

What have we learned so far from the “Children of 1997”?



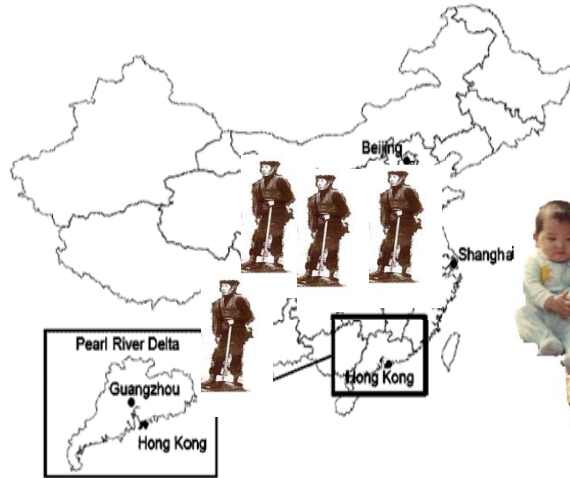
Gabriel M Leung



**SCHOOL OF PUBLIC HEALTH
THE UNIVERSITY OF HONG KONG**

香 港 大 學 公 共 衛 生 學 院

Hong Kong: recent history of rapid transition



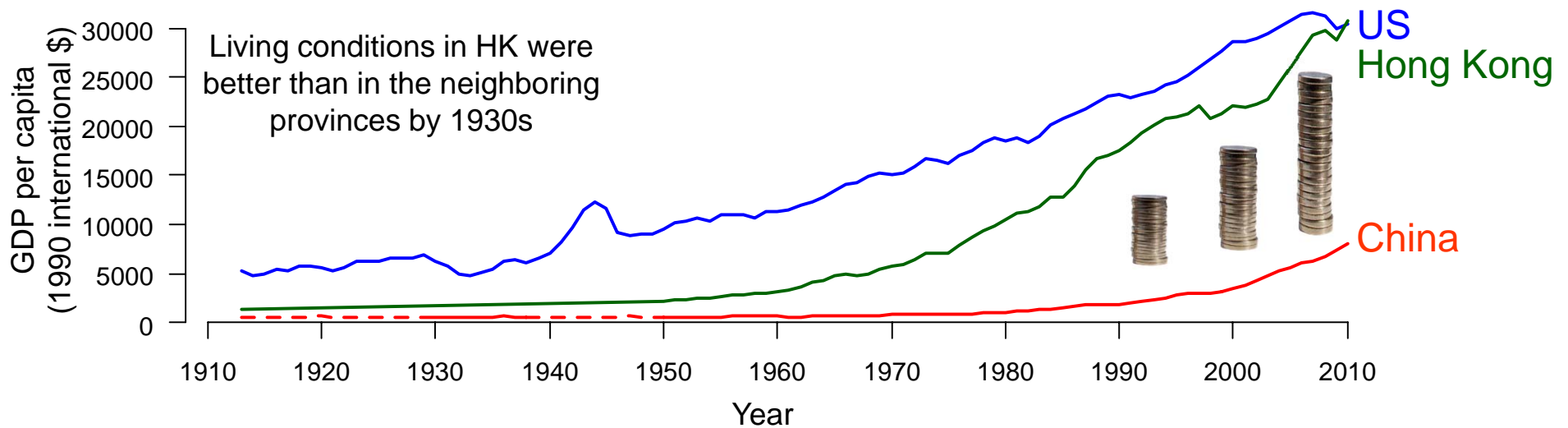
Population mainly temporary
young migrants looking for work



Baby boom



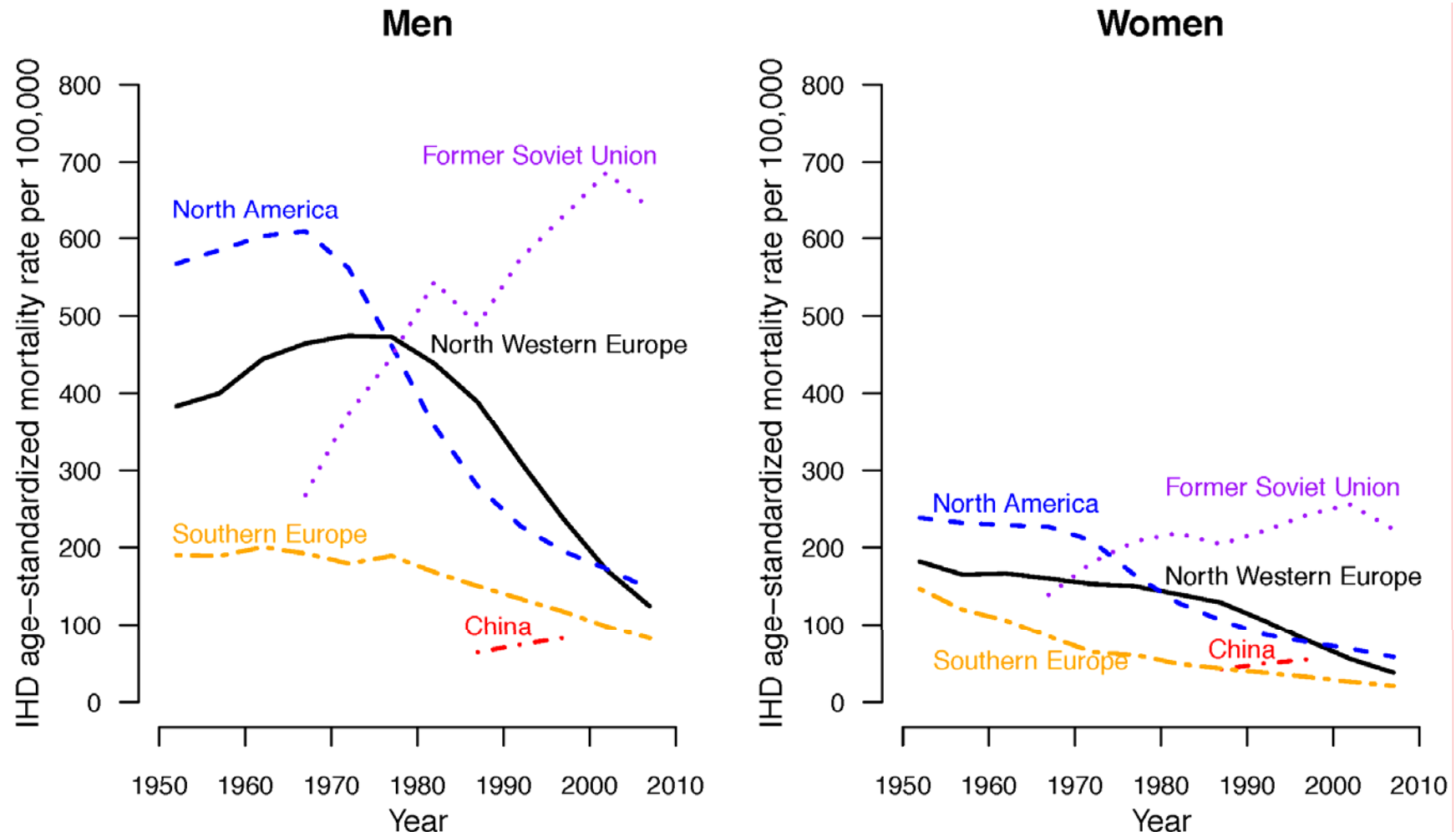
Cross-border
marriage - mainly
migrant mothers
for family union



Maddison A. The world economy: a millennial perspective. Paris, France: Development Centre of the Organisation for Economic Co-operation and Development; 2001.
Bolt J, Van Zanden JL. The first update of the Maddison Project; re-estimating growth before 1820. Maddison Project Working Paper 4. 2013.

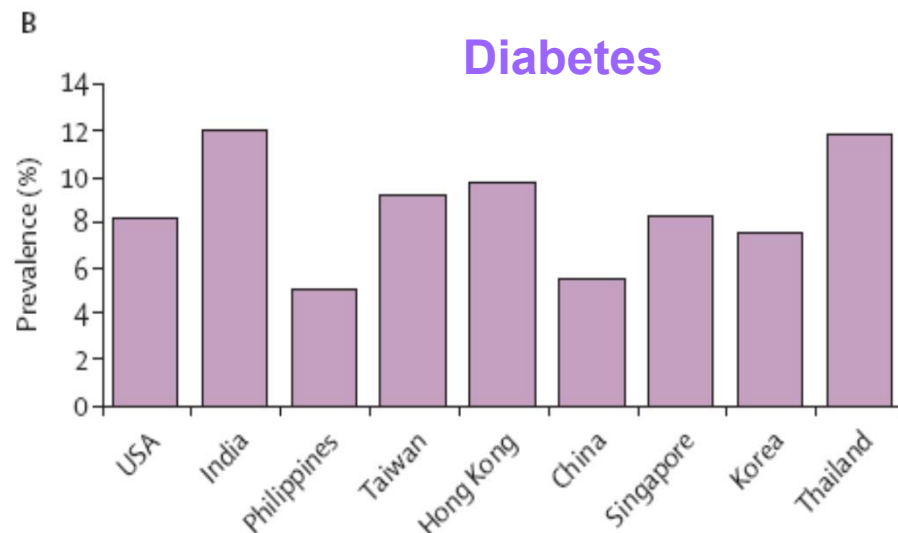
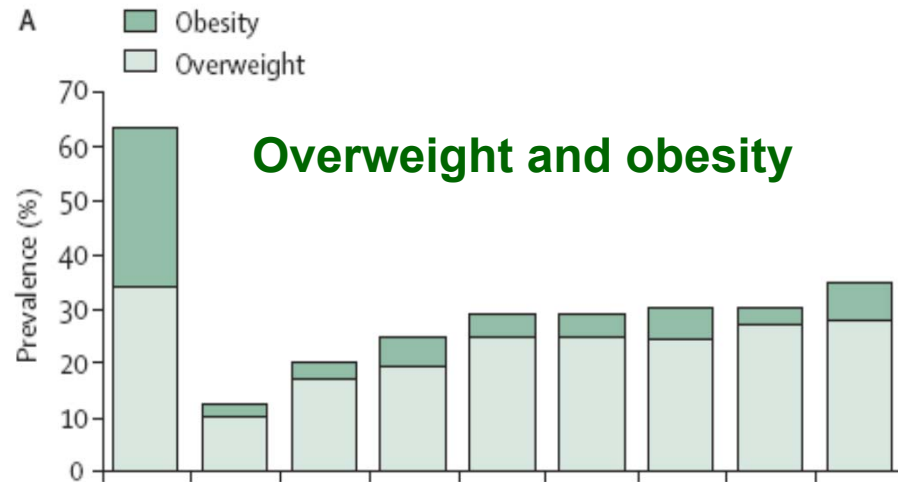
Anomalies in chronic disease - IHD

Why hasn't an epidemic of ischemic heart disease (IHD) among men occurred in China with economic development?



Wong IO, Cowling BJ, Leung GM, Schooling CM. Age-period-cohort projections of ischaemic heart disease mortality by socio-economic position in a rapidly transitioning Chinese population. *PLoS One*. 2013; 8(4): e61495.

Anomalies in chronic disease - Diabetes



- Low rates of IHD in China despite high rates of diabetes
- High rates of diabetes in China at low levels of obesity

Anomalies in chronic disease - COPD

Ranking of age-standardized years of life lost (YLL) rates in 2010 (1 representing country with the lowest YLL)

	Men				Women			
	Stroke	Ischaemic heart disease	Road injury	COPD	Stroke	Ischaemic heart disease	COPD	
Japan	9	2	1	1	7	1	1	
Italy	7	4	8	4	6	4	4	
Australia	2	5	5	6	1	2	2	
Canada	1	8	4	7	3	5	8	
UK	6	9	2	9	11	3	3	
Germany	5	10	3	8	4	8	7	
France	4	3	7	3	2	7	10	
South Korea	11	1	10	5	8	6	14	
USA	3	13	11	11	5	14	17	
Saudi Arabia	12	16	19	2	14	16	5	
China	17	6	13	18	16	10	18	
Argentina	10	15	12	12	10	12	9	
Mexico	8	11	14	10	9	13	13	
Turkey	16	18	6	17	12	15	15	
Brazil	14	14	17	14	17	18	16	
Indonesia	18	12	18	16	18	19	6	
India	13	17	16	19	19	11	12	
Russia	19	19	15	15	13	17	19	
South Africa	15	7	9	13	15	9	11	

- High rates of chronic obstructive pulmonary disease (COPD) in China

Why does economic development have different effects in different places?



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION



The Global Cardiovascular Risk Transition: Associations of Four Metabolic Risk Factors with Macroeconomic Variables in 1980 and 2008

Goodarz Danaei, Gitanjali M. Singh, Christopher J. Paciorek, John K. Lin, Melanie J. Cowan, Mariel M. Finucane, Farshad Farzadfar, Gretchen A. Stevens, Leanne M. Riley, Yuan Lu, Mayuree Rao and Majid Ezzati

on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group

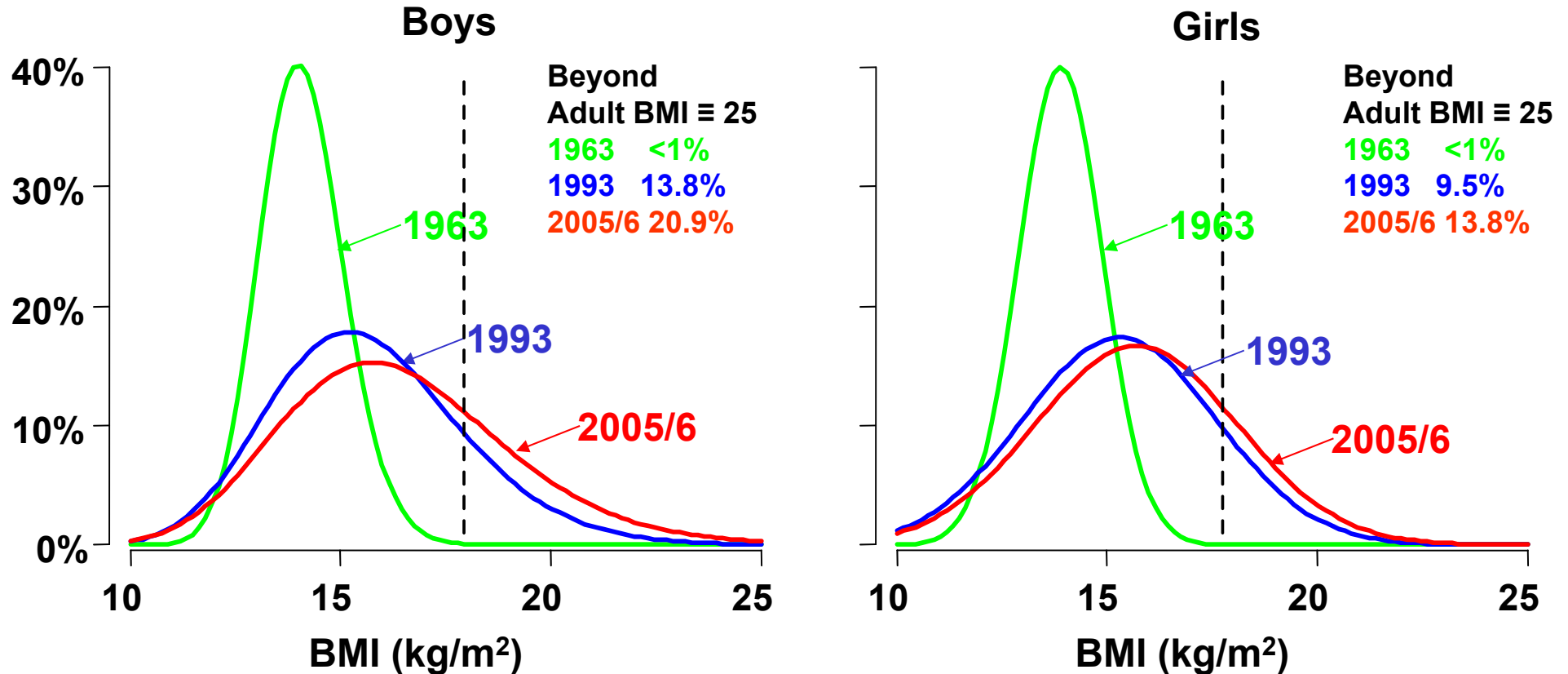
Circulation. published online March 12, 2013;

“If the observed trends continue, **developed countries** will continue to face an **obese population a high prevalence of diabetes mellitus and hypercholesterolemia**, whereas **developing countries** will be confronted by a combination of **obesity, hypertension and diabetes mellitus**. The diseases of affluence paradigm seems inadequate for explaining the nuances in the global epidemiology of cardiovascular risk factors and should be replaced with a more refined framework that better informs policy and intervention.”

Childhood adiposity epidemic in Hong Kong



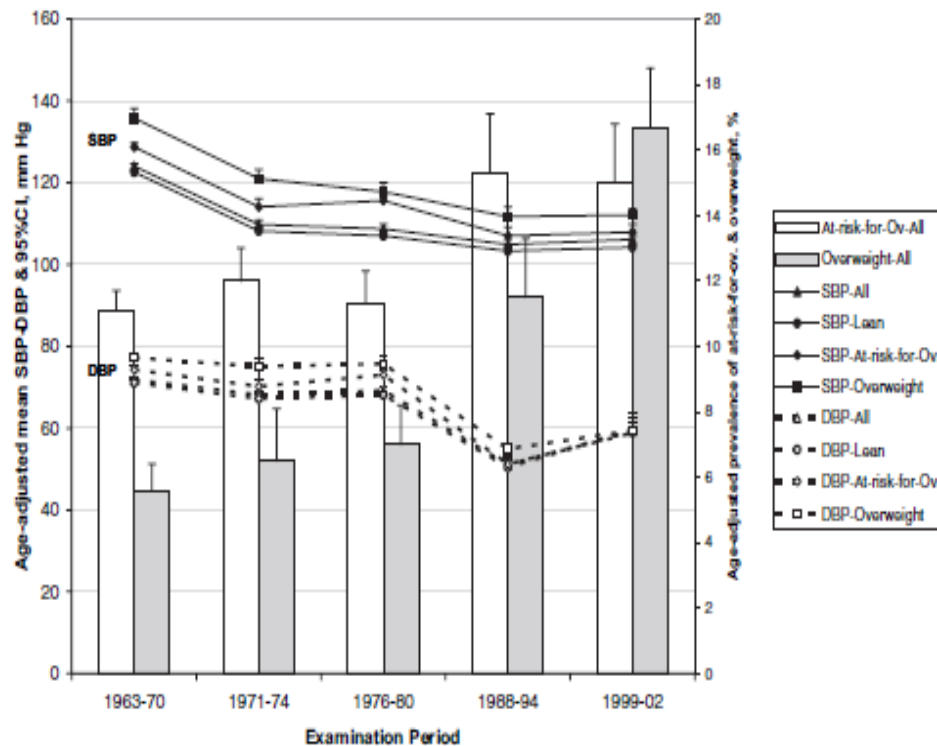
Upward trend of childhood adiposity has concomitantly occurred with economic development over the past 50 years, with a clear shift of the entire BMI distribution



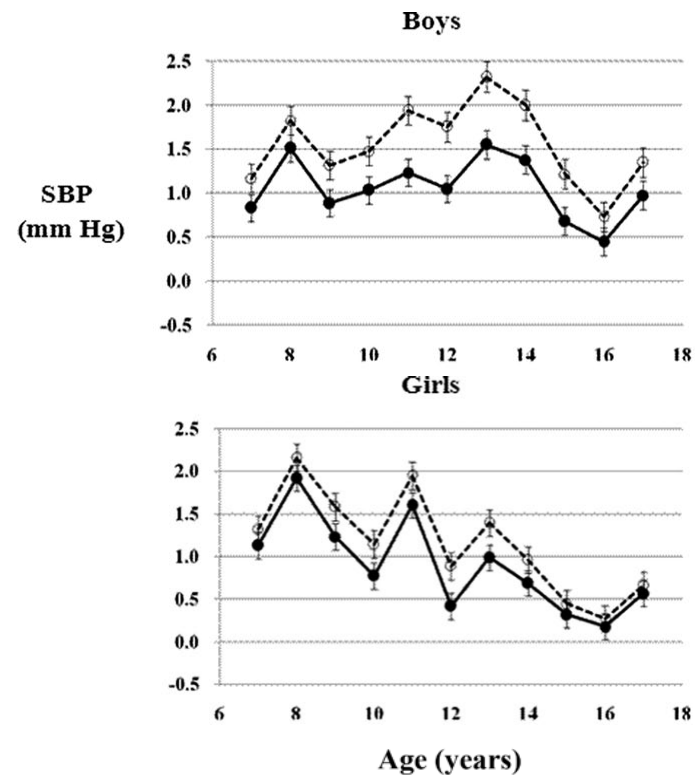
Divergent trends of childhood blood pressure



Secular trend of childhood BP in Hong Kong remains unknown; downward BP trend in US persists despite increasing overweight trend while upward BP and overweight trends concur in China



US - Trends of childhood blood pressure and overweight (1963-2002)

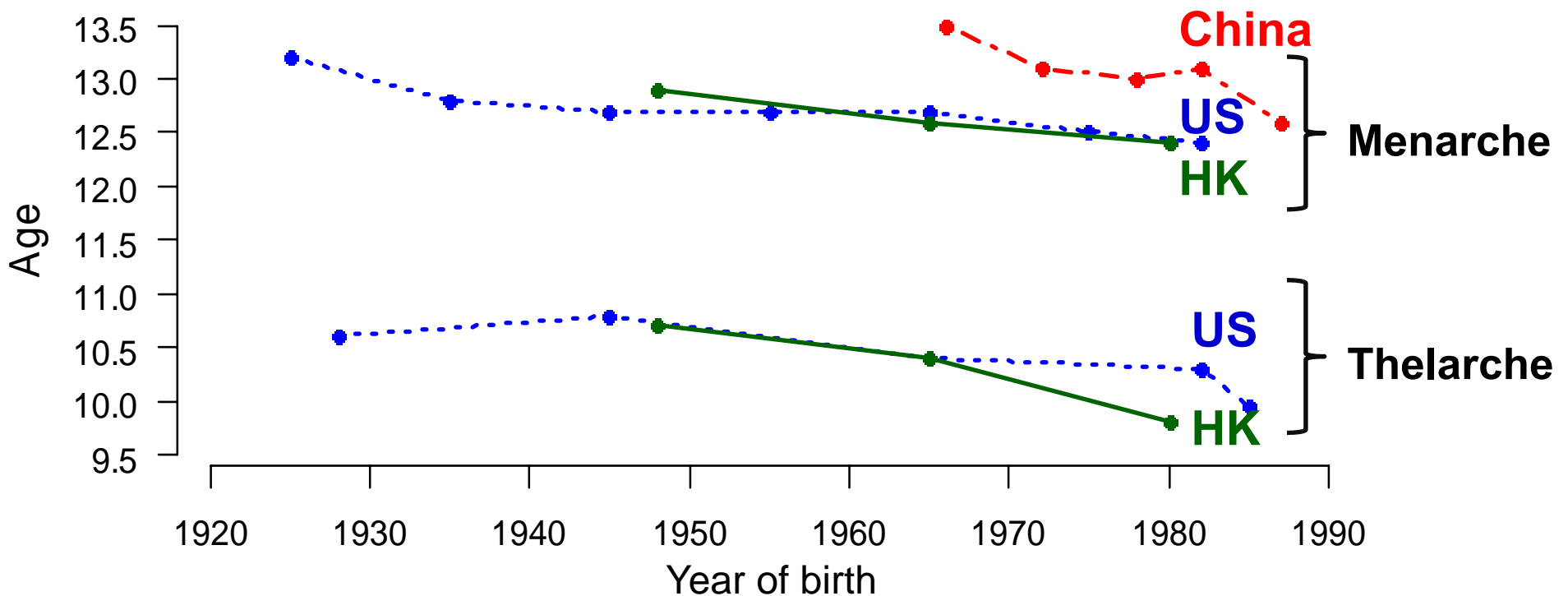


China - Systolic blood pressure (2005-2010) before (grey dot) and after (black dot) BMI adjustment

Din-Dzietham R, Liu Y, Bielo M-V, Shamsa F. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation*. 2007; 116(13): 1488-96.
 Dong B, Wang H-J, Wang Z, Liu J-S, Ma J. Trends in blood pressure and body mass index among Chinese children and adolescents from 2005 to 2010. *American Journal of Hypertension*. 2013.

Declining trends of pubertal timing

Early puberty is associated with IHD and hormone-related cancer with average age at puberty has decreased sharply with economic development. Girls with earlier menarche also have twice the risk of developing asthma than those with later menarche.

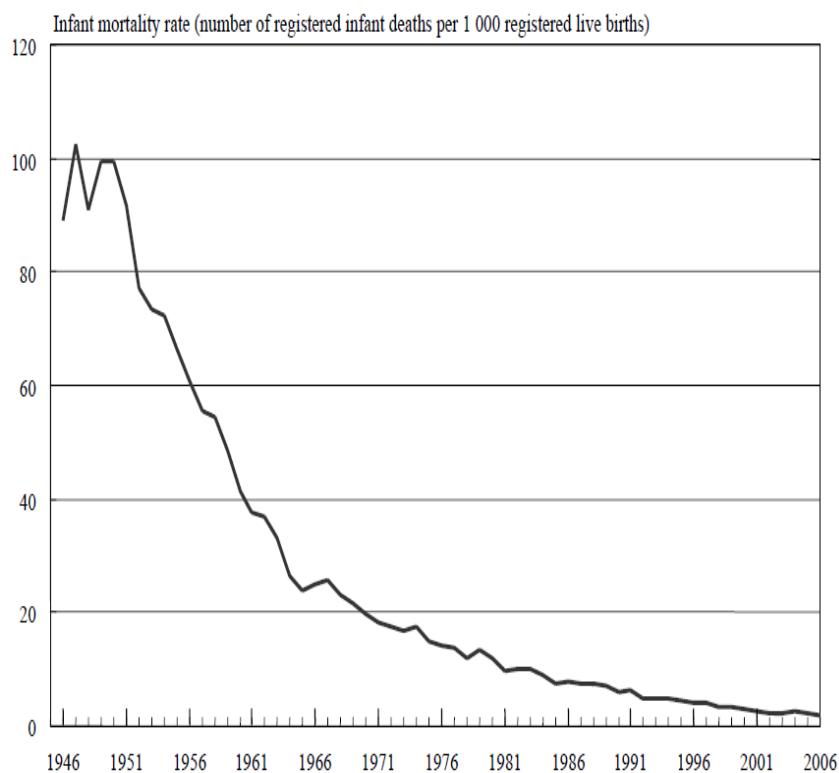


Ma HM, Du ML, Luo XP, et al. Onset of breast and pubic hair development and menses in urban Chinese girls. *Pediatrics*. 2009; 124(2): e269-77.
 Huen KF, Leung SS, Lau JT, Cheung AY, Leung NK, Chiu MC. Secular trend in the sexual maturation of southern Chinese girls. *Acta Paediatr*. 1997; 86(10): 1121-4.
 Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008; 121(Suppl 3): S172-91.

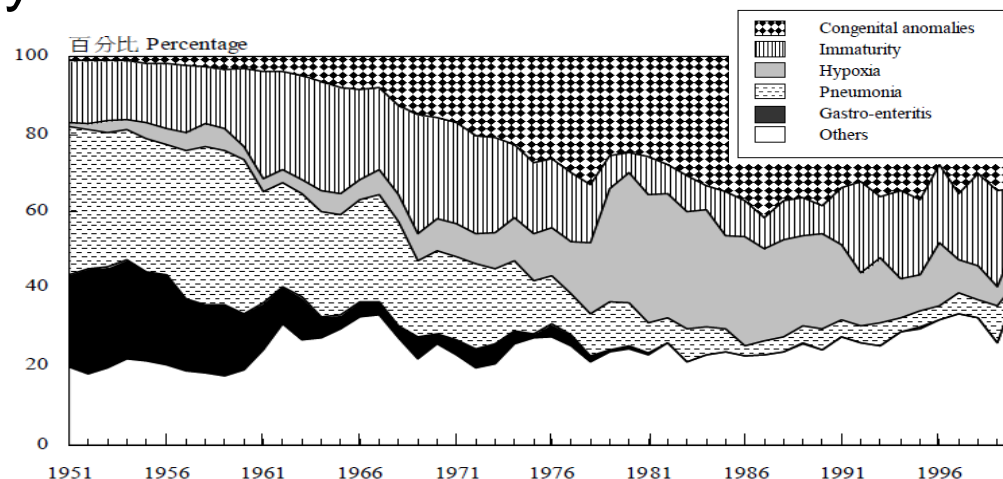
Declining trends of infectious disease burden



Infant mortality rate had significantly declined since 1950s in Hong Kong. Infection-related mortality for Infants and children under 5 maintains at very low rate.



Trends of infant mortality rate in Hong Kong (1946-2006)



Causes of infant mortality in Hong Kong (1951-2000)

	Study dates	Case fatality for influenza-associated severe ALRI
Developed countries		
South Australia, Australia ⁴⁸	1996-2006	4/626 (0.64%)
Hong Kong ^{34*}	1997-99	7/5471 (0.13%)
Philadelphia, PA, USA ⁵¹	2000-04	5/573 (0.87%)
Leicester, UK ³¹	2001-02	0/33
Gipuzoka, Spain ³²	2001-04	0/70
Salt Lake County, UT, USA ³⁸	2001-04	1/325 (0.31%)
Sydney, Australia ⁶⁰	2003	1/16 (6.25%)
Canada ⁵⁶	2003-04	1/424 (0.23%)
Multicentre, USA ⁴⁰	2003-08	7/2998 (0.23%)
Hong Kong, China ^{57*}	2005	1/86 (1.16%)

Influenza-related mortality under 5 in developed settings

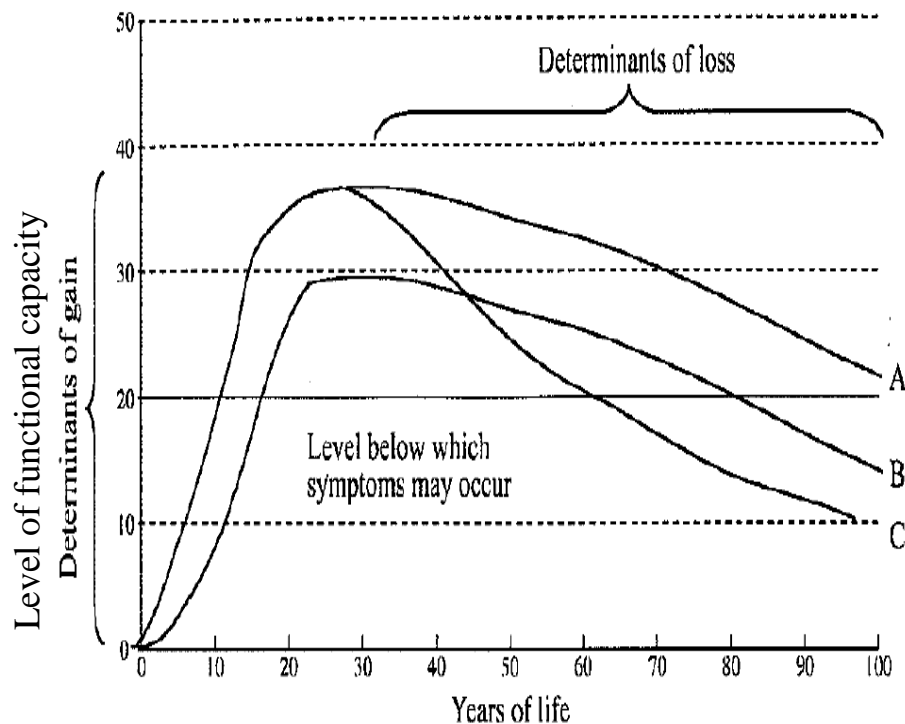
Census and Statistics Department. Trends of infant mortality in Hong Kong, 1946 to 2006. Hong Kong: The Government of Hong Kong Special Administrative Region; 2008.

Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*. 2011; 378(9807): 1917-30.

Life course approach



Exposures at critical window or accumulating across different life course contribute to natural history of disease



THE BARKER THEORY

“low birth weight bad”

Some factors which result in low birth weight might also cause diabetes, but seem unlikely that these same factors also cause ischemic heart disease

What about the role of overall growth patterns and early life exposures on health?

A = normal development and decline;
B = exposure in early life reducing functional capacity;
C = exposure acting in mid to later accelerating age-related decline

Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol.* 2002; 31(2): 285-93.

Barker DJP, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *The Lancet.* 1986; 327(8489): 1077-81.

Potential determinants of childhood health



Secondhand smoking



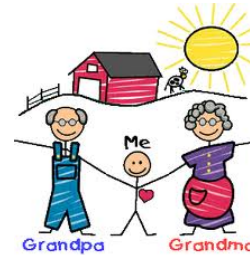
Timing of solid food introduction



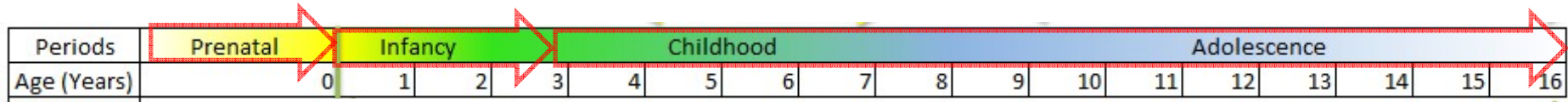
Dairy product



Breastfeeding



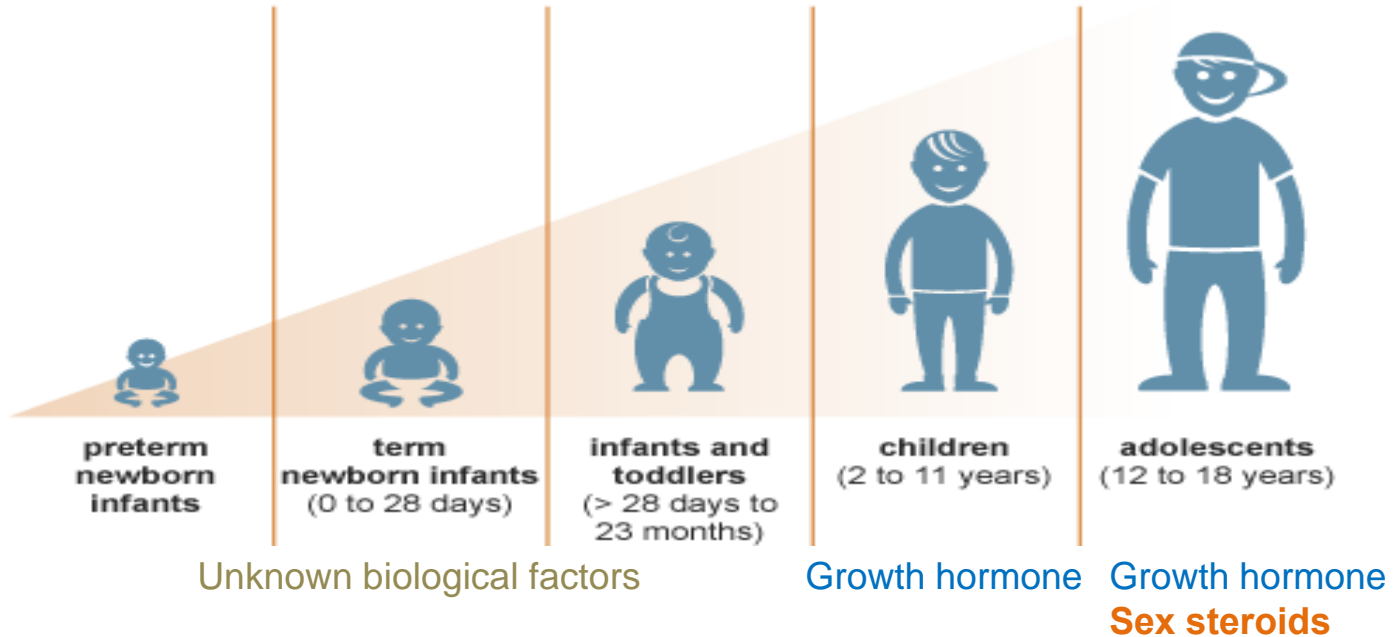
Child care



Mode of delivery



Birth weight
Gestational age
Birth order

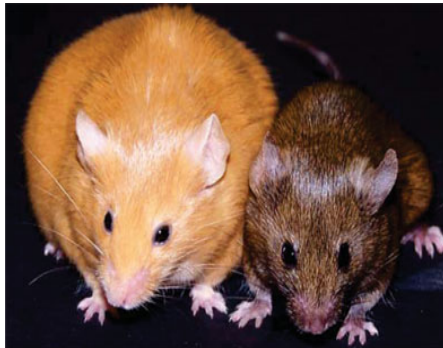


Growth patterns at different phases

“Imprint of time”

1. Supreme difficulty of reversing disparities in health within a short time frame suggests a role for cohort/inter-generational effects
2. Cohort effects are increasingly recognized
Trends in U.S. adult chronic disease mortality, 1960-1999: age, period, and cohort variations. Yang Y. *Demography*. 2008;45(2):387-416
Trends in US older adult disability: exploring age, period, and cohort effects. Lin SF, Beck AN, Finch BK, Hummer RA, Masters RK. *Am J Public Health*. 2012;102(11):2157-63
3. Epigenetics provides a mechanism

Genetically identical



different maternal diet

Check consistency in different settings



Problems:

- Many epidemiologic findings are a reflection of confounding
- Some well-accepted dogmas are myths
- Implementing public health policy based on myths may be harmful

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Myths, Presumptions, and Facts
about Obesity

Solutions:

- Check the associations in a **'negative control'** setting i.e., with different confounding structure
- Do an RCT

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International Journal of Epidemiology 2009;1-9
doi:10.1093/ije/dyp274

Does breastfeeding protect against childhood overweight? Hong Kong's 'Children of 1997' birth cohort

Man Ki Kwok, C Mary Schooling,* Tai Hing Lam and Gabriel M Leung

Uniqueness of Hong Kong's "Children of 1997"



First post-colonial generation

- Chinese identity mixed with a western heritage
- First Chinese "first-world" generation
- Growing up in a resource-rich Chinese environment



Last Hong Kong generation with grandparents mainly born and brought up in pre-industrial China



Only large active Chinese birth cohort, with many differences from more commonly studied western populations

- Diet and lifestyle
- Child care, child rearing
- Less socio-economic patterning of BMI



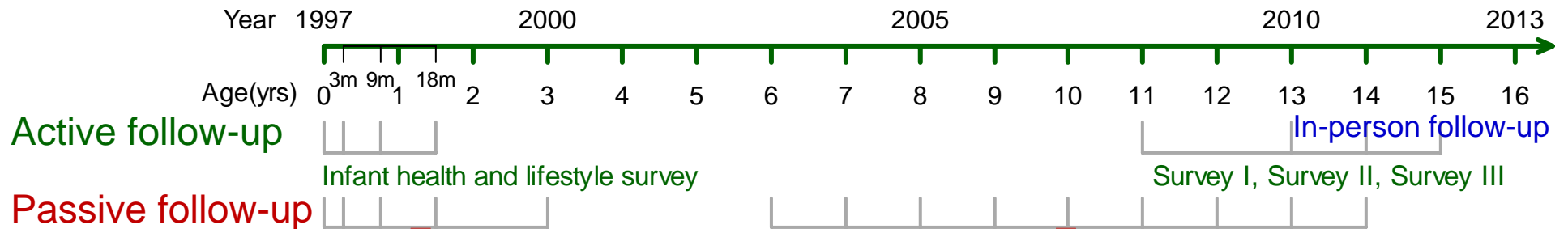
Provides local evidence



Overview of Hong Kong's "Children of 1997"



8,327 infants born in Hong Kong in April and May 1997



Body Mass Index $BMI = \text{weight} / \text{height}^2 \text{ (kg/m}^2\text{)}$
Weight and height: record linkage with Maternal and Child Health Centres, Student Health Service

1. Sex and age specific **BMI z-score** relative to WHO growth standard
2. **Overweight/obesity**: international obesity task force (IOTF)

Public hospital use

Physical and psychological assessments from the Student Health Service

Deaths from the Department of Health

“Infant lifestyle and health survey”



Originated by

- **Professor TH Lam** (HKU) with Department of Health

Research question

- The effect of secondhand smoking and breastfeeding on infant health

Design

- Recruited from all government well-baby clinics
- Carer completed questionnaires at 0, 3, 9 and 18 months

Participants

- All infants born in Hong Kong in April and May 1997 (88% of index births)



兒童健康生活環境調查



香港大學社會醫學系及衛生署現正聯合舉辦一項兒童健康和生
活環境調查，希望你能用數分鐘時間，填妥這份問卷，在稍後見護士時交給
護士。你所提供的答案，祇會用於統計分析。一切個人資料，絕對保密，
請你放心。你的參與，純屬自願。你是否參與，絕不會影響你所接受的服
務。

香港大學社會醫學系

香港政府衛生署

Revive “Infant lifestyle and health survey”



Resurrected and conceived by

- **Professor Gabriel Leung** and **Dr Mary Schooling** with Department of Health

1) Record linkage (2004-06)

2) Re-establish contact (2007-08)

- Letters
- Newsletters
- Cards, gifts
- Phone calls
- Press release
- Website

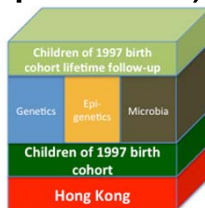


3) Postal and telephone surveys (2008-12)

- Family history and lifestyle (2008-10)
- Psychological well-being (2010-12)
- Waist and hip circumference (2012)

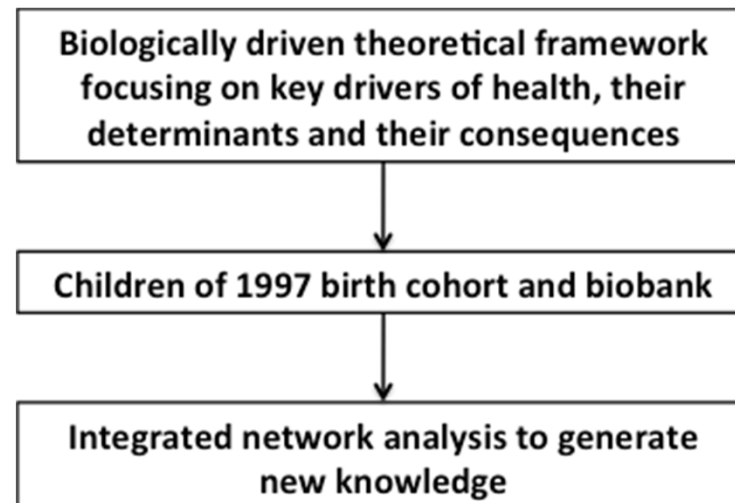
4) In-person follow-up (2010 to present)

- Pilot 1 of 40 in 2010
- Pilot 2 of 225 in 2011
- Pilot 3 of 502 in 2012
- Create **Biobank** in 2013



Approach to research

- Confirm or refute empirically driven hypotheses in a ‘**negative control**’ setting
- Use methods more suited to establishing causality
- Follow a coherent research program



Widely published findings



- Important information concerning the local health effects of secondhand smoking

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Effects of Environmental Tobacco Smoke on Health Services Utilization in the First Eighteen Months of Life

Tai-Hing Lam, MD; Gabriel M. Leung, MD; and Lai-Ming Ho, PhD
PEDIATRICS Vol. 107 No. 6 June 2001

Paediatric and Perinatal Epidemiology

Affiliated to the Society for Pediatric and Perinatal Epidemiologic Research

Maternal, paternal and environmental tobacco smoking and breast feeding

Gabriel M. Leung, Lai-Ming Ho and Tai-Hing Lam
Department of Community Medicine, The University of Hong Kong, Hong Kong

Paediatric and Perinatal Epidemiology 2002, 16, 236-245

JAMA Pediatrics

Formerly Archives of Pediatrics & Adolescent Medicine

ARTICLE

Secondhand Smoke Exposure, Smoking Hygiene, and Hospitalization in the First 18 Months of Life

Gabriel M. Leung, MD, MPH; Lai-Ming Ho, PhD; Tai-Hing Lam, MD, MSc

Arch Pediatr Adolesc Med. 2004;158:687-693

Archives of DISEASE IN CHILDHOOD

ORIGINAL ARTICLE

The economic burden of environmental tobacco smoke in the first year of life

G M Leung, L-M Ho, T-H Lam

Arch Dis Child 2003;88:767-771

- Contributed to the **ban on smoking in all indoor public places** subsequently implemented in Hong Kong

Widely published findings



- Important information concerning the local health effects of breastfeeding

BIRTH

Breastfeeding Rates in Hong Kong: A Comparison of the 1987 and 1997 Birth Cohorts

Gabriel M. Leung, MD, MPH, Lai-Ming

EPIDEMIOLOGY Full Text
OVID

Health Consequences of Breast-feeding

*Doctors' Visits and Hospitalizations During the First 18 Months of
Life in Hong Kong Chinese Infants*

Gabriel M. Leung,* Tai-Hing Lam,*

EPIDEMIOLOGY Full Text
OVID

Breast-feeding and Childhood Hospitalizations for
Infections

Marie Tarrant,^a Man-Ki Kwok,^b Tai-Hing Lam,^b Gabriel M. Leung,^b and C. Mary Schooling^b

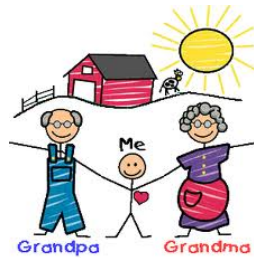
(*Epidemiology* 2010;21: 847–854)

- Contributed to the **a change in the Hospital Authority's infant formula procurement policy** in Hong Kong

Positive findings on childhood overweight



Informal child care



International Journal of
Epidemiology

Published by Oxford University Press on behalf of the International Epidemiological Association
© The Author 2011. All rights reserved. International Journal of Epidemiology 2011;40:
doi:10.1093/ije/dyq366

Is informal child care associated with childhood obesity? Evidence from Hong Kong's "Children of 1997" birth cohort

Shi Lin Lin, Gabriel M Leung, Lai Ling Hui, Tai Hing Lam and C Mary Schooling*

“+” in most Western studies



“+” in our cohort

Childhood obesity



Paternal smoking



PEDIATRICS

Paternal Smoking and Childhood Overweight: Evidence From the Hong Kong "Children of 1997"

Man Ki Kwok, C. Mary Schooling, Tai Hing Lam and Gabriel M. Leung
Pediatrics 2010;126:e46-e56; originally published online Jun 29, 2010;
DOI: 10.1542/peds.2009-2642

Potential explanations (Informal child care):

1. Parents may be more likely to adhere to child rearing recommendation
2. Grandparents or domestic helpers may be less physical active and less likely to restrict child's access to energy-dense favorite foods and television viewing

Potential explanation (Paternal smoking):

1. Adverse effect of secondhand smoke on child cognition and social behavior implies its possibility on appetite or metabolic control

Null findings on childhood overweight



Cesarean birth



Never breastfeeding



Early solid food introduction



Low dairy product intake



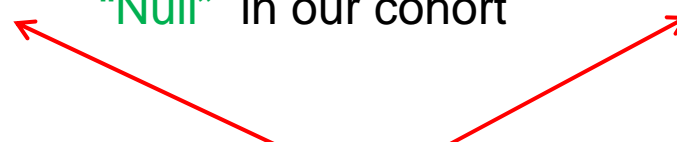
Childhood obesity



“+” in most Western studies



“Null” in our cohort



Key confounders in Western population

Low socioeconomic position (SEP)

Maternal overweight

Maternal smoking

Less influential factors in our Chinese cohort

Not always associated with low SEP

Maternal overweight – less prevalent

Maternal smoking – uncommon



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Does breastfeeding protect against childhood overweight? Hong Kong's 'Children of 1997' birth cohort

Man Ki Kwok, C. Mary Schooling,* Tai Hing Lam and Gabriel M Leung

International Journal of Epidemiology 2009, 38:4
doi:10.1093/ije/dyn274



OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Timing of Solid Food Introduction and Obesity: Hong Kong's "Children of 1997" Birth Cohort

Shi Lin Lin, Gabriel M. Leung, Tai Hing Lam and C. Mary Schooling
Pediatrics 2013;131:e1459; originally published online April 8, 2013;
DOI: 10.1542/peds.2012-2643



Mode of delivery and adiposity: Hong Kong's "Children of 1997" birth cohort
Shi Lin Lin MPH^a, Gabriel M. Leung MD^a, C. Mary Schooling PhD^{a,b,*}

OPEN ACCESS Freely available online



The Role of Dairy Products and Milk in Adolescent Obesity: Evidence from Hong Kong's "Children of 1997" Birth Cohort

Shi Lin Lin¹, Marie Tarrant², Lai Ling Hui¹, Man Ki Kwok¹, Tai Hing Lam¹, Gabriel M. Leung¹, C. Mary Schooling^{1,2*}
December 2012 | Volume 7 | Issue 12 | e52575

Findings on adolescent blood pressure



Breastfeeding

“+” in most Western studies

“Null” in our cohort

Adolescent blood pressure

Breastfeeding was unrelated to adolescent blood pressure in our cohort, perhaps because **high SEP** is **key confounder** in Western population but is **not associated** with sustained breastfeeding in our Chinese cohort

Birth weight

Infant growth

Weight

Age

Infancy

Childhood

Adolescence

Birth weight and infant growth had limited impacts on adolescent **blood pressure**, which was more **strongly related to recent growth and current size**



Original Contribution

Breastfeeding and Adolescent Blood Pressure: Evidence From Hong Kong's "Children of 1997" Birth Cohort

Man Ki Kwok, Gabriel M. Leung, and C. Mary Schooling*

Am J Epidemiol. 2013;178(6):928-936

PEDIATRICS

Lifetime Growth and Blood Pressure in Adolescence: Hong Kong's "Children of 1997" Birth Cohort

Michelle Heys, Shi Lin Lin, Tai Hing Lam, Gabriel M. Leung and C. Mary Schooling
Pediatrics; originally published online December 10, 2012;
 DOI: 10.1542/peds.2012-0574

Journal of Hypertension

Simulated growth trajectories and blood pressure in adolescence: Hong Kong's Chinese Birth Cohort

Man Ki Kwok*, Guy Freeman*, Shi Lin Lin*, Tai Hing Lam*, and Catherine M. Schooling**
Journal of Hypertension 2013, 31:1785-1797

Findings on pubertal timing



Breastfeeding Dairy product



Pubertal onset



Breastfeeding and childhood dairy product intake was not associated with pubertal timing

Early infection

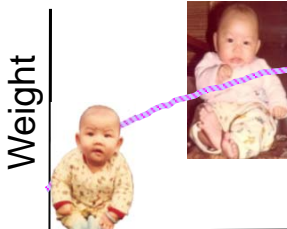


“null”

“+”

Early infection was associated with later puberty, suggesting that less infection with economic development could contribute to earlier puberty

Birth weight Infant growth



Faster childhood height growth was associated with earlier puberty, but not birth weight

Premature births was associated with later puberty



Original Contribution

Early Life Infections and Onset of Puberty: Evidence From Hong Kong's Children of 1997 Birth Cohort

Man Ki Kwok, Gabriel M. Leung, Tai Hing Lam, and C. Mary Schooling*

Am J Epidemiol. 2011;173(12):1440–1452



Original Contribution

Small for Gestational Age and Age at Puberty: Evidence From Hong Kong's "Children of 1997" Birth Cohort

L. L. Hui, Gabriel M. Leung, Man-Yu Wong, T. H. Lam, and C. M. Schooling*

Am J Epidemiol. 2012;176(9):785–793

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Breastfeeding, Childhood Milk Consumption, and Onset of Puberty
Man Ki Kwok, Gabriel M. Leung, Tai Hing Lam and C. Mary Schooling
Pediatrics 2012;130:e631; originally published online August 20, 2012;
DOI: 10.1542/peds.2011-3697

EPIDEMIOLOGY

Full Text
oVID

Premature Birth and Age at Onset of Puberty

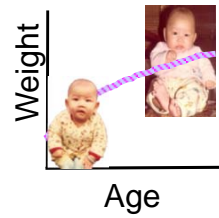
Lai Ling Hui, Gabriel M. Leung, Tai Hing Lam, and C. Mary Schooling

(Epidemiology 2012;23: 415–422)

More findings from “Children of 1997”



Rapid infant growth

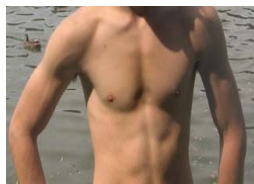


“+”

Higher childhood BMI



Lower pubertal muscle mass

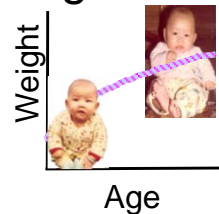


“+”

Higher blood glucose



Rapid infant growth



“Null”

Infection



Breastfeeding



“Not clear”

Mental health



JAMA Pediatrics
Formerly Archives of Pediatrics & Adolescent Medicine

ARTICLE

Birth Weight, Infant Growth, and Childhood Body Mass Index

Hong Kong's Children of 1997 Birth Cohort

L. L. Hui, MPhil; C. Mary Schooling, PhD; Shirley Sze Lee Leung, MBBS; Kwok Hang Mak, MBBS; Lai Ming Ho, PhD; Tai Hing Lam, MD; Gabriel M. Leung, MD
Arch Pediatr Adolesc Med. 2008;162(3):212-218

AMERICAN JOURNAL OF HUMAN BIOLOGY

AMERICAN JOURNAL OF HUMAN BIOLOGY 24:183-185 (2012)

Short Report

Pubertal Muscle Mass and Diabetes Markers in Chinese Adolescents

SHI LIN LIN,¹ SO LUN LEE,² LAI LING HUI,¹ SHIU LUN AU YEUNG,¹ MICHAEL A. TSE,¹ GABRIEL M. LEUNG,¹ AND C. MARY SCHOOLING^{1*}

EPIDEMIOLOGY

Infant Growth During the First Year of Life and Subsequent Hospitalization to 8 Years of Age

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Archives of DISEASE IN CHILDHOOD

Breast feeding and early adolescent behaviour, self-esteem and depression: Hong Kong's 'Children of 1997' birth cohort

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Public health implications

- Short-term effects of second-hand smoke and breastfeeding
- Long-term effects of second-hand smoke
 - More infections into childhood
 - Obesity in childhood
- Little long-term effect of breastfeeding on obesity, infections, blood pressure, timing of puberty or mental health
- Little effect of Cesarean section, timing of solid food introduction or use of dairy products on obesity
- Childhood BMI has changed dramatically in the last 50 years. Modifiable factors driving early BMI, such as informal child care or paternal smoking are important, but unlikely to explain all the change

Etiological implications

- Little effect of birth weight on blood pressure or timing of puberty
- Early infections and premature birth associated with later puberty
- Lack of muscle mass at puberty may be a key driver of diabetes
- Unclear role of rapid infant weight growth
 - No reduction in infectious illness
 - Higher BMI
- Faster height growth is associated with earlier puberty



Strengths and limitations

Strengths

- Large sample
- Detailed information on growth and BMI
- Unique setting, enables us to test empirically derived hypotheses from the west
- Provides useful etiological information

Limitations

- Exposures not always well defined
- Associations may be different at the completion of growth
- Cannot identify body composition from BMI



Future directions

Epigenetics

- Are there epigenetic effects on growth axes and do they affect health?

Genetics

- GWAS
- Mendelian randomization

Microbiome

- Effects on obesity and metabolism
- Trade-offs of chronic infections
- As an endocrine organ

Publications



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Discussion Session



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COHORT PROFILE

Cohort Profile: 'Children of 1997': a Hong Kong Chinese birth cohort

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