Population based research for cardio-metabolic disease in Asia

Professor John Chambers
LKC Medicine, Singapore

Importance of T2D and CVD in Asia

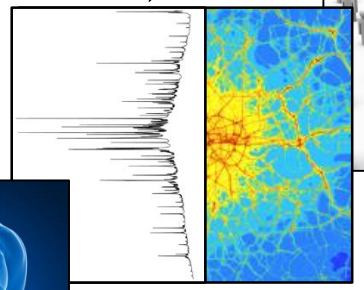
- T2D and CVD are leading **GLOBAL** challenges
  - **422M** people with T2D in 2016
  - **17.5M** deaths from CVD in 2012 (31% of total mortality)

- Burden of T2D and CVD highest in **Asia**
  - **Risk**↑: T2D x3-4 and CVD x2-4 compared to Europeans
  - **T2D Burden: 159M** in Western Pacific, **85M** in SEA
  - Singapore: **13.7%** [606K]
  - **Early onset** → high morbidity and costs

Population Science approach

Genes & Environment

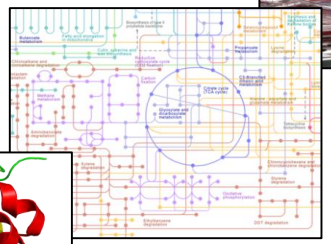
Population cohort



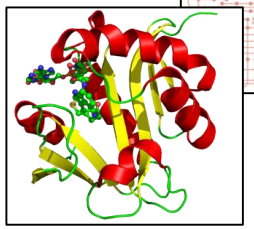
Molecular phenotyping

Biomarkers

Systems Biology



Pathways



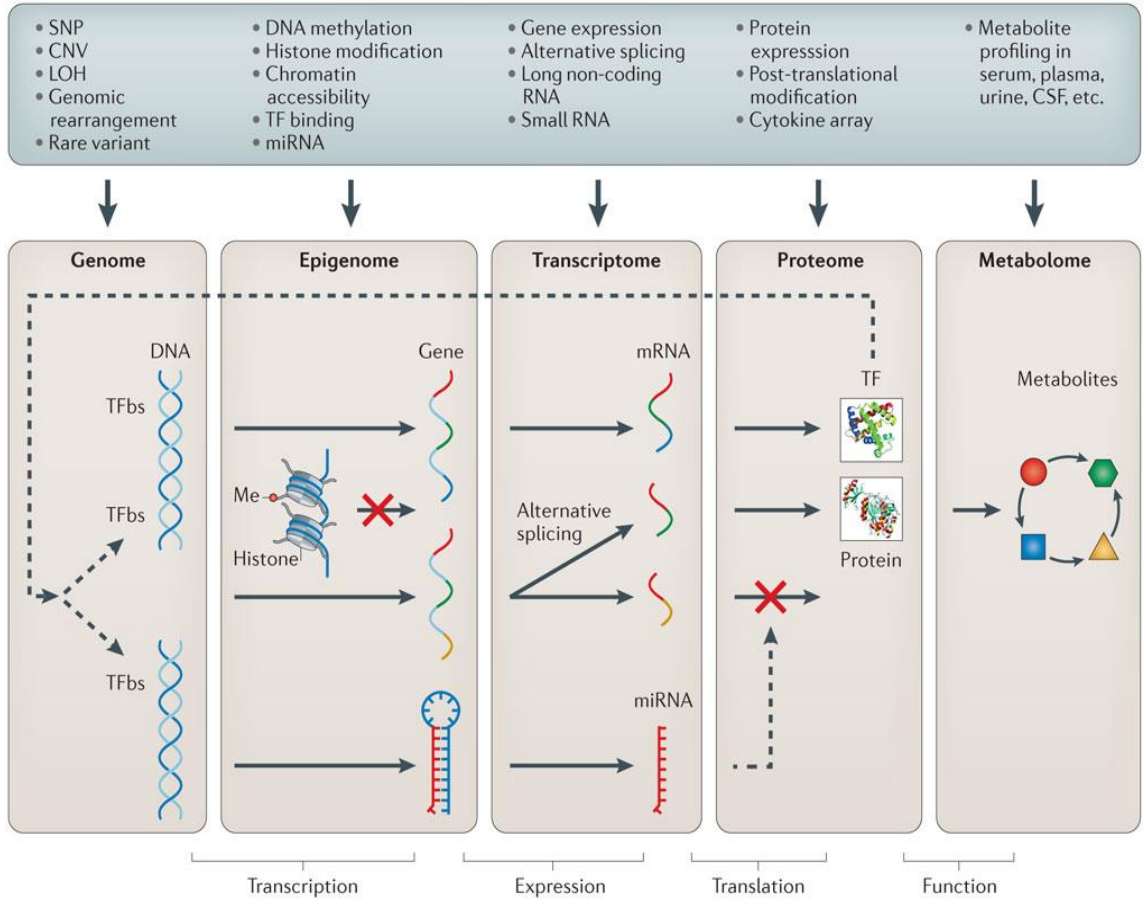
Molecular Insights

Linkage and Integration

Policy & Action

Precision medicine

Molecular phenotyping



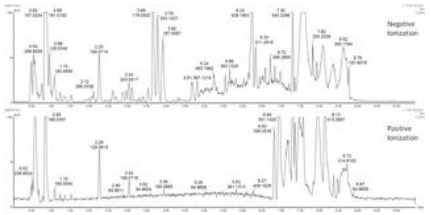
Biomarkers

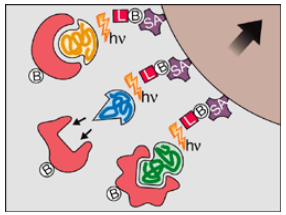
Pathways

Targets

Better prediction

Better prevention





nature genetics

Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians

Yoon Shin Cho[1,46], Chien-Hsiun Chen[2,3,46], Cheng Hu[4,46], Jirong Long[5,46], Rick Twee Hee Ong[6,46], Xueling Sim[7,46], Fumihiko Takeuchi[8,46], Ying Wu[9,46], Min Jin Go[1,46], Toshimasa Yamauchi[10,46], Yi-Cheng Chang[11,46], Soo Heon Kwak[12,46], Ronald C W Ma[13,46], Ken Yamamoto[14,46], Linda S Adair[15], Tin Aung[16,17], Qiuyin Cai[5], Li-Ching Chang[2], Yuan-Tsong Chen[2], Yutang Gao[18], Frank B Hu[19], Hyung-Lae Kim[1,20], Sangsoo Kim[21], Young Jin Kim[1], Jeannette Jen-Mai Lee[22], Nanette R Lee[23], Yun Li[9,24], Jian Jun Liu[25], Wei Lu[26], Jiro Nakamura[27], Eitaro Nakashima[27,28], Daniel Peng-Keat Ng[22], Wan Ting Tay[16], Fuu-Jen Tsai[3], Tien Yin Wong[16,17,29], Mitsuhiro Yokota[30], Wei Zheng[5], Rong Zhang[4], Congrong Wang[4], Wing Yee So[13], Keizo Ohnaka[31], Hiroshi Ikegami[32], Kazuo Hara[10], Young Min Cho[12], Nam H Cho[33], Tien[illegible] Con[illegible] Lee-[illegible] Jer-[illegible] Nor[illegible]

ARTICLE

doi:10.1038/nature18642

The genetic architecture of type 2 diabetes

A list of authors and affiliations appears in the online version of the paper

The genetic architecture of common traits, including the number, frequency, and effect sizes of inherited variants that contribute to individual risk, has been long debated. Genome-wide association studies have identified scores of common variants associated with type 2 diabetes, but in aggregate, these explain only a fraction of the heritability of this disease. Here, to test the hypothesis that lower-frequency variants explain much of the remainder, the GoT2D and T2D-GENES consortia performed whole-genome sequencing in 2,657 European individuals with and without diabetes, and exome sequencing in 12,940 individuals from five ancestry groups. To increase statistical power, we expanded the sample size via genotyping and imputation in a further 111,548 subjects. Variants associated with type 2 diabetes after sequencing were overwhelmingly common and most fell within regions previously identified by genome-wide association studies. Comprehensive enumeration of sequence variation is necessary to identify functional alleles that provide important clues to disease pathophysiology, but large-scale sequencing does not support the idea that lower-frequency variants have a major role in predisposition to type 2 diabetes.

Diabetologia (2017) 60:107–115
DOI 10.1007/s00125-016-4132-z

CrossMark

ARTICLE

Exome-chip association analysis reveals an Asian-specific missense variant in *PAX4* associated with type 2 diabetes in Chinese individuals

Chloe Y. Y. Cheung[1] · Clara S. Tang[2] · Aimin Xu[3,4,5] · Chi-Ho Lee[1] · Ka-Wing Au[1] · Lin Xu[6] · Carol H. Y. Fong[1] · Kelvin H. M. Kwok[1] · Wing-Sun Chow[1] · Yu-Cho Woo[1] · Michele M. A. Yuen[1] · JoJo S. H. Hai[1] · Ya-Li Jin[7] · Bernard M. Y. Cheung[1] · Kathryn C. B. Tan[1] · Stacey S. Cherny[8] · Feng Zhu[7] · Tong Zhu[7] · G. Neil Thomas[9] · Kar-Keung Cheng[9] · Chao-Qiang Jiang[7] · Tai-Hing Lam[6,7] · Hung-Fat Tse[1,10] · Pak-Chung Sham[8,11,12] · Karen S. L. Lam[1,3,4]

LETTERS

nature genetics

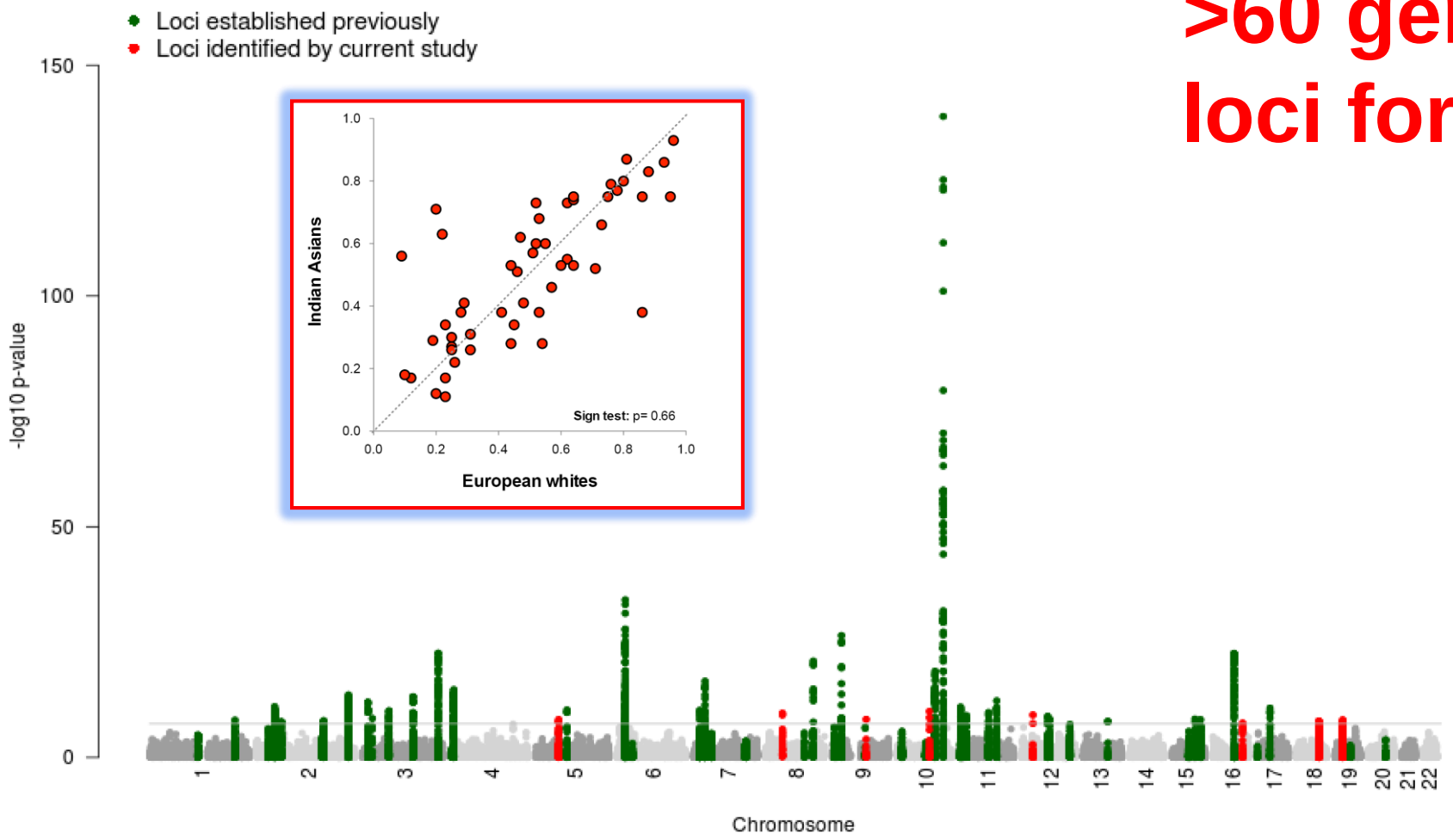
Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci

Jaspal S Kooner[1–3,46], Danish Saleheen[4,5,46], Xueling Sim[6,46], Joban Sehmi[1,2,46], Weihua Zhang[7,46], Philippe Frossard[4,46], Latonya F Been[8], Kee-Seng Chia[6,9], Antigone S Dimas[10,11], Neelam Hassanali[12], Tazeen Jafar[13,14], Jeremy B M Jowett[15], Xinzhong Li[1], Venkatesan Radha[16], Simon D Rees[17,18], Fumihiko Takeuchi[19], Robin Young[5], Tin Aung[20,21], Abdul Basit[22], Manickam Chidambaram[16], Debashish Das[2], Elin Grundberg[23], Åsa K Hedman[11], Zafar I Hydrie[22], Muhammed Islam[13], Chiea-Chuen Khor[6,21,24], Sudhir Kowlessur[25], Malene M Kristensen[15], Samuel Liju[16], Wei-Yen Lim[6], David R Matthews[12], Jianjun Liu[24], Andrew P Morris[11], Alexandra C Nica[10], Janani M Pinidiyapathirage[26], Inga Prokopenko[11], Asif Rasheed[4], Maria Samuel[4], Nabi Shah[4], A Samad Shera[27], Kerrin S Small[23,28], Chen Suo[6], Ananda R Wickremasinghe[26], Tien Yin Wong[20,21,29], Mingyu Yang[30], Fan Zhang[30], DIAGRAM[31], MuTHER[31], Goncalo R Abecasis[32], Anthony H Barnett[17,18], Mark Caulfield[33], Panos Deloukas[34], Timothy M Frayling[35], Philippe Froguel[36], Norihiro Kato[19], Prasad Katulanda[12,37], M Ann Kelly[17,18], Junbin Liang[30], Viswanathan Mohan[16,38], Dharambir K Sanghera[8], James Scott[1], Mark Seielstad[39], Paul Z Zimmet[15], Paul Elliott[7,40,46], Yik Ying Teo[6,9,24,41,42,46], Mark I McCarthy[11,12,43,46], John Danesh[5,46], E Shyong Tai[9,44–46] & John C Chambers[2,3,7,46]

DIAGRAM+

12,171 T2D cases and 56,862 controls; replication in >100K people

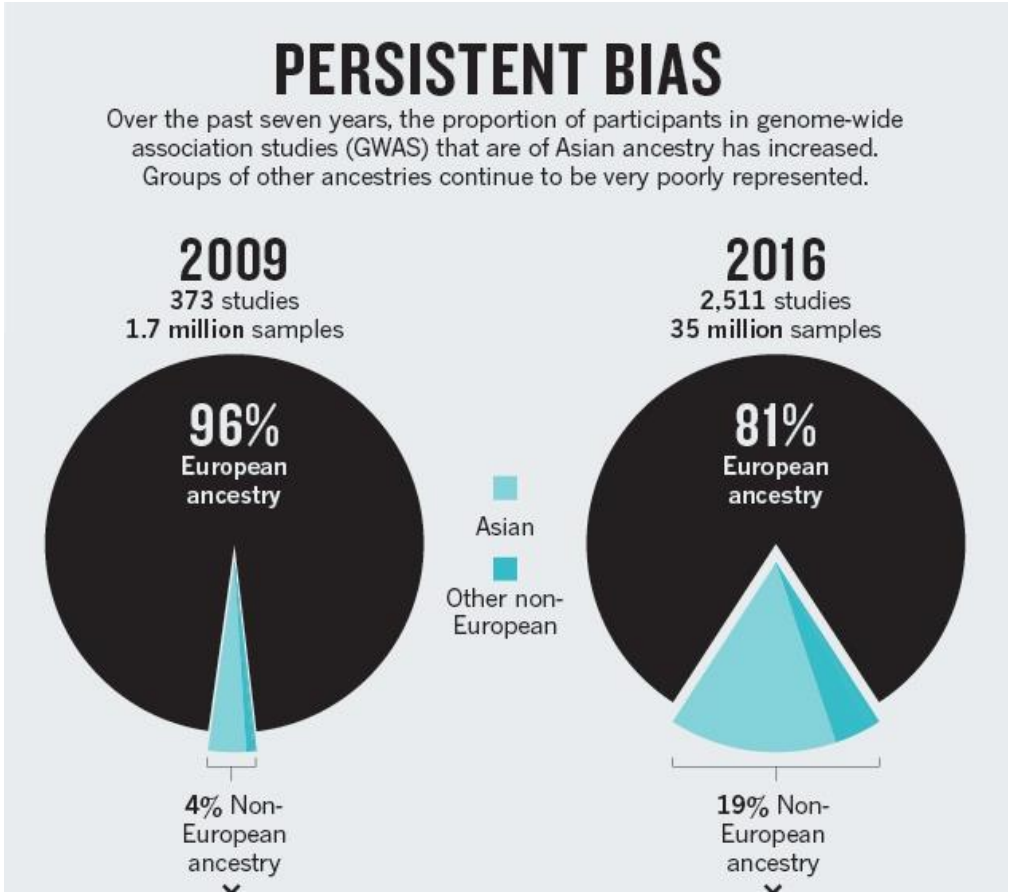
>60 genetic loci for T2D



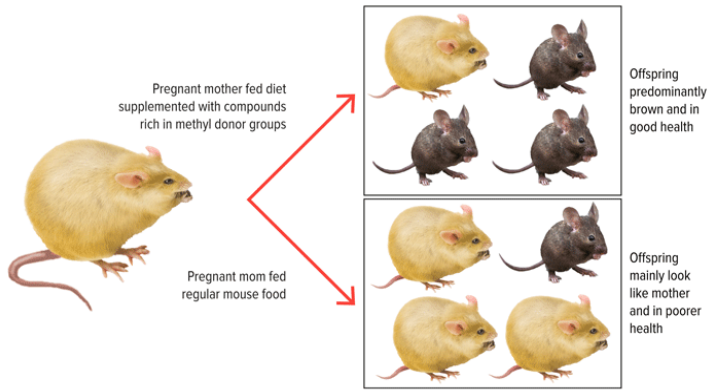
South / South-East Asian samples

HapMap samples

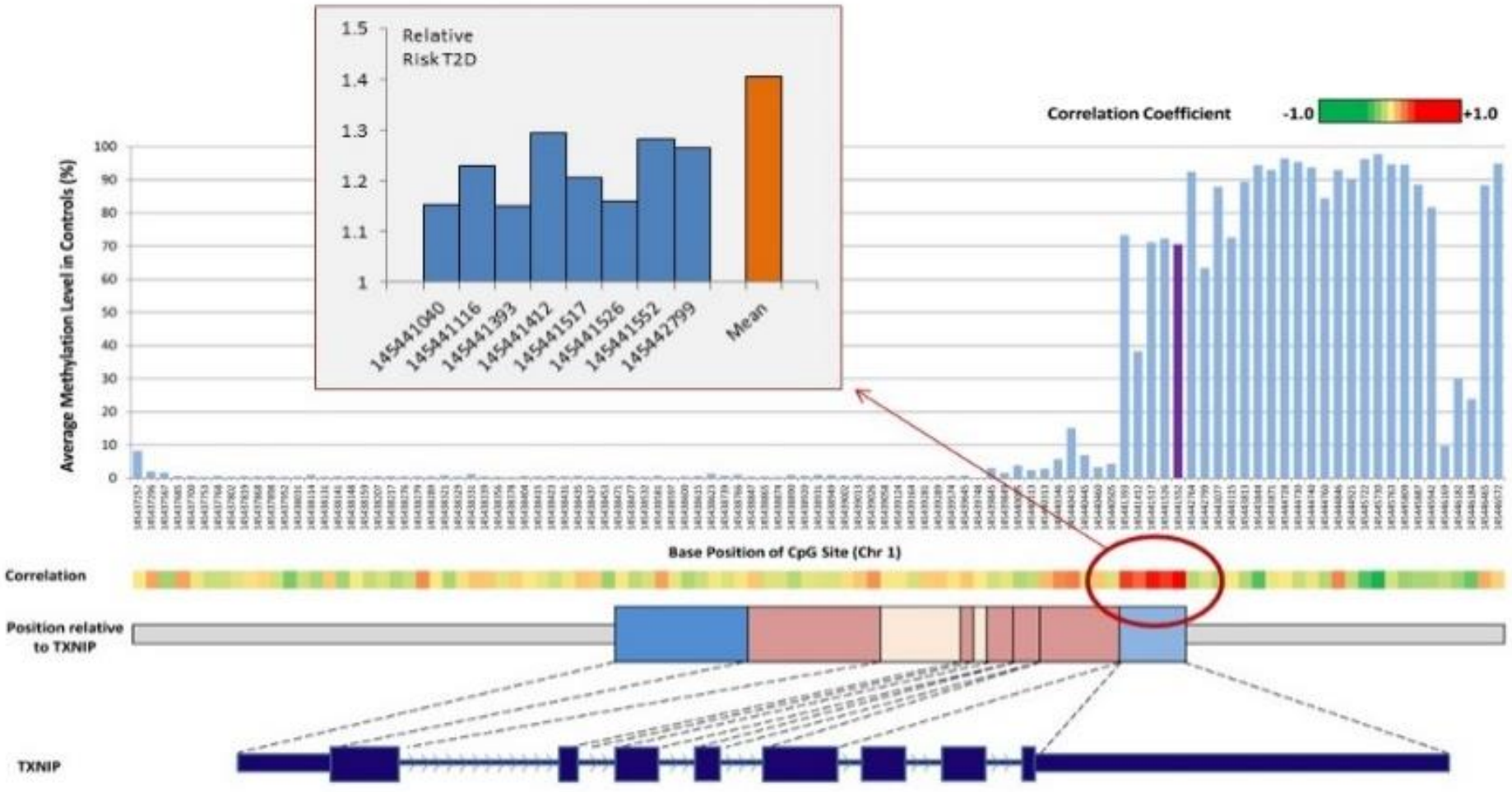
- 90 Europeans (Utah)
- 90 East Asians (CHB / JPT)
- 90 Yorubans (Africa)



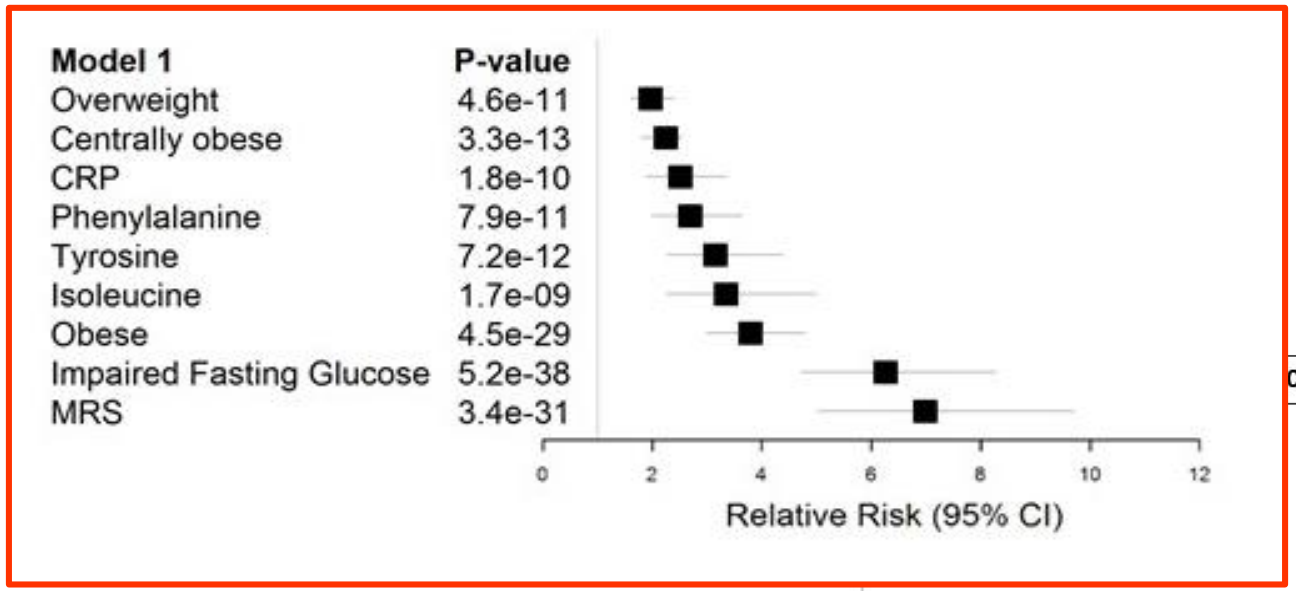
Epigenomics and the life course



DNA methylation at the *TXNIP* locus



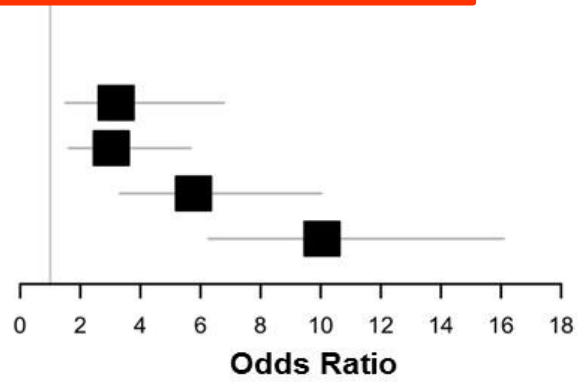
DNA methylation identifies metabolically unhealthy adiposity



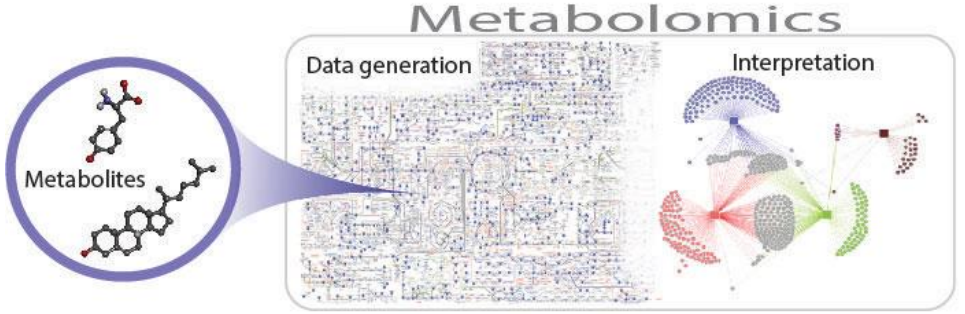
0.56

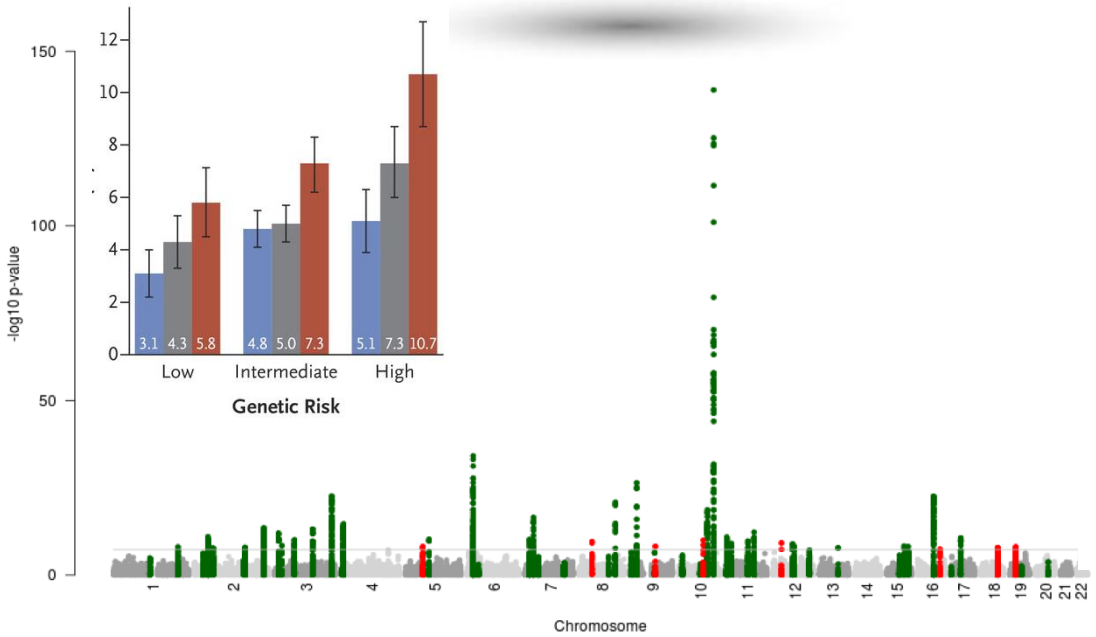
Obese

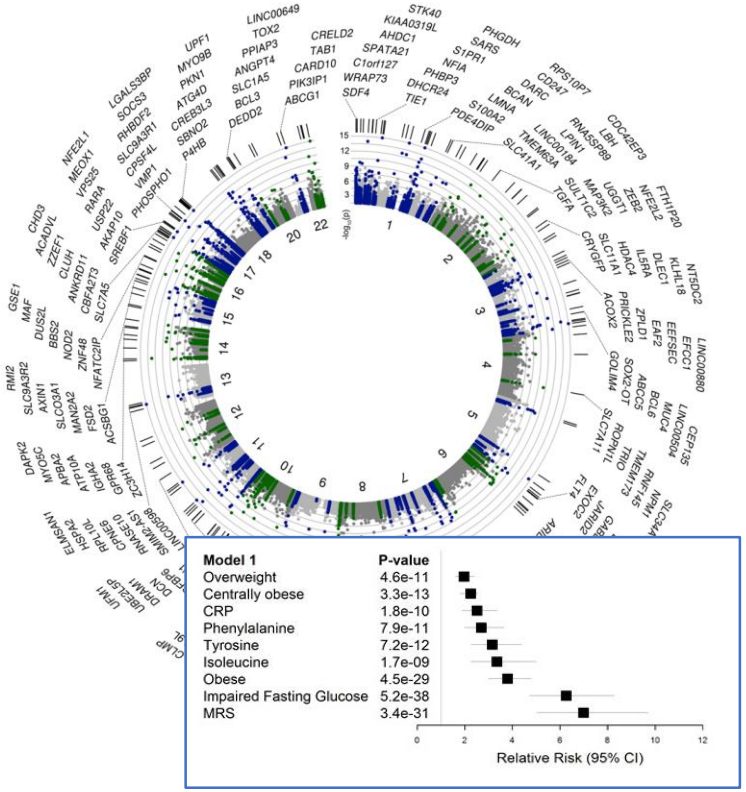
Q1	27/17	2.5E-3	4.19E-7
Q2	50/28	5.2E-4	
Q3	59/61	5.1E-10	
Q4	149/255	7.9E-22	



Multiple molecular markers for prediction of T2D







NMRC National Medical Research Council Singapore

MINISTRY OF HEALTH SINGAPORE

Extend / replicate molecular markers for prediction of T2D in South/East Asians
N=1,000

Develop and validate molecular risk score for prediction of T2D
N=2,000

Screen obese normoglycaemic
M&F 30-65yrs

Identify 1,000 at highest risk of T2D (>10%pa)

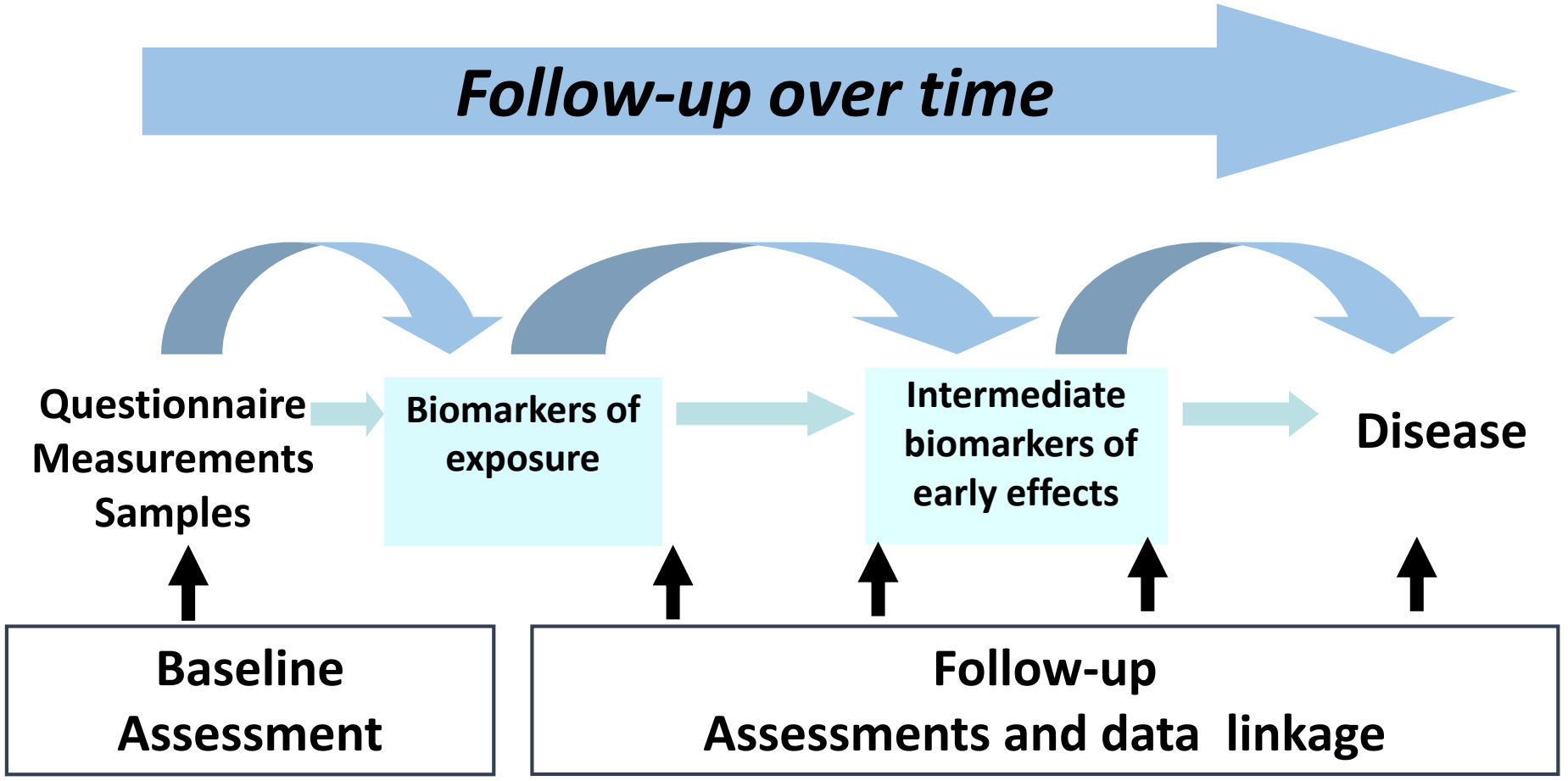
Usual care
N=500

Intervention
(N=500)

3 year follow-up for
Incident T2D (N=450 events)

Translating 'Omics Into A Stratified Approach For Prevention Of Type 2 Diabetes

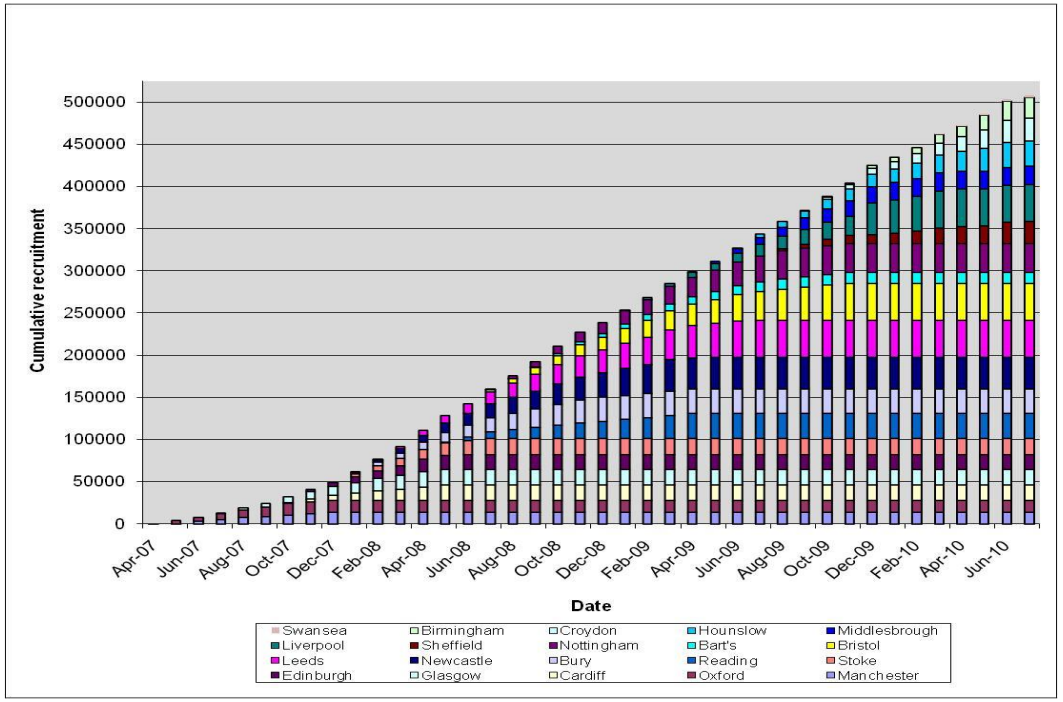
DESIGN of Prospective Cohort Study



Advantages of Prospective Cohort Studies

- Risk factors and biomarkers can be **measured before the disease develops** (helping to avoid “reverse causality”)
- The **only** suitable design for identification of non-genetic biomarkers for **future** health trajectories
- Associations can be assessed with **a range of diseases**
- Appropriate **controls** can be selected **from within the same population** as the disease cases
- Consistent high quality phenotyping: enhances risk relationships: favourable for **systems biology**

500,000 participants recruited in 3.5 years (£62M = SG$230 per participant)



- 9M invites generated from NHS register
- 22 assessment centres in rented office space

wellcome trust

MRC Medical Research Council

Northwest Regional Development Agency

DH Department of Health

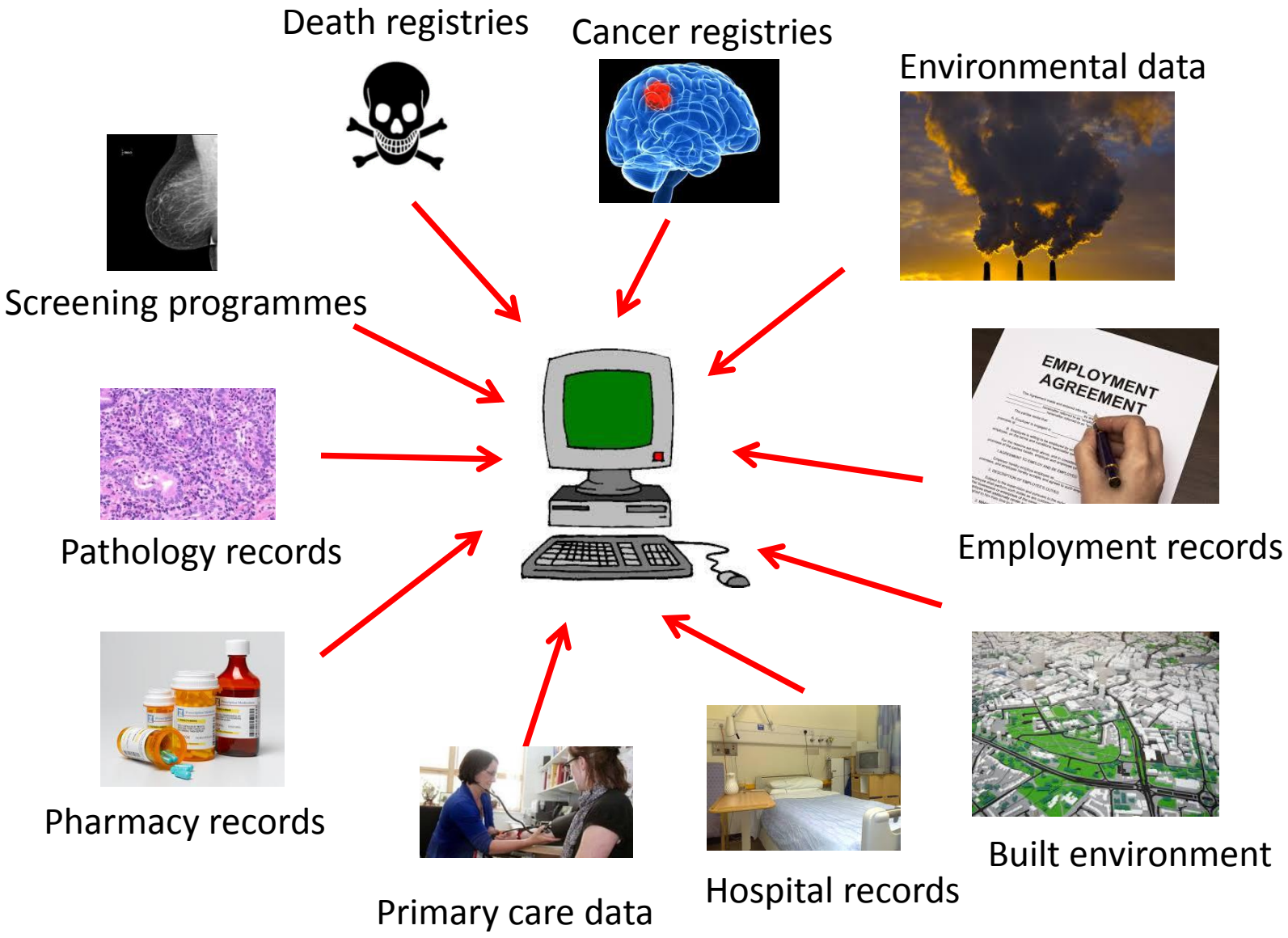
The Scottish Government

Llywodraeth Cynulliad Cymru Welsh Assembly Government

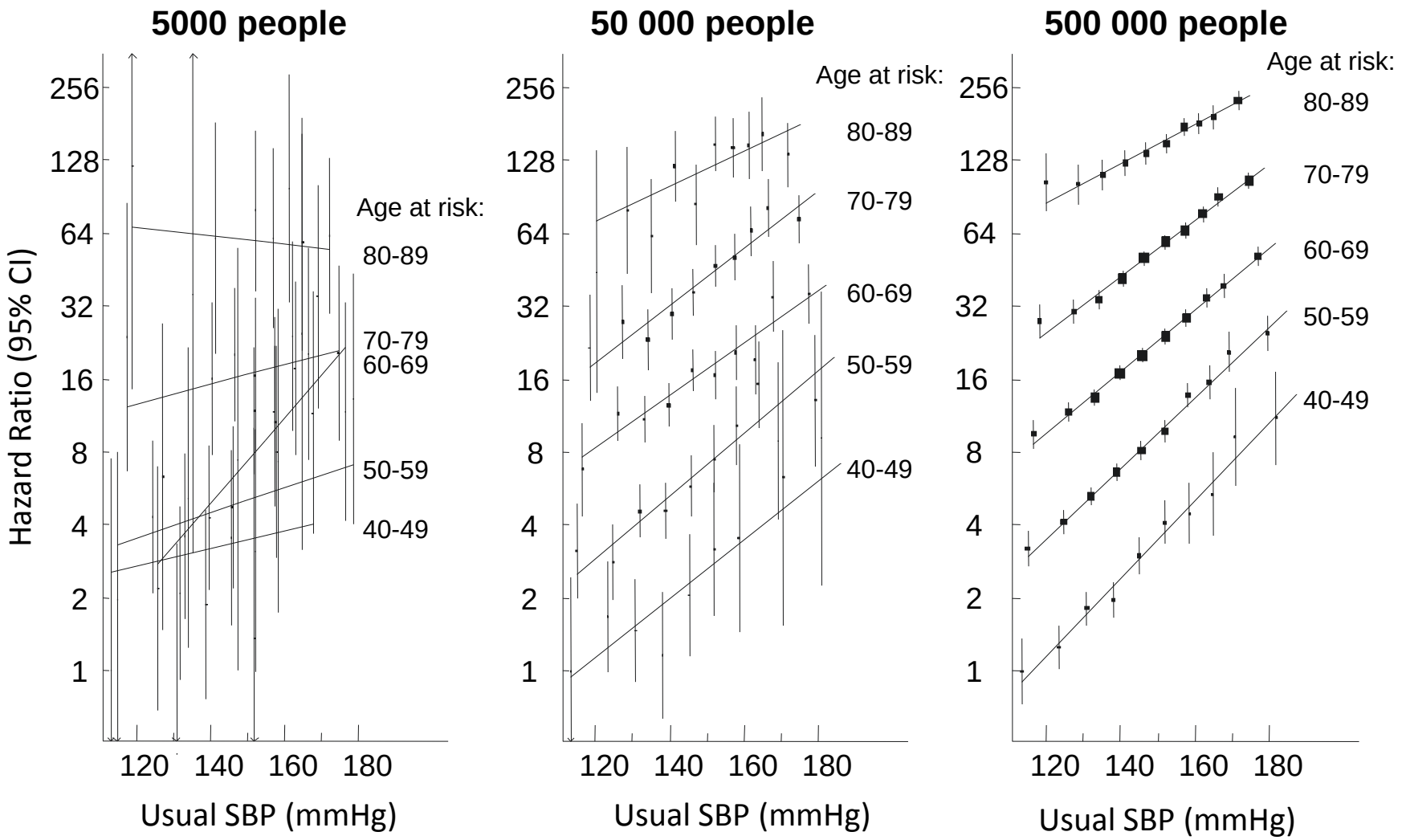
British Heart Foundation

biobank uk
Improving the health of future generations

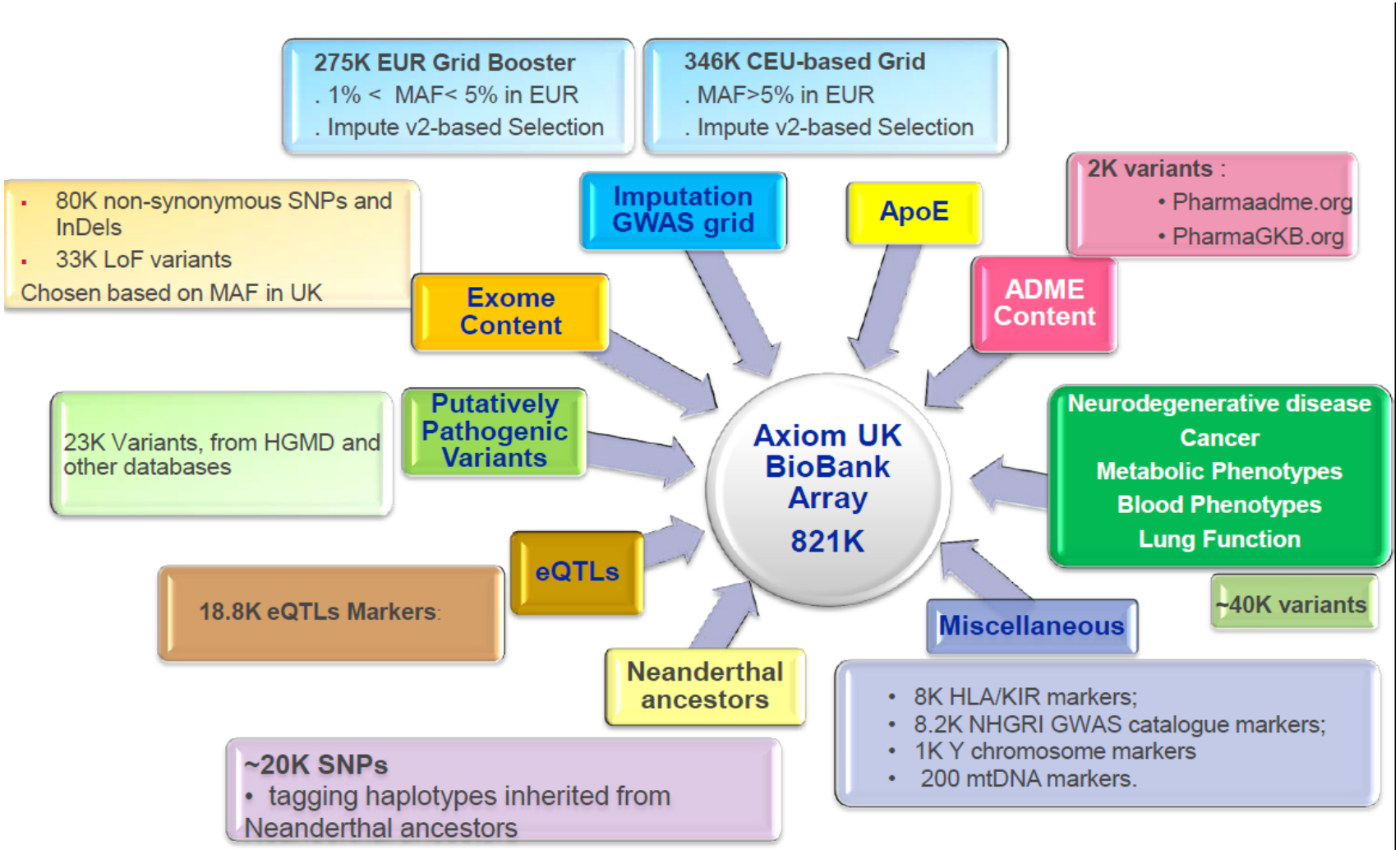
Record linkage



Large numbers bring PRECISION: Ischaemic heart disease vs. Systolic BP



Genotyping Array Content Summary
(Plus imputation using reference sequence data ~ 70M variants)



biobank uk
Improving the health of future generations

Large numbers bring DISCOVERY

- T2D
  - 2007: FTO paper — 5K people — N=1 SNP
  - 2010: Diagram v2 — 69K people — N=12 SNPs
  - 2012: Diagram v3 — 149K people — N=10 SNPs
  - 2018: Diagram v4 — 880K people — >>100 SNPs

- Previous GWAS identify only common variants with small effects

  →large scale GWAS now identifies a good number of novel, rare variants with big effect

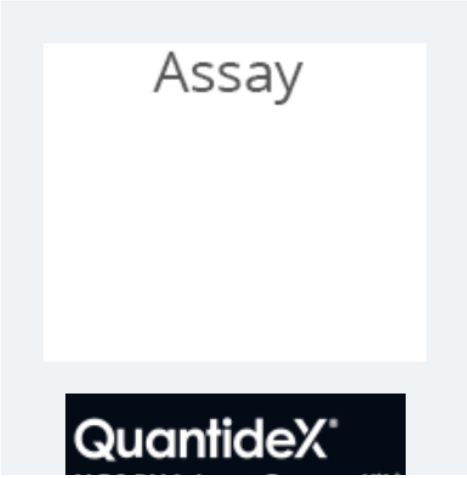
UK Biobank - fertile discovery pipeline

Regeneron Partners With AbbVie, Alnylam, AstraZeneca, Biogen, Pfizer to Sequence UK Biobank Samples

Jan 08, 2018 | Julia Karow

NEW YORK (GenomeWeb) – Regeneron Pharmaceuticals said today that it has formed a pre-competitive consortium with AbbVie, Alnylam Pharmaceuticals, AstraZeneca, Biogen, and Pfizer to sequence the exomes of all 500,000 participants in the UK Biobank.

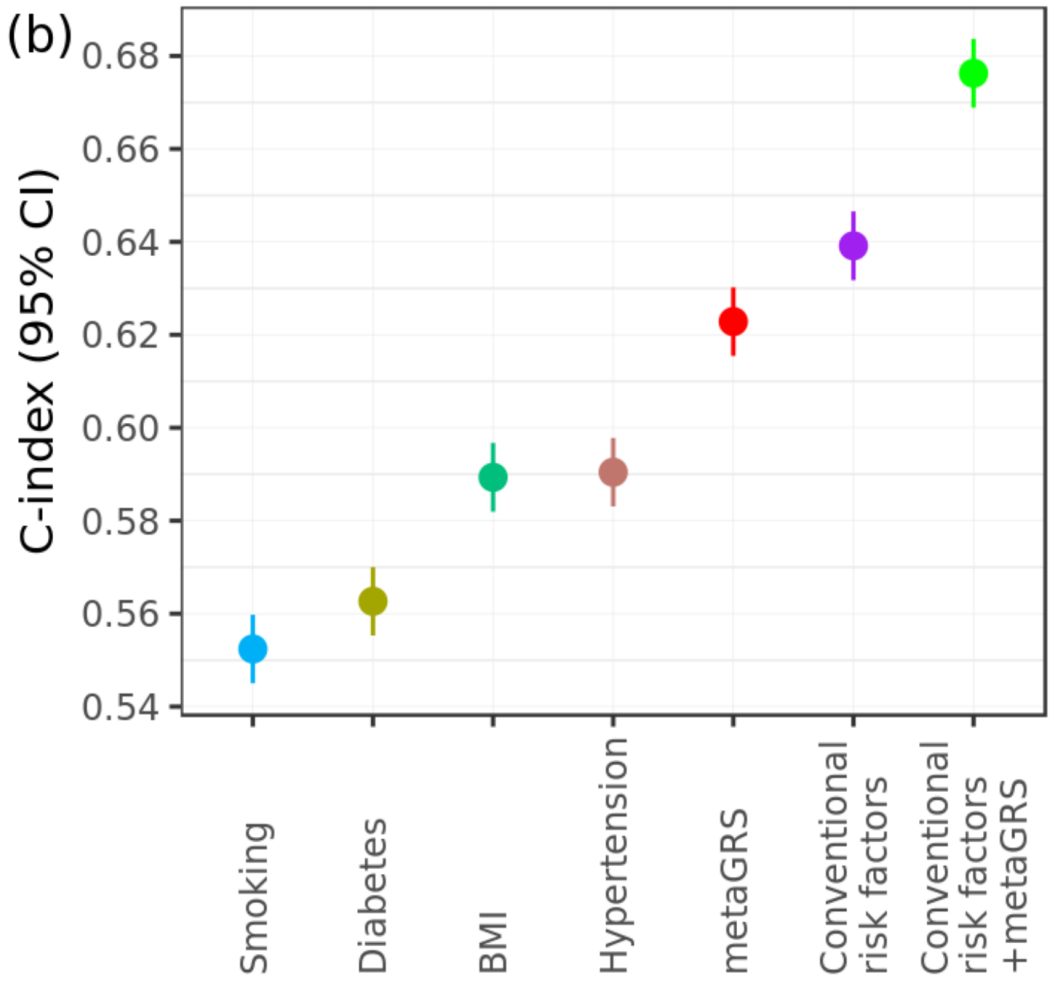
"All of us involved have a shared belief in the power of genetics to facilitate and guide drug discovery and development," said Aris Baras, vice president and head of the Regeneron Genetics Center (RGC), a wholly-owned subsidiary of Regeneron.

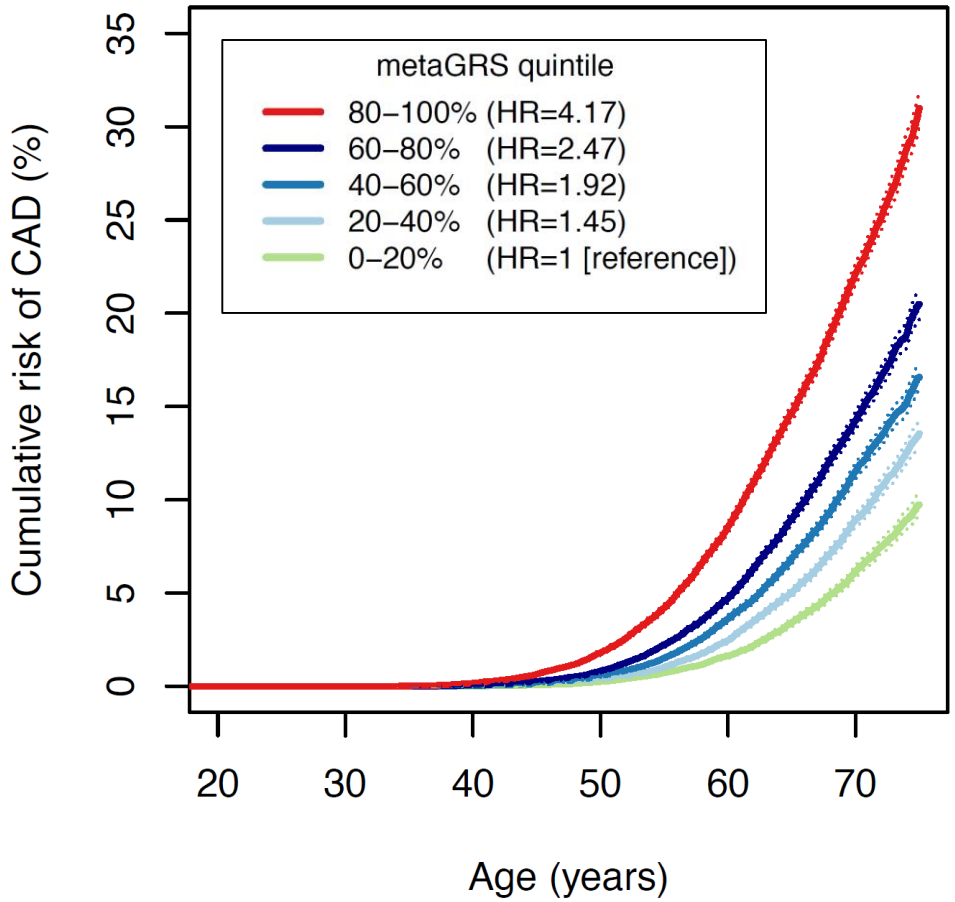


Under the agreement, AbbVie, Alnylam, AstraZeneca, Biogen, and Pfizer will each contribute $10 million to the project. Regeneron will provide an undisclosed amount of its own funding, and the RGC will conduct the sequencing for the project. Additional companies are currently considering joining the consortium.

The goal is to sequence the exomes of all 500,000 biobank participants by the end of 2019, and to make all sequence data available to other researchers, in accordance with UK Biobank's access policies, by the end of 2020. Consortium members will have exclusive access to the data for a limited period of time — between six and 12 months — and plan to publish their research findings in peer-reviewed journals or on open-source sites.

DISCOVERY and PRECISION
Genetic risk scores predict risk of CVD

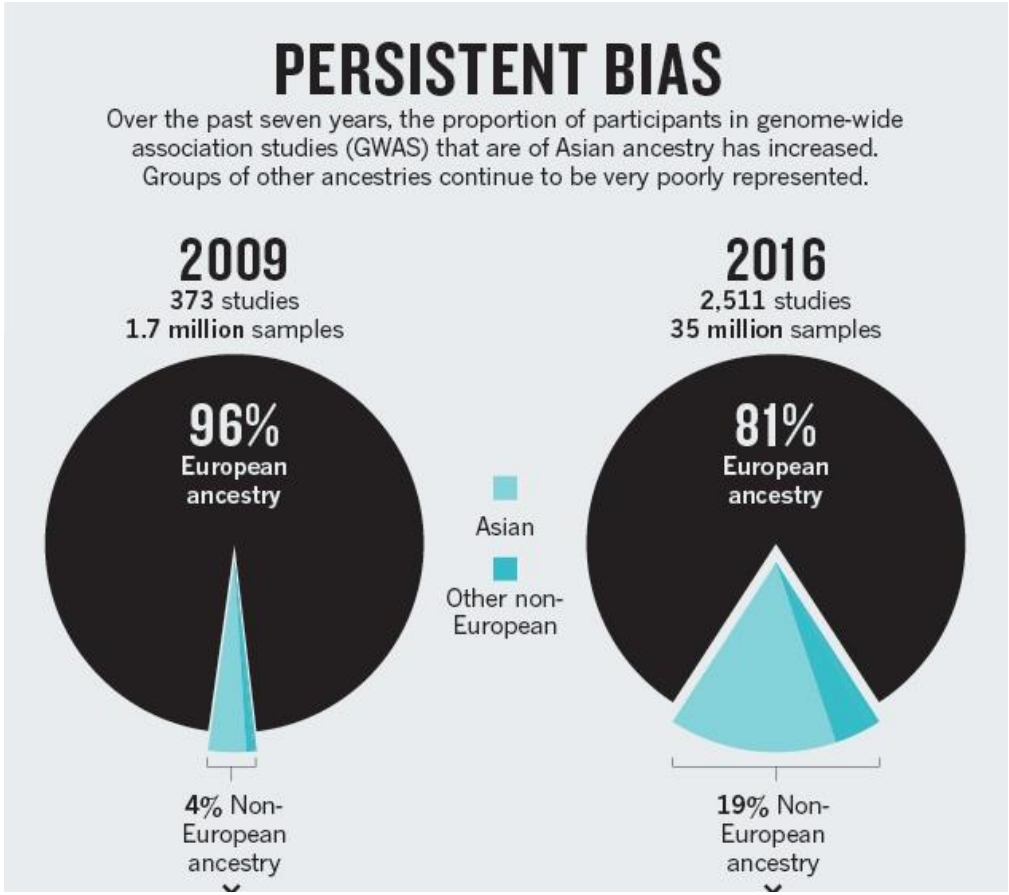




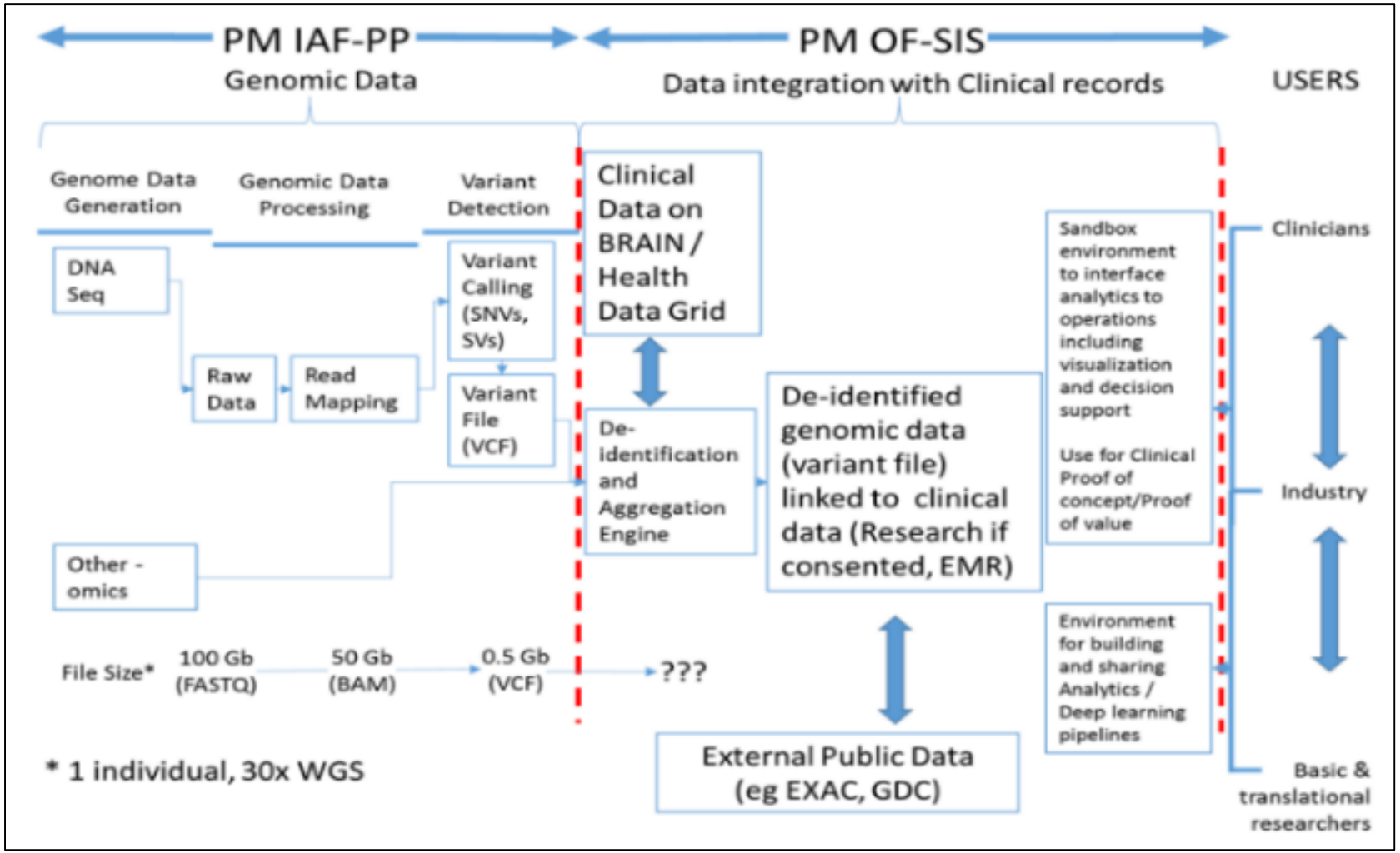
South / South-East Asian samples

HapMap samples

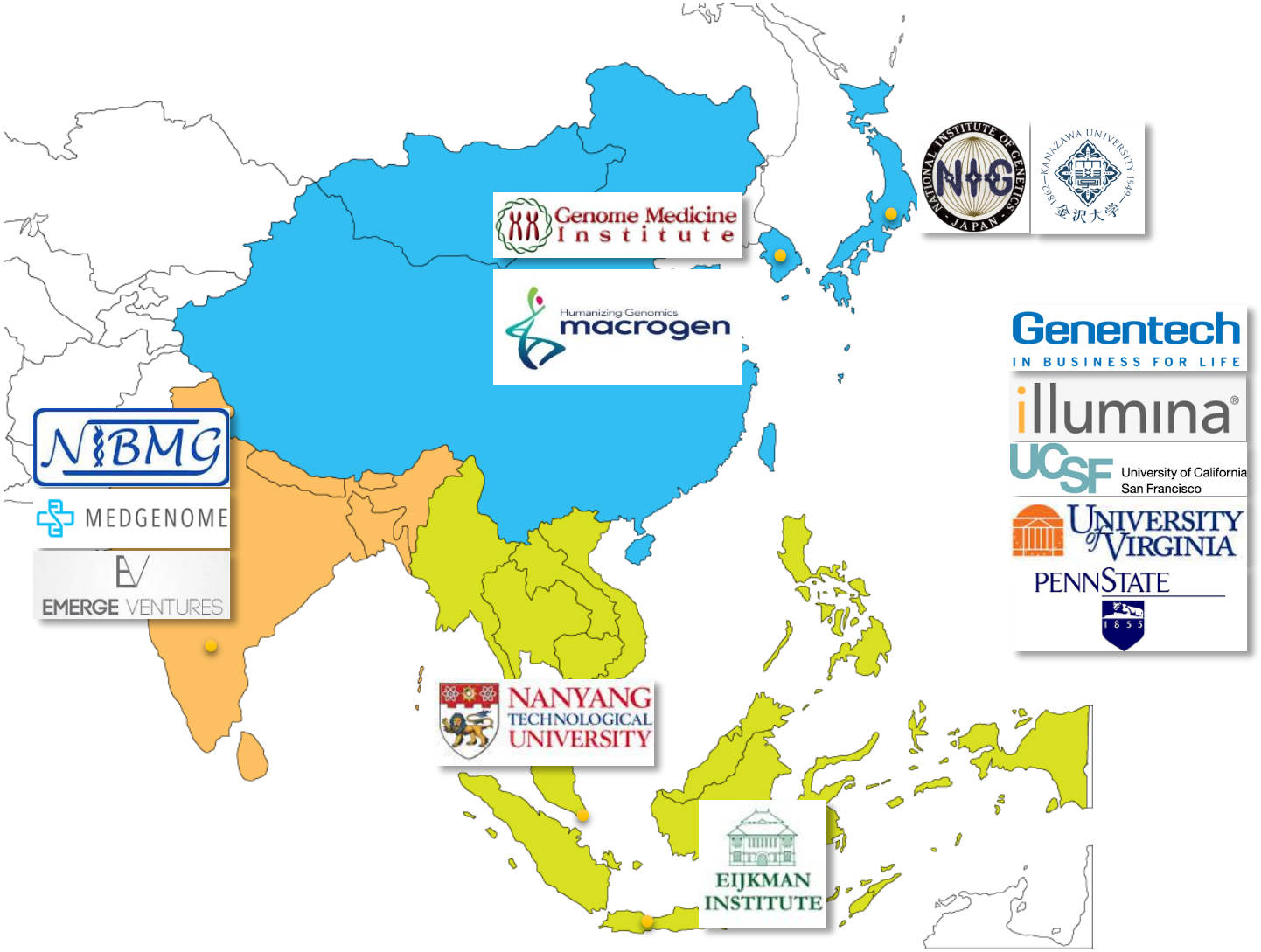
- 90 Europeans (Utah)
- 90 East Asians (CHB / JPT)
- 90 Yorubans (Africa)



Singapore National Precision Medicine Project



Genome Asia 100K



International cohort studies >100K

The need for a Regional Biobank

- Investigate a wide spectrum of phenotypes and diseases important to Asia
- Generate accurate estimates of incidence and risk relationships
- Discovery of population specific biomarkers and pathways
- Innovation and improved healthcare

Conclusions

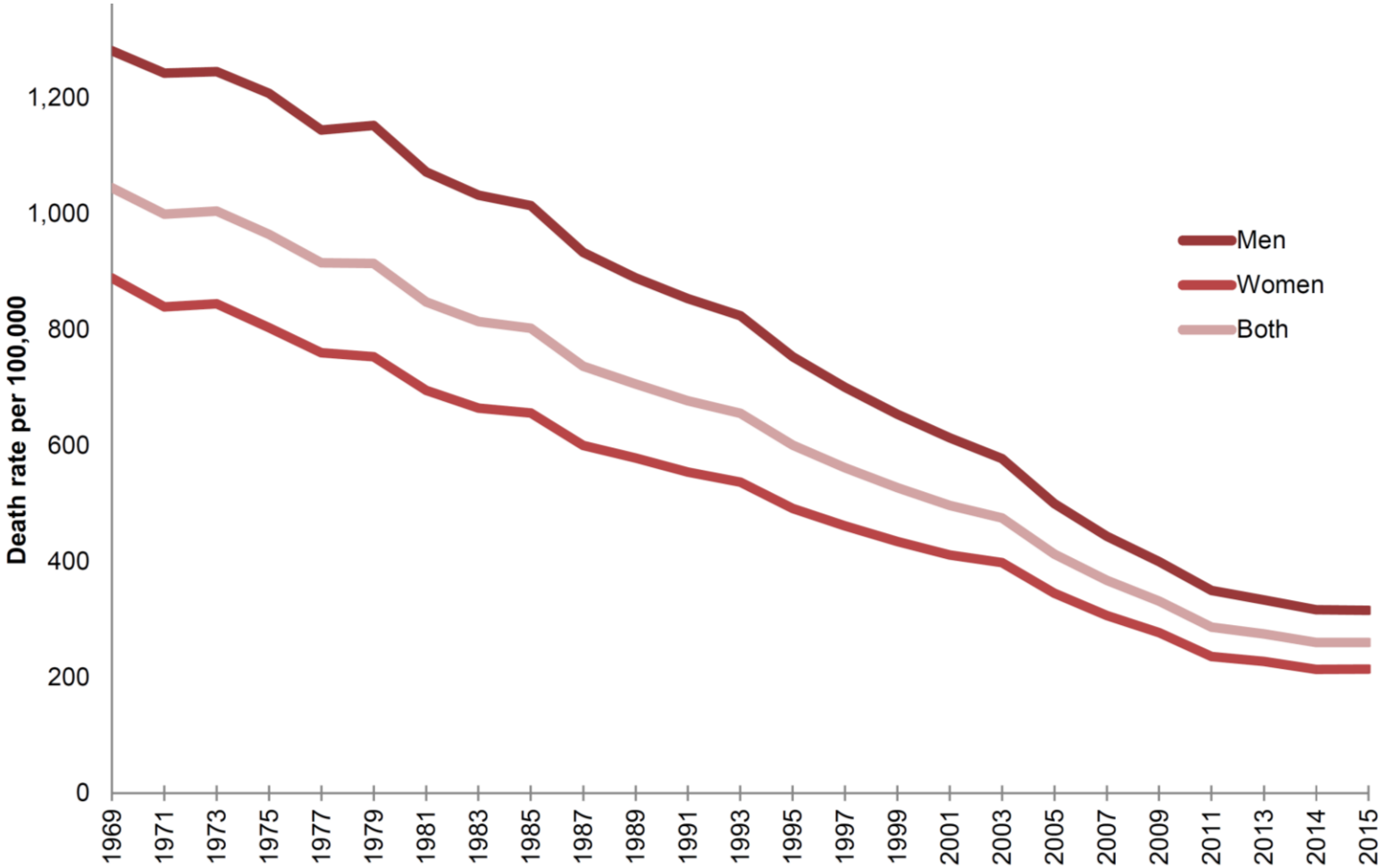
- **Population science** is a powerful approach to identification of new **biomarkers** and new **pathways**

- Multiple molecular markers for T2D & CVD: these look strong candidates for translation to **clinical benefit**?

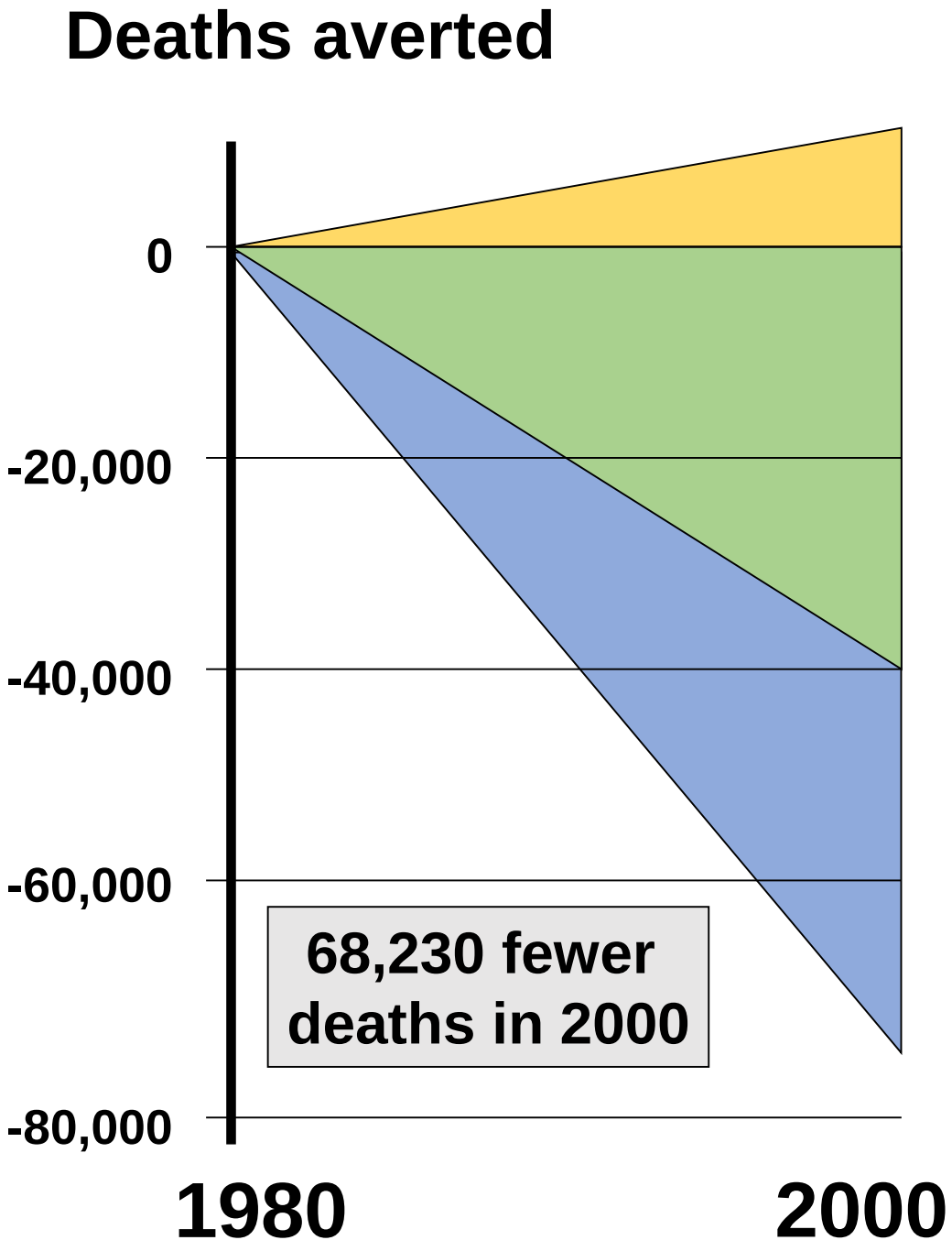
- High dimensional complex ‘omic data in large, well characterised population cohorts are a rich source for ‘**unsupervised**’ biological discovery.

Thank you

CHD mortality in the UK 1969-2015



~50% reduction in CHD also seen in UK Asians



Risk factors worse	**+13%**
Obesity	+3.5%
Diabetes	+4.8%
Less physical activity	+4.4%

Primary prevention	**-58%**
Smoking	-40%
Cholesterol	-9%
Blood pressure	-9%

CHD treatment	**-42%**
AMI treatment	-8%
Secondary prevention	-11%
Heart failure	-12%
CABG/PCI	-4%