwek, Leher Singh, Jenny Richmond, Pratibha Agarwal, Anqi Qiu, Seng Mei Saw, Fabian Yap, Keith M Godfrey, Peter D Gluckman, Yap-Seng Chong, Michael J Meaney, Michael S Kramer, and Anne Rifkin-Graboi on behalf of the GUSTO Study Group

ABSTRACT

Background: Breastfeeding has been shown to enhance global measures of intelligence in children. However, few studies have examined associations between breastfeeding and specific cognitive task performance in the first 2 y of life, particularly in an Asian population. **Objective:** We assessed associations between early infant feeding and detailed measures of cognitive development in the first 2 y of life in healthy Asian children born at term. **Design:** In a prospective cohort study, neurocognitive testing was performed in 408 healthy children (aged 6, 18, and 24 mo) from uncomplicated pregnancies (ie, birth weight >2500 and <4000 g, gestational age ≥37 wk, and 5-min Apgar score ≥9). Tests included memory (deferred imitation, relational binding, habituation) and attention tasks (visual expectation, auditory oddball) as well as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Children were stratified into 3 groups (low, intermediate, and high) on the basis of breastfeeding duration and exclusivity. **Results:** After potential confounding variables were controlled for, significant associations and dose-response relations were observed for 4 of the 15 tests. Higher breastfeeding exposure was associated with better memory at 6 mo, demonstrated by greater preferential looking toward correctly matched items during early portions of a relational memory task (ie, relational binding task; $P_{\text{trend}} = 0.015$ and 0.050 for the first two 1000-ms time bins, respectively). No effects of breastfeeding were observed at 18 mo. At 24 mo, breastfed children were more likely to display sequential memory during a deferred imitation memory task ($P_{\text{trend}} = 0.048$), and toddlers with more exposure to breastfeeding scored higher in receptive language [4.09 (0.23, 1.65) and 4.108 (0.10, 2.07) for intermediate- and high-breastfeeding groups, respectively, compared with the low-breastfeeding group], as well as expressive language [40.58 (−0.06, 1.23) and 41.22 (0.32, 2.12) for intermediate- and high-breastfeeding groups, respectively] assessed via the BSID-III. **Conclusions:** Our findings suggest small but significant benefits of breastfeeding for some aspects of memory and language development in the first 2 y of life, with significant improvements in only 4 of 15 indicators. Whether the implicated processes confer developmental advantages is unknown and represent an important area for future research. This trial was registered at www.clinicaltrials.gov as NCT01134755. *Am J Clin Nutr* doi: 10.3945/ajcn.114.095414.

INTRODUCTION

Although breastfeeding is generally thought to positively influence cognitive development, research over 80 y (1) has yielded discrepant results. Some studies reported that breastfeeding enhances performance on global measures of intelligence (2–5), whereas others found small or no effects (6–8). Studies that combine exclusively and partially breastfed infants are likely to attenuate effects when assessing the influence of breastfeeding on cognition (9). Variations in formula composition (10) and dietary differences

¹ Inborn: Departments of Obstetrics and Gynecology (SC, WW, LF, YSC, and MSK), Department of Psychological Medicine (SPPB), Yong Loo Lin School of Medicine, the Department of Psychology (LS) and Biomedical Engineering and Clinical Imaging Research Centre (AQ), and the Saw Swee Hock School of Public Health (MS), National University of Singapore, National University Health System, Singapore; the Abbott Nutrition Research and Development Asia-Pacific Centre, Singapore (YL); the Singapore Institute for Clinical Sciences, Agency for Science and Technology Research (A*STAR), Singapore (UKS, SCS, MBS, RQW, AQ, HWP, PDL, Y-CC, MM, and AB-G); the School of Psychology, University of New South Wales, Sydney, Australia (BR); the Departments of Neurology (PA) and Pediatrics (PV), Kandang Kerbau Women's and Children's Hospital, Singapore; the Medical Research Council Lifecourse Epidemiology Unit and National Institute for Health Research Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton National Health Service Foundation Trust, Southampton, UK (DMG); Liggins Institute, University of Auckland, Auckland, New Zealand (OCG); and the Departments of Epidemiology, Biostatistics, and Occupational Health (MSK), Pediatrics (MSK), and Psychiatry and Neurology and Neurosurgery (MDM), McGill University, Montreal, Canada.

² Supported by the Translational Clinical Research (TCR) Flagship Program on Developmental Pathways to Metabolic Disease funded by the National Research Foundation and administered by the National Medical Research Council (NMRC), Singapore (NMRC/TX/09A/0015/001). This work was also supported by the Singapore Institute for Clinical Sciences (A*STAR) and Abbott Nutrition Research and Development Asia-Pacific Center.

³ Supplemental materials are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.
⁴ Address reprint requests to A Rifkin-Graboi, Singapore Institute for Clinical Sciences, Agency for Science and Technology Research (A*STAR), Biotech Centre for Molecular Medicine, 30 Medical Drive, Singapore 117600. E-mail: anne_rifkin@sics.a-star.edu.sg.
Received July 22, 2014. Accepted for publication November 17, 2014. doi: 10.3945/ajcn.114.095414.

The GUSTO Research team includes Dennis Bar, Arif Bawa, Cal Shiang, Hsiao Chen, Jerry Chan, Yong Hsiao Chen, Camilla Chee, Audrey Chia, Chiang Wen Chen, Jenisha Chitrampal, Qing Chai Eai, May Chong, Chong Shang Cheo, Chua Mei Chen, Wayne Cutfield, Mary Daniel, Ding Chan Meng, Keith Godfrey, Ayesha Begum-Godini, Eric Andrew Huijckeb, Markella Horne, Doris Kok, Anne Koh, Daniel Koh, Joshua J Goolley, Han Wei Meng, Mark Brown, Mikael Hartman, Michael Heymann, Stephen Hsu Chin-Ying, Hani Indip, Joseph Kapur, Lee See Wah, Lay Yung Seng, B F P Laitinen-Swintman, Lim Sok Lee, Loh Seong Hui, Low Yen Ling, Hana Maglar, Susan Minton, Krishnasoorthy N, Cheryl Ngo, Ding Wei Wei, Pratibha Agarwal, Qiu Anqi, Quah Soon Long, Victor S. Rajadurai, Jen Richmond, Anne Rifkin-Graboi, Allan Sheppard, Lynette Phyllis Owe, Roya Shaker, Leher Singh, So Meng Chew, Soh Shu E, Su Lin Lin, Tan Kok Han, Teoh Chun Hwe, Terry Yoke Yin Tong, Mya Thway Tin, Hugo Van Bever, Rob van Don, Susharita Vankatamb, Helena Marlene Vankatamb, Inee By Wong, P. C. Wong, Fabian Yap, and George S. H. Yeo.

This research was conducted under the auspices of a Translational Clinical Research Flagship program grant from the Singapore National Medical Research Council, which supports the GUSTO Cohort. SICS investigations are supported in part through Agency for Science Technology and Research (A*STAR) funding. We would like to thank the participants and their families for their involvement in this research.

Correspondence on matters related to this article should be addressed to Leher Singh, Department of Psychology, National University of Singapore, 9 Arts Link, Singapore 117570. Electronic mail may be sent to ps@nus.edu.sg.

Infants raised in a bilingual environment show remarkable gains in their ability to learn. Nevertheless, the upon a bilingual infant infants must differential sounds from each lang correspondences, and is of two systems that o Mastering independent between languages ha sharpen an important / bilingual known as ssa. In a substantial body for abilities to manage attention have been v (e.g., Bialystok, 1999; B Bialystok & Martin, 20 Biligual advantage. Rosse

© 2014 The Authors
Child Development © 2014 Society
All rights reserved. 0009-8630/2014
DOI: 10.1111/j.1469-7610.2014.02811.x

Keywords: Asia, breastfeeding, cognition, infant, memory, toddler, attention, nutrition, electrophysiology, e-tracting

Am J Clin Nutr doi: 10.3945/ajcn.114.095414. Printed in USA. © 2014 American Society for Nutrition



Maternal Glycaemia and Influence on Infant Cognition



Effect of GDM on conditional difference in EP max amplitude towards oddball and standard stimuli, stratified by hemispheres.

	Adjusted mean condition difference*† (95% CI)	
6 months (n=104 control, 25 GDM)		p value
Left Hemisphere (μV)	-0.76 (-1.49 to -0.04)	0.039
Right Hemisphere (μV)	-0.02 (-0.80 to 0.77)	0.964

Maternal glycemia levels influence infant neural activity predicting vulnerability for attentional difficulties such as ADHD

EPmax amplitude condition difference‡ in left hemisphere (μV)	Fasting PG	2 hours PG
	Adjusted† β (95% CI)	Adjusted† β (95% CI)
6 months	-0.04 (-0.78 to 0.70)	-0.19 (-0.42 to 0.04)
18 months	-0.36 (-1.04 to 0.31)	-0.27 (-0.49 to -0.06)

†Adjusted for maternal age, maternal education, sex and gestational age of child, ethnic group, 26 weeks STAI-state, maternal pre-pregnancy BMI and gestational weight gain at 26 weeks gestation. ‡ Condition difference= oddball - standard

Maternal Stress and Brain Development of the Newborn



Maternal anxiety and depression



	During pregnancy	Postpartum
Singapore	<ul style="list-style-type: none"> • 12.2% with depression • 11% with major depression and 7% with minor depression in high-risk group • 12.5% with anxiety disorder in high-risk group 	7% with depression
GUSTO cohort study	<ul style="list-style-type: none"> • 12% with depression • 12% with high anxiety symptoms • 21% with high anxiety personality traits 	<ul style="list-style-type: none"> • 11% with depression • 13% with high anxiety symptoms • 20% with high anxiety personality traits

- At least 1 in 9 women in Singapore experience anxiety and/or depression during and after pregnancy.
- Anxiety rates in Singapore are higher than what was reported by other groups (roughly double).

Depression is *the leading cause of disability worldwide* and a major contributor to the global burden of disease (WHO: <http://www.who.int/mediacentre/factsheets/fs369/en/>)

Archival Report

Prenatal Maternal Depression Associates with Microstructure of Right Amygdala in Neonates at Birth

Anne Rifkin-Graboi^a, Jordan Bai^c, Helen Chen^c, Waseem Bak'r Hameed^a, Lit Wee Sim^a, Mya Thway Tint^d, Birit Leutscher-Broekman^{a, d}, Yap-Seng Chong^d, Peter D. Gluckman^a, Marielle V. Fortier^c, Michael J. Meaney^{a, e}, Anqi Qiu^{a, b}  

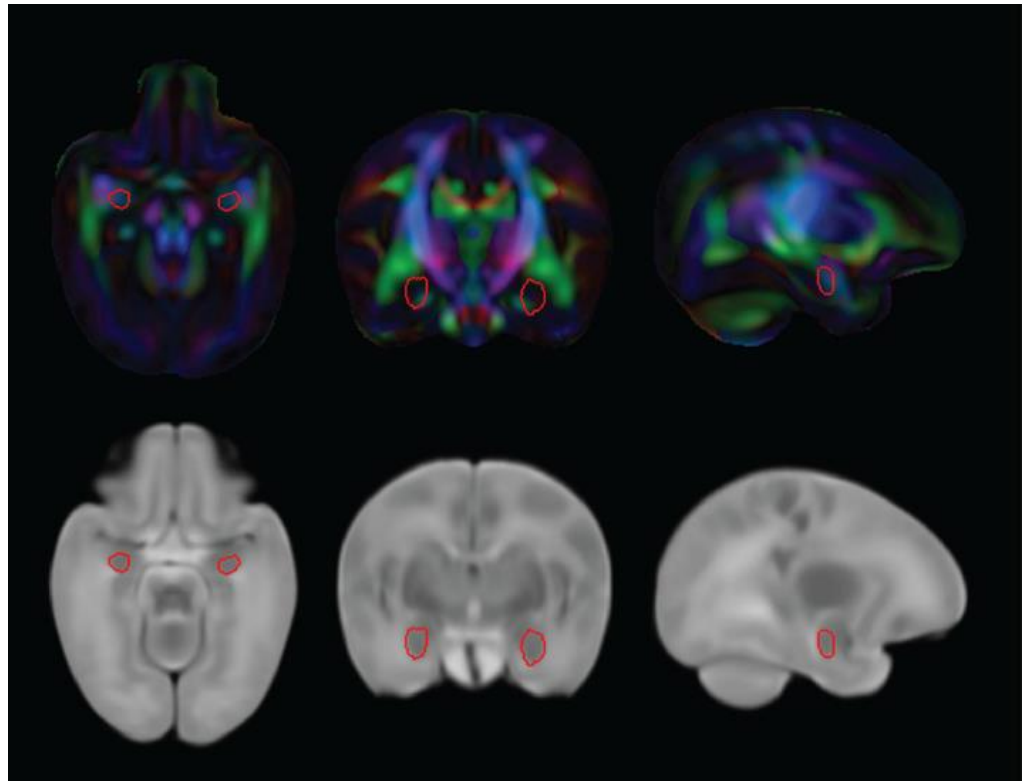


Figure 1: The red contour indicates the amygdala on diffusion tensor imaging and T2-weighted magnetic resonance imaging.

Maternal depression during pregnancy affects the brain of the newborn

(less ordered neural pathways in a brain region closely associated with **vulnerability for mood anxiety disorders**).

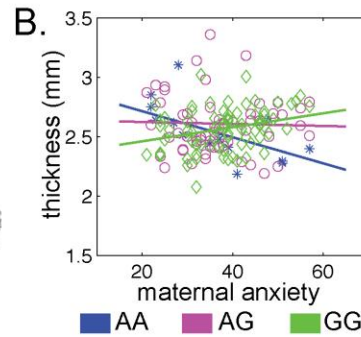
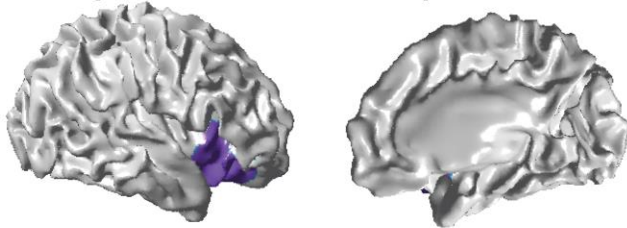
Suggest the transmission of vulnerability for depression from mother to child.

Catechol-O-methyltransferase (COMT) Haplotypes Modulate Associations of Antenatal Maternal Anxiety and Neonatal Cortical Morphology

A. rs4680 (val158met)

Right Lateral View

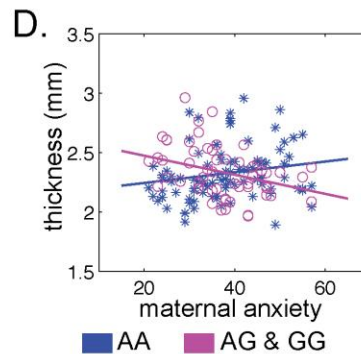
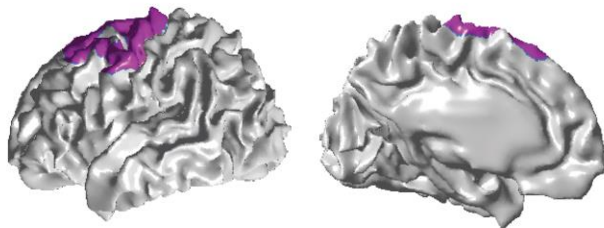
Right Medial View



C. rs737865

Left Lateral View

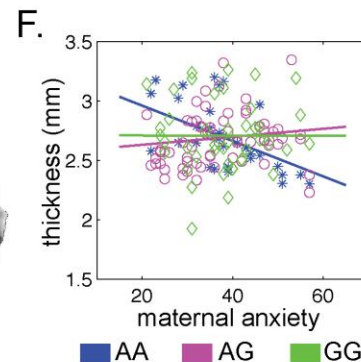
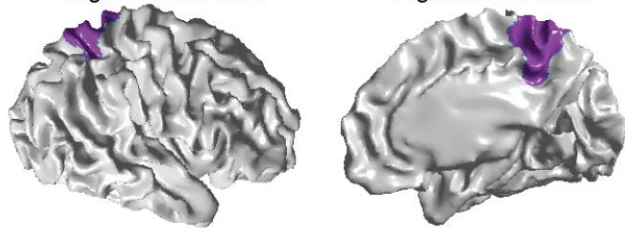
Left Medial View



E. rs165599

Right Lateral View

Right Medial View



corrected p-value

0 0.01 0.02 0.03 0.04 0.05

Antenatal **maternal anxiety** affects the prefrontal and parietal **cortical thicknesses** of neonatal brains (involved in **executive functioning & sensory processing**).

This association is modulated by the babies' COMT SNPs (val158met, rs737865, and rs165599).

COMT Haplotypes Modulate Associations of Antenatal Maternal Anxiety and Neonatal Cortical Morphology

Anqi Qiu, Ph.D., Ta Anh Tuan, M.S., Mei Lyn Ong, Ph.D., Yue Li, B.S., Helen Chen, M.D., Anne Rifkin-Graboi, Ph.D., Birrit F.P. Broekman, M.D., Kenneth Kwek, M.D., Seang-Mei Saw, Ph.D., Yap-Seng Chong, M.D., Peter D. Gluckman, Ph.D., Marielle V. Fortier, M.D., Joanna Dawn Holbrook, Ph.D., Michael J. Meaney, Ph.D.

This article is discussed in an **Editorial** by Dr. Hudziak (p. 111)

Am J Psychiatry 172:2, February 2015

Recognition of GUSTO's value

FEBRUARY 2015 | VOLUME 172 | NUMBER 2

The American Journal of Psychiatry



Treatment of Psychosis and Mania in the Postpartum Period

Uncovering the Hidden Risk Architecture of the Schizophrenias: Confirmation in Three Independent Genome-Wide Association Studies

Paraprofessional-Delivered Home-Visiting Intervention for American Indian Teen Mothers and Children: 3-Year Outcomes From a Randomized Controlled Trial

COMT Haplotypes Modulate Associations of Antenatal Maternal Anxiety and Neonatal Cortical Morphology

Official Journal of the American Psychiatric Association
ajp.psychiatryonline.org

- An editorial in the February 2015 issue of the prestigious *American Journal of Psychiatry* lauded the study, remarking that **“the GUSTO design is unique in that it (doing MRI at 1 week of life) removes the biggest scientific obstacle that faces most birth cohort studies that aim to examine antenatal factors.”**

- Deputy Prime Minister Teo Chee Hean**, in his speech at the 30th anniversary of Institute of Molecular & Cell Biology on 8 May 2015, described GUSTO as **“a national birth cohort study of Singaporean mothers and babies on how environmental factors affect the development of diseases in later years.**

- For example, the research findings showed how a mother’s anxiety from pregnancy could affect her child intellectually and emotionally from birth.”**



Mr Teo Chee Hean
Deputy Prime Minister

FINDINGS

- **More than 1 in 9 Singaporean women suffer from anxiety and depression** during and/or after pregnancy.
- Findings from GUSTO show that poor maternal mental health may be associated with **increased neurodevelopmental disorders in the offspring** including anxiety, depressive or disruptive behavior disorders, **even in sub-clinical ranges of maternal anxiety and depression.**

RECOMMENDATIONS TO MOH, 3 SEP 2015

1. Integrate **screening** for anxiety and depression into routine prenatal and postnatal care across all government and private maternity hospitals.
2. Provide professional emotional health **support** for women during pregnancy and continuity of care services from hospital to home.
3. Identify risk factors and **social determinants** for perinatal anxiety and depression and provide targeted help for high-risk groups.



Maternal Emotional Well-being:
Screening and Management may benefit
Singapore's future generations.

3 September 2015

Prepared by:

Dr Cai Shirong, NUHS; Prof Michael Meaney, SICS & McGill University; Dr Anne Rifkin-Graboi, SICS; Dr Birit Leutscher-Broekman, NUHS & SICS, Dr Qiu Angi, NUS; Dr Soh Shu E, SICS; Prof Kenneth Kwek, KK Women's & Children's Hospital; and A/Prof Chong Yap Seng, NUHS & SICS

Collaborators:



Administered by:



Special Communication | USPSTF RECOMMENDATION STATEMENT

Screening for Depression in Adults

US Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH; and the US Preventive Services Task Force (USPSTF)

DESCRIPTION Update of the 2009 US Preventive Services Task Force (USPSTF) recommendation on screening for depression in adults.

METHODS The USPSTF reviewed the evidence on the benefits and harms of screening for depression in adult populations, including older adults and pregnant and postpartum women; the accuracy of depression screening instruments; and the benefits and harms of depression treatment in these populations.

POPULATION This recommendation applies to adults 18 years and older.

RECOMMENDATION The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. (B recommendation)

JAMA. 2016;315(4):380-387. doi:10.1001/jama.2015.18392

← Editorial pages 349 and 351

+ Author Audio and Video Interviews and JAMA Report Video at jama.com

← Related article page 388 and JAMA Patient Page page 428

+ CME Quiz at jamanetworkcme.com and CME Questions page 411

+ Related articles at jamapsychiatry.com, jamainternalmedicine.com, and jamaneurology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Authors/Group Information: The USPSTF members are listed at the end of this article.

Corresponding Author: Albert L. Siu, MD, MSPH (albert.siu@mssm.edu).

True Translation: GUSTO findings inspire cartoon

the **sunday** times

home 17

May 4, 2014 thesundaytimes

Anxious mums = smaller babies

Study finds that the mental state of pregnant women can affect their infants' brain development

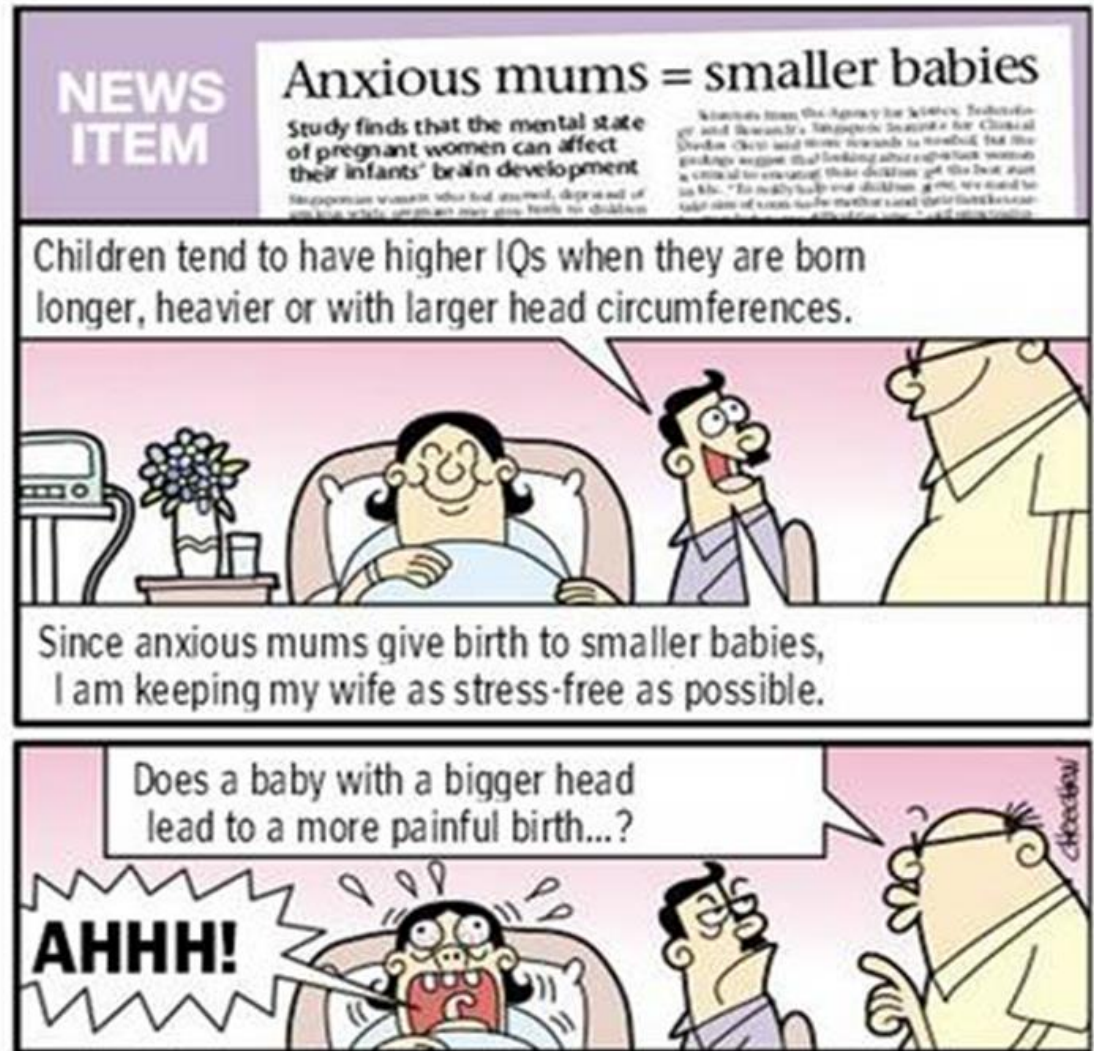
Feng Zengkun

Singaporean women who feel stressed, depressed or anxious while pregnant may give birth to children who are more easily distracted and have poorer memory, according to the preliminary findings of a landmark study.

The mental distress may even cause the babies to be born physically shorter, which is an issue as Asian children tend to have higher IQs when they are born longer, heavier or with larger head circumferences.

Scientists from the Agency for Science, Technology and Research's Singapore Institute for Clinical Studies (Sics) said more research is needed, but the findings suggest that looking after expectant women is critical to ensuring their children get the best start in life. "To really help our children grow, we need to take care of soon-to-be mothers and their families early, even before any difficulties arise," said principal investigator Anne Rifkin-Graboi.

PUNCH LINES May 5, 2014 The Straits Times





Deep Phenotyping

Demographics & Social Determinants

Maternal Health e.g. gestational diabetes mellitus

Maternal Emotional Well-Being

Nutrition & Metabolism

Cardiovascular changes (including retinal vessels changes)

Endocrine changes

Body Composition (e.g. MRI) & Growth (including fetal ultrasounds)

Oral Health

Neurodevelopment

Child Health & Allergy

Longitudinal measures

throughout the Life Course



Pre-conception



Pregnancy



Postnatal and non-gravid

Early childhood and later life

Genomics

Epigenomics

Transcriptomics

Proteomics

Metabolomics

Interaction with environment e.g. the Exposome

Microbiome

Metagenomics & Metatranscriptomics



Singapore PREconception Study of long-Term maternal and child Outcomes

Preconception influences on maternal and offspring outcomes

- Unprecedented opportunity to study how a woman's health, nutritional and emotional state **before** pregnancy can influence:
 - Their pregnancy outcome
 - Their child's health and development
 - Their own health after pregnancy
- Help us develop guidelines for all reproductive-age women:
 - to give their **babies** the **best start to life**
 - **improve the nation's health**
- **Launched Q2 2015, with over 300 pre-pregnant women enrolled, 50 pregnancies, and 4 deliveries so far.**

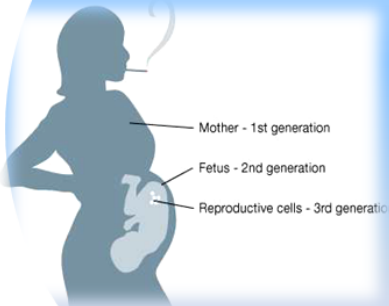
S-PRESTO

pre-conception cohort

n=1000
women

n=400
pregnancies

Postpartum women &
Offspring (0 - 2 yrs)





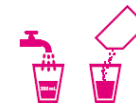
Nipper

**CHF 22m
deal
signed
Oct 2014**

**Nutritional Intervention Preconception and During
Pregnancy to Maintain Healthy Glucose Metabolism &
Offspring Health**



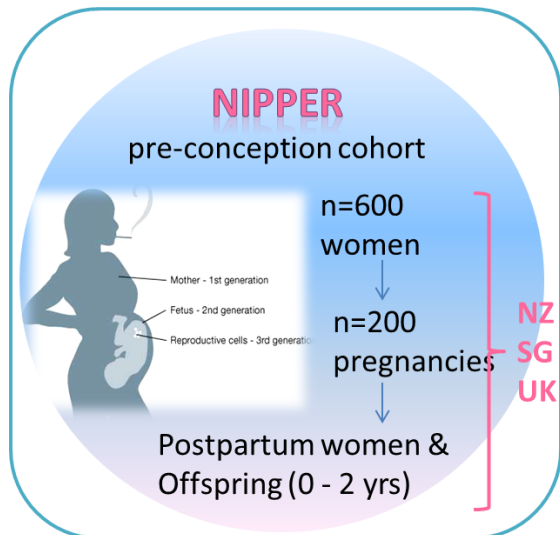
Taken orally, twice a day



Directions for use:

Empty content of the sachets in a small glass (200 mL) of water at room temperature

Stir well with a spoon and consume immediately



- **High rate of micronutrient deficiency in GUSTO mothers with Gestational Diabetes.**
- **Randomised controlled trial of a pre-pregnancy nutritional drink:**
 - Healthier blood glucose levels in mothers
 - Healthier babies
 - Better long term health for mothers
- **Validate findings across 3 populations:**
 - Auckland, Singapore, Southampton (EpiGen)
- **Launched August 2015: 144 subjects randomised, with 13 pregnancies so far.**

14.17.NRC



The NIPPeR nutritional drink is designed to assist in maintaining healthy glucose levels in the body and to provide standard vitamins and minerals recommended for pregnancy. In the clinical study, 50% of the participants will receive a control drink, which only includes standard vitamins and minerals recommended for pregnancy

Rising obesity among young set to worsen diabetes rate

The Straits Times, February 22, 2016

Experts warn that 34% of those aged 24 to 35 this year may become diabetic by age 65

Salma Khalik
Senior Health Correspondent

Rising obesity in children and young adults will push up the rate of diabetes in Singapore – already among the highest in the developed world – going by recent studies.

for some children, there is a cycle of weight gain during long holidays followed by weight loss during term time as a result of physical activities and weight-management programmes in school.

Stallholders in school canteens have been encouraged to use healthier ingredients, and drinks

Key Area Going Forward:

Early detection & prevention of Diabetes



GUSTO revealed alarming rates of missed GDM and subsequent development of T2D



Singapore PRReconception Study of long-Term maternal and child Outcomes

S-PRESTO designed to study factors leading to development of GDM and subsequent T2D

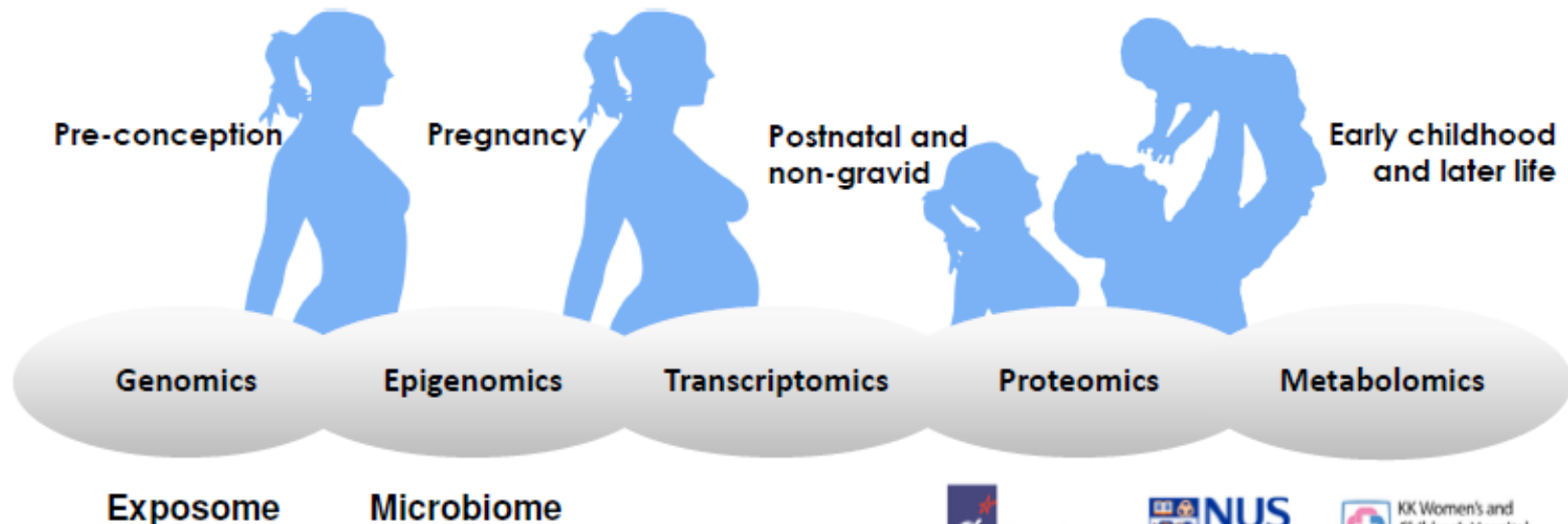


Nutritional PRreconception and During Pregnancy to Maintain Healthy GlucosE Metabolism & OffspRing Health

NIPPER designed to prevent GDM and subsequent T2D with pre-pregnancy nutritional supplementation

Deep Phenotyping

Longitudinal cohorts throughout the Life Course



Achievements to date

Metabolic TCR Flagship Programme, NUS Medicine
Singapore Institute for Clinical Sciences, A*STAR,
Singapore Centre for Nutritional Sciences, Metabolic Diseases,
and Human Development (SiNMeD) and
KK Women's & Children's Hospital



ACADEMIC IMPACT	>350 scientific papers	> \$120M in grant funding secured	Nestle 2015 R&D Award, Innovation Partnership Category	12 patent filings	47 Students (Masters, PhD & Post doctoral)	>200 staff + 35 Faculty members + 3 new faculty recruits
------------------------	----------------------------------	---------------------------------------------	--------------------------------------------------------	--------------------------	---------------------------------------------------	--------------------------------------------------------------------

RESEARCH CAPABILITIES	GUSTO Birth Cohort (launched 2009)	Neurodevelopment Research Centre (launched 2010)	Clinical Nutrition Research Centre (launched 2014)	S-PRESTO & NIPPER Pre-conception Cohorts (launched 2015)
------------------------------	------------------------------------	--------------------------------------------------	----------------------------------------------------	----------------------------------------------------------

SOCIETAL VALUE	<i>Advancement in MRI technique to improve the quality of patient care</i>	<i>Optimising maternal & offspring health through changing national health policy</i>	<i>Improving understanding of factors influencing early school performance</i>	<i>Community engagement & education for health & nutritional literacy</i>
-----------------------	----------------------------------------------------------------------------	-------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------	-----------------------------------------------------------------------------------

ECONOMIC VALUE	12 patent filings at the national phase, including 9 with major industry partners	Deep collaborations with major nutrition companies like Abbott, Danone & Nestle have led to establishment of new research facilities in Singapore	>\$28M in direct industry funding for R&D in Singapore with another \$10M in the pipeline
-----------------------	------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------

We are doing all this to benefit
Singaporeans and to
Change Tomorrow's Health, *Today*...



CHONG Yap Seng	NUHS	Walter STÜNKEL	SICS	Elizabeth SPELKE	Harvard, US
LEE Yung Seng	NUHS, SICS	Neerja KARNANI	SICS	YONG Eu Leong	NUHS
QIU Anqi	NUS	SAW Seang Mei	NUS	Arijit BISWAS	NUHS
Kenneth KWEK	KKH	Lynette SHEK	NUHS	TAN Heng Hao	KKH
Bryan Emmett OGDEN	SEMC, Duke-NUS	Stephen HSU	NUHS	Shephali TAGORE	KKH
Joanna D. HOLBROOK	SICS	CHAN Yiong Huak	NUS	Bernard CHERN	KKH
Fabian YAP	KKH	Jonathan CHOO T.L.	KKH	SU Lin Lin	NUHS
Peter GLUCKMAN	SICS	QUEK Swee Chye	NUHS	Melvin LEOW	SICS
Marielle FORTIER	KKH	Robert GRIGNANI	NUHS	HUANG Zhongwei	NUHS
LING Lieng Hsi	NUHS	Sendhil VELAN	SICS, SBIC	Claudia CHI	NUHS
Jeyakumar HENRY	SICS	Philip LEE Teck Hock	SBIC	LI Jun	NUHS
Mary CHONG	SICS	Jeevesh KAPUR	NUHS	Philip BAKER	UoA, NZ
Rob Martinus VAN DAM	NUHS	Micheal LIM C.M.	KKH	Paul ROBSON	GIS
LEK Ngee	KKH	HAN Wee Meng	KKH	NG Huck Hui	GIS
CHEUNG Yin Bun	Duke-NUS	Keith GODFREY	Southampton, UK	HAN Weiping	SBIC
Michael MEANEY	SICS	Mark HANSON	USoton, UK	Mark VICKERS	UoA, NZ
Birit Broekman	NUHS, SICS	Wayne CUTFIELD	Auckland, NZ	DING Chun Ming	SICS
Anne Rifkin-Graboi	SICS	John WONG	NUS	TAN Chuen Seng	NUS
Leher SINGH	NUS	Daniel FUNG	IMH	CHNG Chai Kiat	KKH
Joshua GOOLEY	Duke-NUS	Michael CHEE	Duke – NUS	Cheryl NGO	NUHS
Helen CHEN	KKH	Eric FINKELSTEIN	Duke – NUS	LEE Bee Wah	NUHS
Prathiba AGARWAL	KKH	Cornelia CHEE	NUHS	Hugo van BEVER	NUHS
CHONG Shang Chee	NUHS	Iliana MAGIATI	NUS	QUAH Boon Long	KKH/ SNEC
TAI E Shyong	NUHS	Daniel GOH	NUHS	Tony PLEASANTS	AgResearch, NZ
TAN Kok Hian	KKH	Mahesh RAMAMURTHY	NUHS	Sheila BARTON	USoton, UK
George YEO SH	KKH	Mary DANIEL	KKH	Allan SHEPPARD	UoA, NZ
Jerry CHAN Kok Yen	NUHS, KKH	LIM Sok Bee	KKH	Karen LILLYCROP	USoton, UK
Citra MATTAR	NUHS	Anne GOH	KKH	Laurent FAY	Nestlé
Victor Samuel RAJADURAI	KKH	Oon Hoe	KKH	Thomas BECK	Nestlé
Anne Ferguson-Smith	Cambridge	Pauline TAY STRAUGHAN	NUS	James KAPUT	Nestlé
				Irma SILVA-ZOLEZZI	Nestlé