

# Income inequality and cardiovascular health in China



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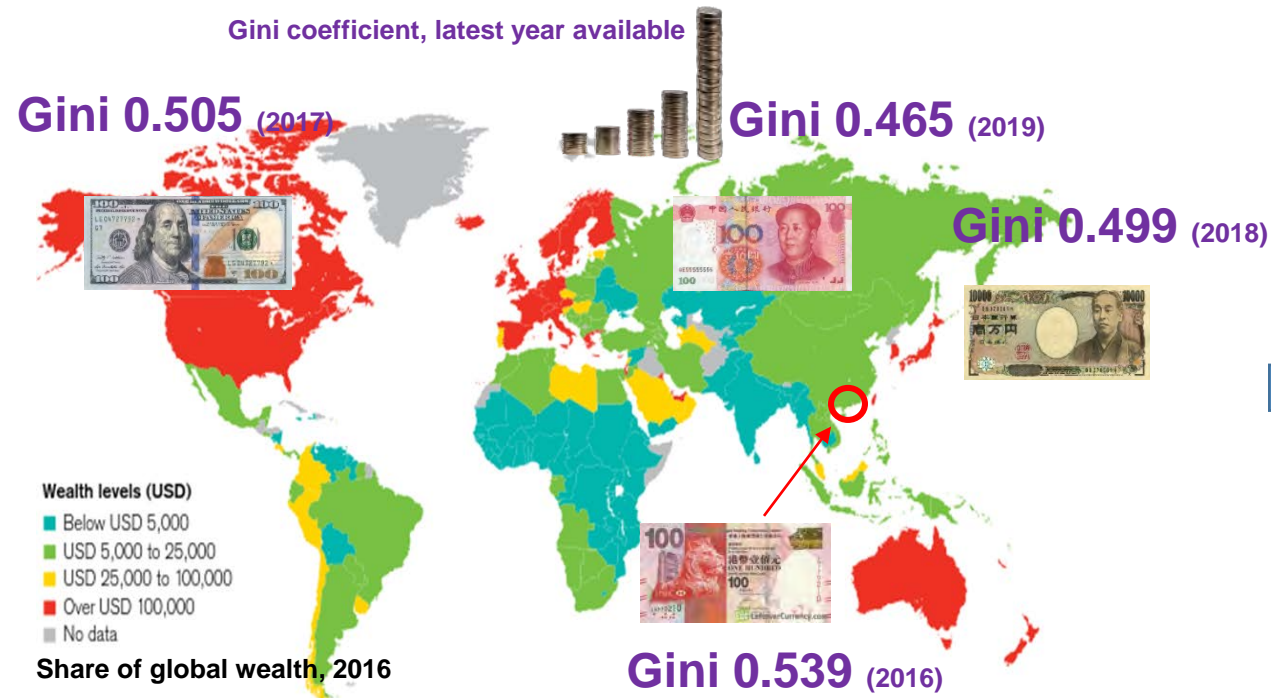


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# Income inequality in rapidly developing China



Source: Credit Suisse Global Wealth Report 2016; World Bank Gini index 2019



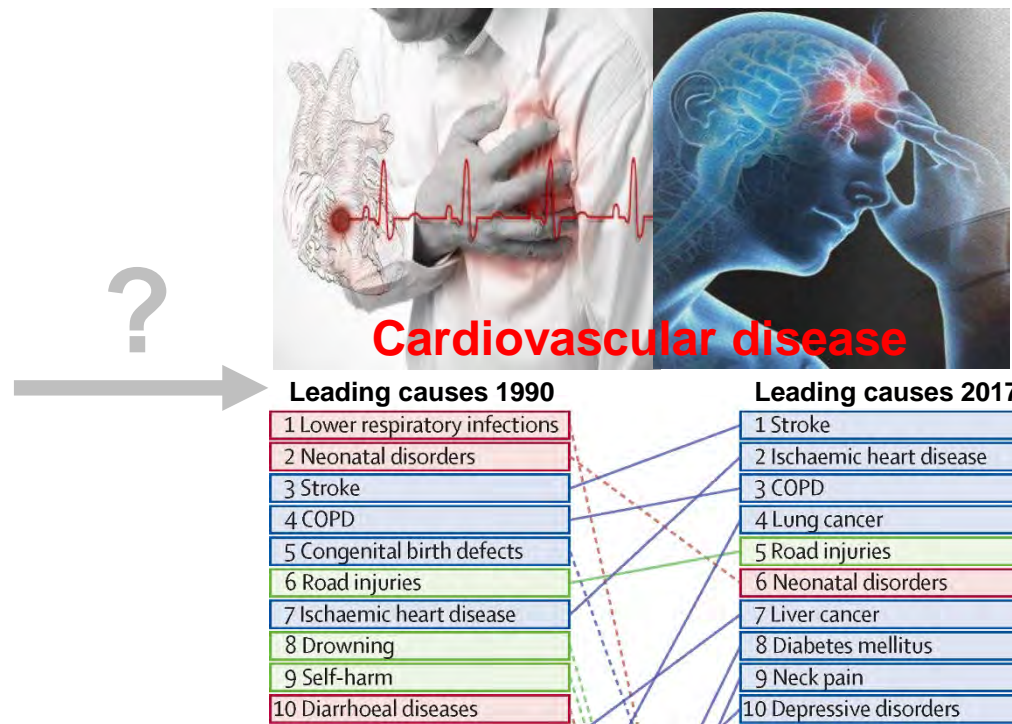
- Since 1978, China has been rapidly developing (2019 GDP growth at 5.6%)
- China is the 2nd largest economy, sharing 17.7% of total global wealth (2019)
- **Income inequality** is a key concern (Gini=0.465 in 2019), and has **increased** from 0.16 (1978) to 0.36 (2013) in **urban China**
- It is imperative to identify the income inequality-associated disease burden

# Income and cardiovascular disease in China

## Relative Income



## Absolute Income



Source: Hungry Planet: What The World Eats 2013; Liu et al. China CDC Weekly 2021; Zhou M et al. Lancet 2019

- **Cardiovascular disease (CVD)** is the leading cause of morbidity and mortality in China (5.09 million deaths which accounted for **47% of total deaths** in 2019)
- Income inequality has been associated with CVD mortality and its risk factors in the United States, but not consistently in Europe or New Zealand
- Relative income deprivation is associated with CVD mortality and/or incidence in the West

# Income inequality hypotheses: Does relative income matter?

## Neo-materialist hypothesis

- Relative income is merely a reflection of absolute income
- Investment in public and private infrastructure would be sufficient

Income inequality and mortality: importance to health of individual income, psychosocial environment, or material conditions

John W Lynch, George Davey Smith, George A Kaplan, James S House

BMJ 2000;320:1200-4



**John Lynch**

**The University of Adelaide**

**George Davey Smith**

**The University of Bristol**

## Psychosocial hypothesis

- Relative income plays a role independent of absolute income
- Psychological stress induced by relative deprivation affects health

Psychosocial and material pathways in the relation between income and health: a response to Lynch et al

Michael Marmot, Richard G Wilkinson

BMJ 2001;322:1233-6



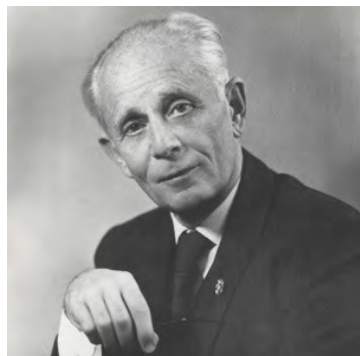
**Michael Marmot**

**University College London**

**Richard Wilkinson**

**The University of Nottingham**

# Origins of stress theory



Dr. Hans Selye

- Coined ‘**general adaptation syndrome**’ as a non-specific body response to insults in “A syndrome produced by diverse noxious agents” *Nature* (1936)



- Used ‘**stress**’ to describe the state manifested by such syndrome



**Does stress cause ill health especially CVD?**

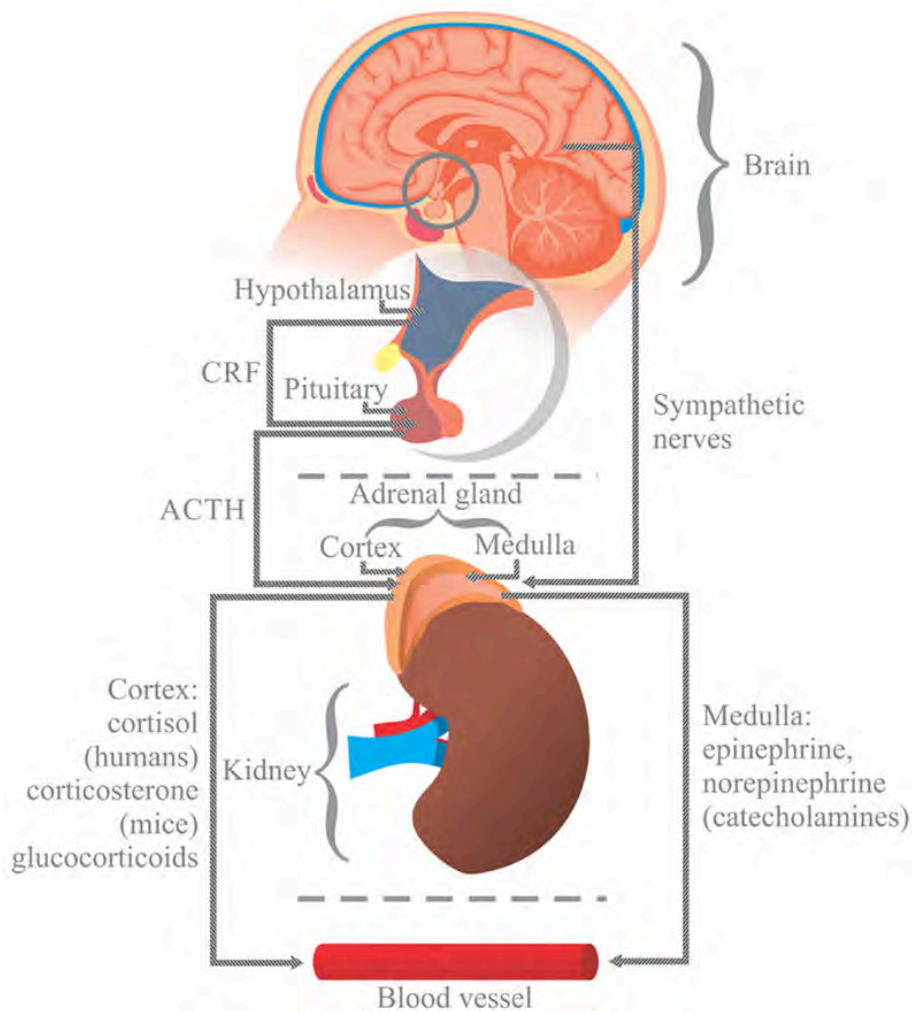
- Popularized the **stress theory** since the 1950s
  - The Stress of Life (1956)
  - From Dream to Discovery: On Being a Scientist (1964)
  - Stress without Distress (1974)



Dr. Jakob Henle (1844)

“**For almost every disease**, after a specific cause or admission that such a cause is not yet know, one finds the **same horde of harmful influences** – poor housing and clothing, liquor and sex, hunger and **anxiety**”

# Physiology of stress response



- In response to stress, hypothalamus initially activates sympathetic nervous system to trigger adrenal medulla to release epinephrine and norepinephrine
- Shortly thereafter, hypothalamic-pituitary-adrenal (HPA) system is activated
- Hypothalamus keeps activating sympathetic nervous system by releasing corticotropin-releasing factor (CRF) to trigger pituitary gland to release adrenocorticotropic hormone (ACTH) so as to trigger adrenal cortex to release **cortisol**
- Elevated **cortisol** elicits many physiological responses:
  - energy mobilization
  - homeostasis maintenance
  - appetite and weight control

Cushing's syndrome (cortisol in excess)



# Cortisol and cardiovascular risk

- Higher plasma cortisol to testosterone ratio was associated with ischemic heart disease (IHD) incidence and mortality, but the association could be mediated by CVD risk factors
- Hair cortisol was positively associated with cardiovascular medication usage and type 2 diabetes mellitus (T2DM)
- Among people with T2DM, higher cortisol is related to higher fasting glucose and total cholesterol and prevalent IHD, but not to glycated hemoglobin (HbA1c) or blood pressure
- People with Addison's disease receiving glucocorticoids have higher HbA1c and a poor lipid profile, but not abdominal fat

## Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

### Cortisol, Testosterone, and Coronary Heart Disease Prospective Evidence From the Caerphilly Study

George Davey Smith, DSc; Yoav Ben-Shlomo, BSc, MBBS, MRCP, FFPHM, PhD;  
 Andrew Beswick, BSc; John Yarnell, MBChB, DPH, MSCM, MD, MFPHM (Ire), FFPHM;  
 Stafford Lightman, MBChB, PhD, FMedSci; Peter Elwood, DSc, MD, FRCP, FFPHM

Davey Smith G et al. *Circulation*. 2005

## Psychoneuroendocrinology



Assessing cortisol from hair samples in a large observational cohort:  
 The Whitehall II study

Jessica G. Abell (PhD)<sup>a,\*</sup>, Tobias Stalder (PhD)<sup>b</sup>, Jane E. Ferrie (PhD)<sup>a,c</sup>,  
 Martin J. Shipley (MSc)<sup>a</sup>, Clemens Kirschbaum (PhD)<sup>b</sup>, Mika Kivimäki (PhD)<sup>a</sup>,  
 Meena Kumari (PhD)<sup>a,d</sup>

Abell JG et al. *Psychoneuroendocrinology*. 2016

## JCEM

THE JOURNAL  
 OF CLINICAL  
 ENDOCRINOLOGY  
 & METABOLISM

### Elevated Fasting Plasma Cortisol Is Associated with Ischemic Heart Disease and Its Risk Factors in People with Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study

Reynolds RM et al. *J Clin Endocrinol Metab*. 2010

## JCEM

THE JOURNAL  
 OF CLINICAL  
 ENDOCRINOLOGY  
 & METABOLISM

### Visceral Fat and Novel Biomarkers of Cardiovascular Disease in Patients With Addison's Disease: A Case-Control Study

Bergthorsdottir R et al. *J Clin Endocrinol Metab*. 2017

# Objectives

1. To examine the associations of absolute and relative income with CVD risk as well as the mediating role of cortisol observationally in Hong Kong Chinese adults
2. To assess the role of cortisol in CVD risk using Mendelian Randomization in Western populations, and as a pilot validation in Chinese populations
  - Evidence on income inequality and CVD risk is inconsistent in China
  - Few studies in China distinguish absolute versus relative income at household and neighbourhood levels
  - Observational studies on cortisol and CVD risk are open to confounding and selection bias, studies in patients are open to selection bias
  - No adequately large randomized controlled trials (RCTs) have examined the effect of glucocorticoids on incident or prevalent CVD
  - No Mendelian randomization (MR) study has explicitly considered the effect of cortisol on CVD using more comprehensive genetic instruments





# Methods

- Associations of income with CVD risk using multilevel logistic or linear models (n=17,607)
- Mediating role of cortisol using mediation analysis (n=1,562)

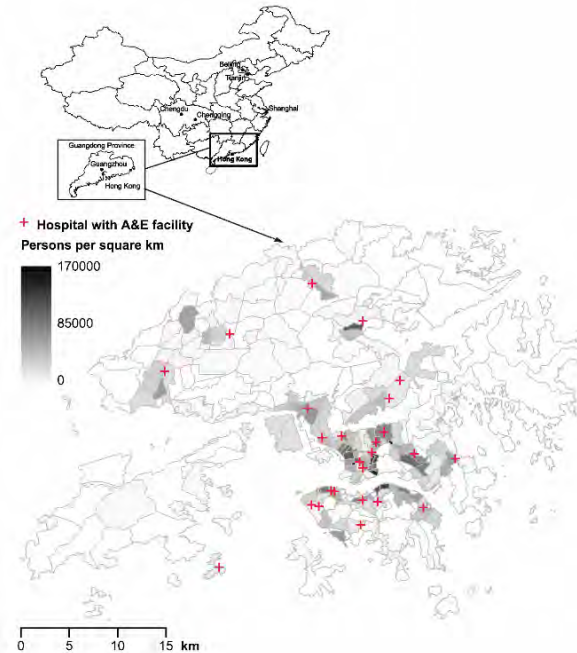
## Income

- Absolute household income
- Absolute neighbourhood median income
- Relative household income
- Neighbourhood income inequality (Gini)



## CVD risk

- Adiposity
- Blood pressure
- Self-reported CVD
- Self-reported diabetes

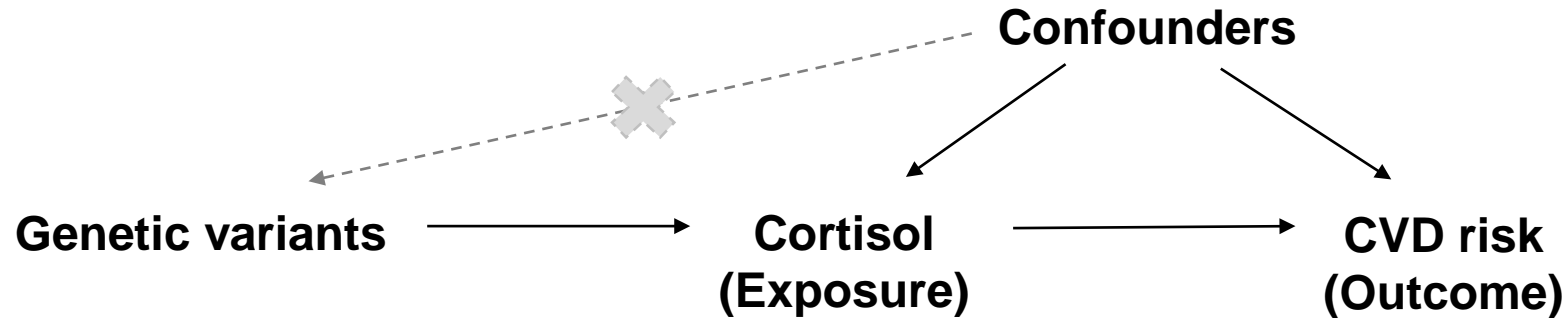


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# Methods

2. To assess the role of cortisol in CVD risk using Mendelian Randomization in Western populations, and as a pilot validation in Chinese populations



## Western (two-sample MR)

- Using genetically predicted cortisol and genetic associations of IHD, ischemic stroke, T2DM and other CVD risk factors to obtain causal association in European descent

## Chinese (one-sample MR)

- Using genetically predicted cortisol to obtain causal association of cortisol with CVD risk (adiposity, blood pressure, self-reported CVD and diabetes) in Hong Kong Chinese adults



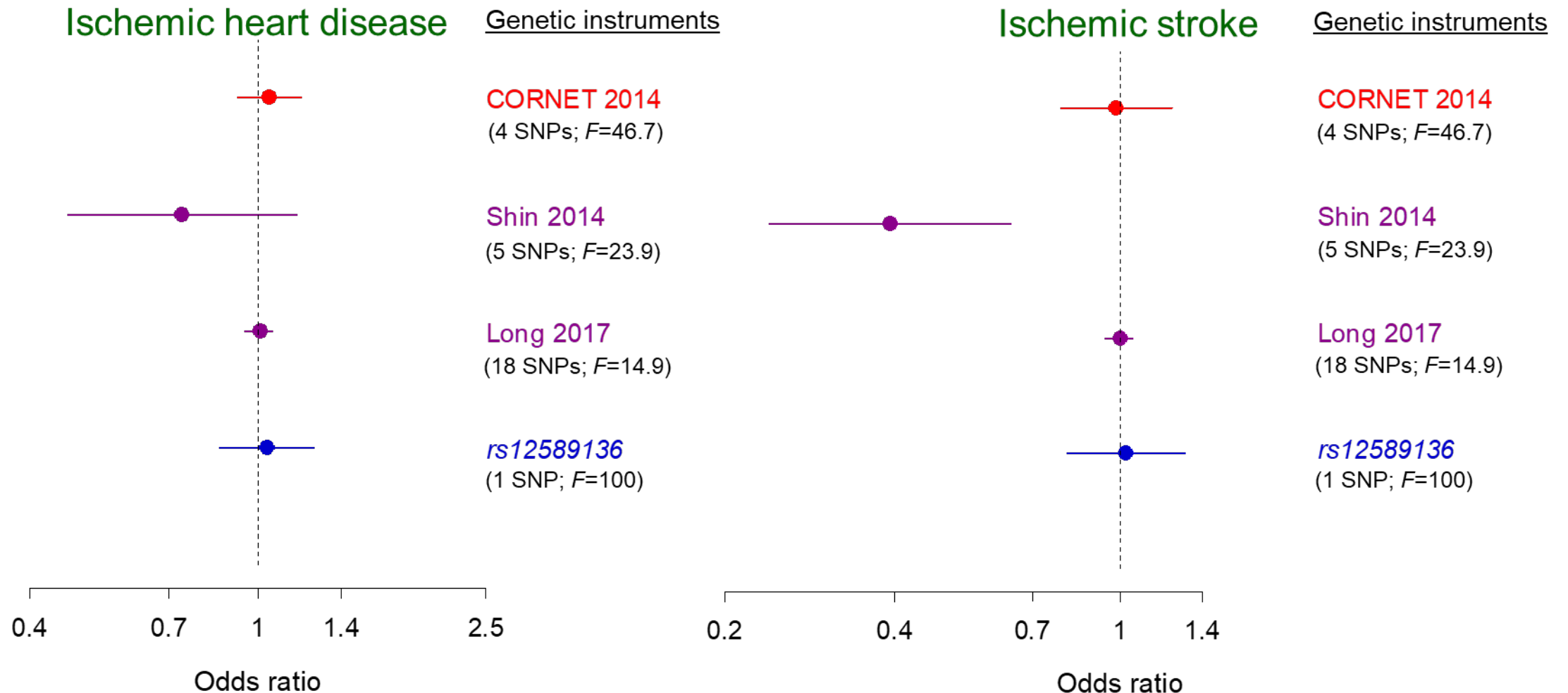
# Association of absolute versus relative income on CVD risk

- Relative household income deprivation was associated with higher systolic blood pressure, but lower BMI, and was unrelated to self-reported CVD or diabetes, independent of absolute income
- Neighbourhood income inequality was generally unrelated to CVD and its risk factors, nor was absolute income at the household or neighbourhood level
- Cortisol did not clearly mediate the association of relative household income deprivation with systolic blood pressure after accounting for multiple comparisons
- Genetically predicted cortisol based on polygenic risk score was unrelated to CVD risk (BMI, body fatness, blood pressure, self-reported CVD or diabetes) in Hong Kong Chinese adults



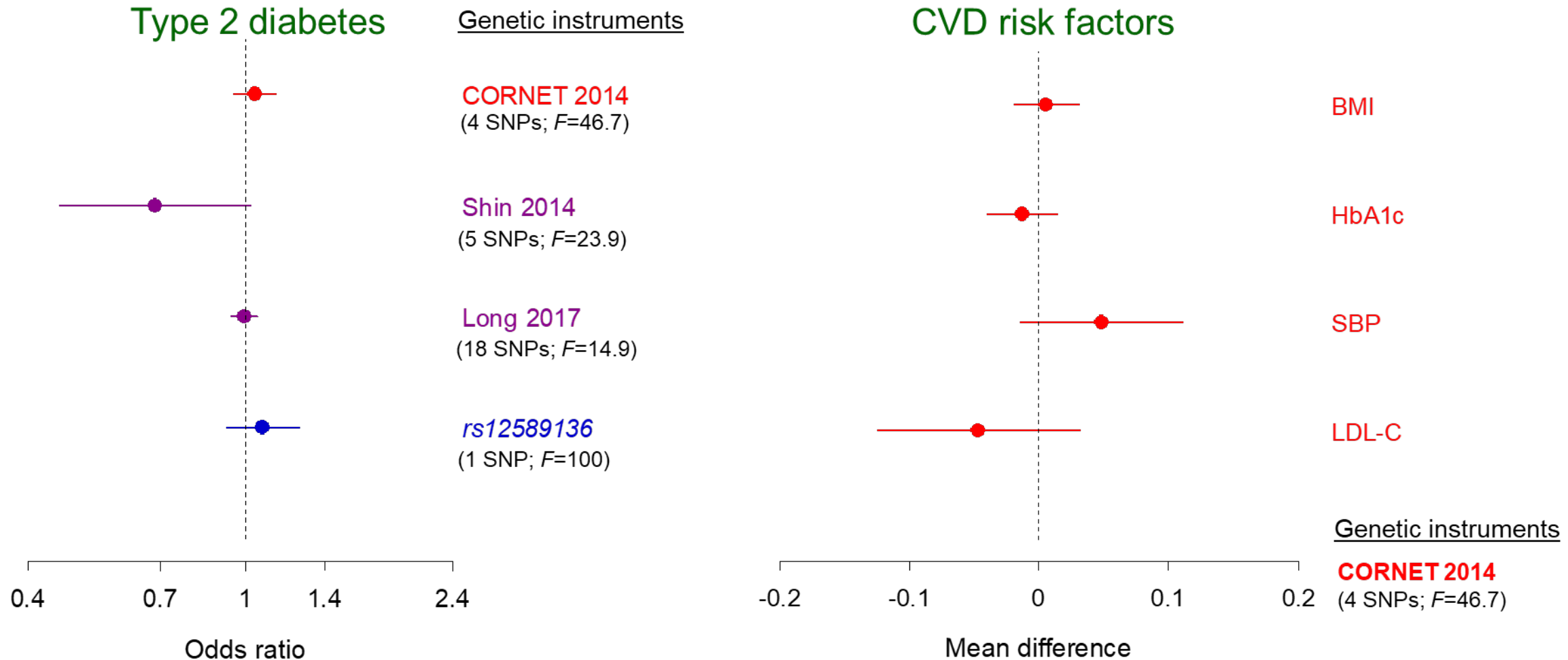
# MR estimates of cortisol on IHD and ischemic stroke

- Genetically predicted cortisol was not associated with IHD or ischemic stroke based on study specific genetic instruments or a genome-wide significant genetic variants in Western populations



# MR estimates of cortisol on T2DM and other CVD risk factors

- Genetically predicted cortisol was not associated with T2DM or CVD risk factors (including systolic blood pressure, BMI, HbA1c, LDL-cholesterol) in Western populations



# Discussion

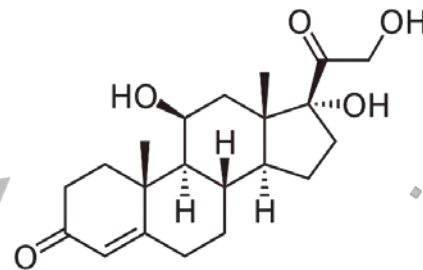
- Observationally, this study found **no clear associations of relative household income deprivation or neighbourhood income inequality with poorer adult cardiovascular health** in Hong Kong Chinese adults, independent of absolute income
- **Cortisol (as a biomarker of stress)** did not clearly mediate any association between relative income and CVD risk
- The null findings for relative income suggest that the effects of income disparities across neighbourhoods might have been buffered by social infrastructure and resources



**Relative income**



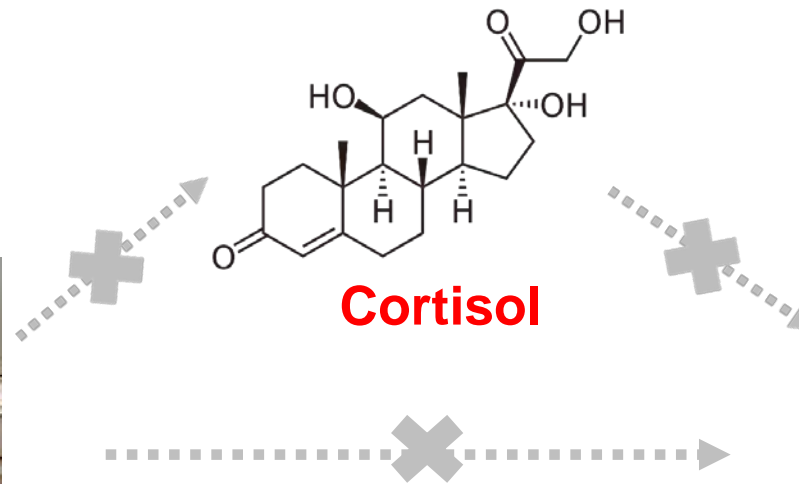
**Absolute Income**



**Cortisol**



**Cardiovascular disease risk**

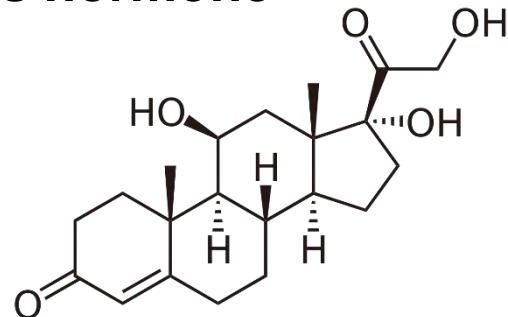


# Discussion

- Based on Mendelian randomization, this study found **no evidence that cortisol causes IHD, ischemic stroke, T2DM or CVD risk factors** in Western populations
- Our null findings are inconsistent with a previous one-sample MR among healthy participants and patients with suspected or confirmed IHD, which may be subject to selection bias given prior deaths and/or healthy controls were excluded
- These findings are consistent with a previous two-sample MR study showing null effects of subjective well-being on IHD and CVD risk factors and a Bayesian network study suggesting depression may not directly affect T2DM or other CVD risk factors



**Stress hormone**



**Cortisol**



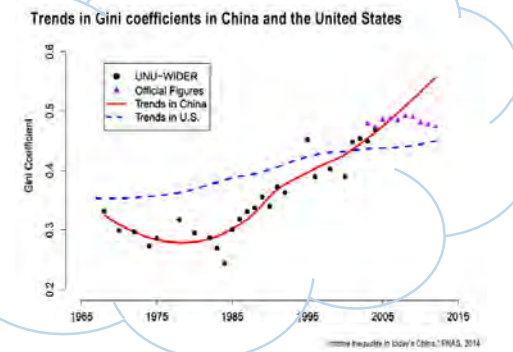
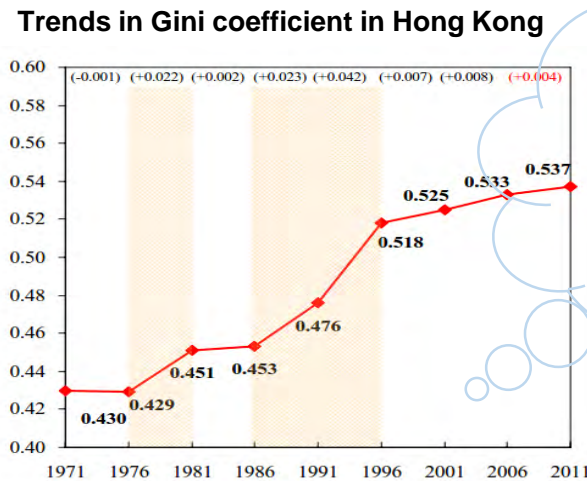
**Cardiovascular disease risk**





# Implication

- Our findings may stimulate discussion on the potential to alleviate the effect (if any) of relative income on cardiovascular disease risk by social infrastructure and resources (e.g. public transportation, health care system, and social protection)
- As a sentinel, economically developed Hong Kong helps presage any disease burden arising from income inequality and formulate the prioritization of public resource allocation for other currently rapidly developed Chinese mega-cities



Source: Hong Kong Economy, HKSARG. Half-yearly Economic Report 2012, Xie Y et al. Proc Natl Acad Sci USA 2016; United Nations Sustainable Development Goals

# Acknowledgements



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- Teammates and colleagues

