Diabetes, Tuberculosis, and HIV – a deadly Threat - and a unique Opportunity (for collaboration in fight against them)

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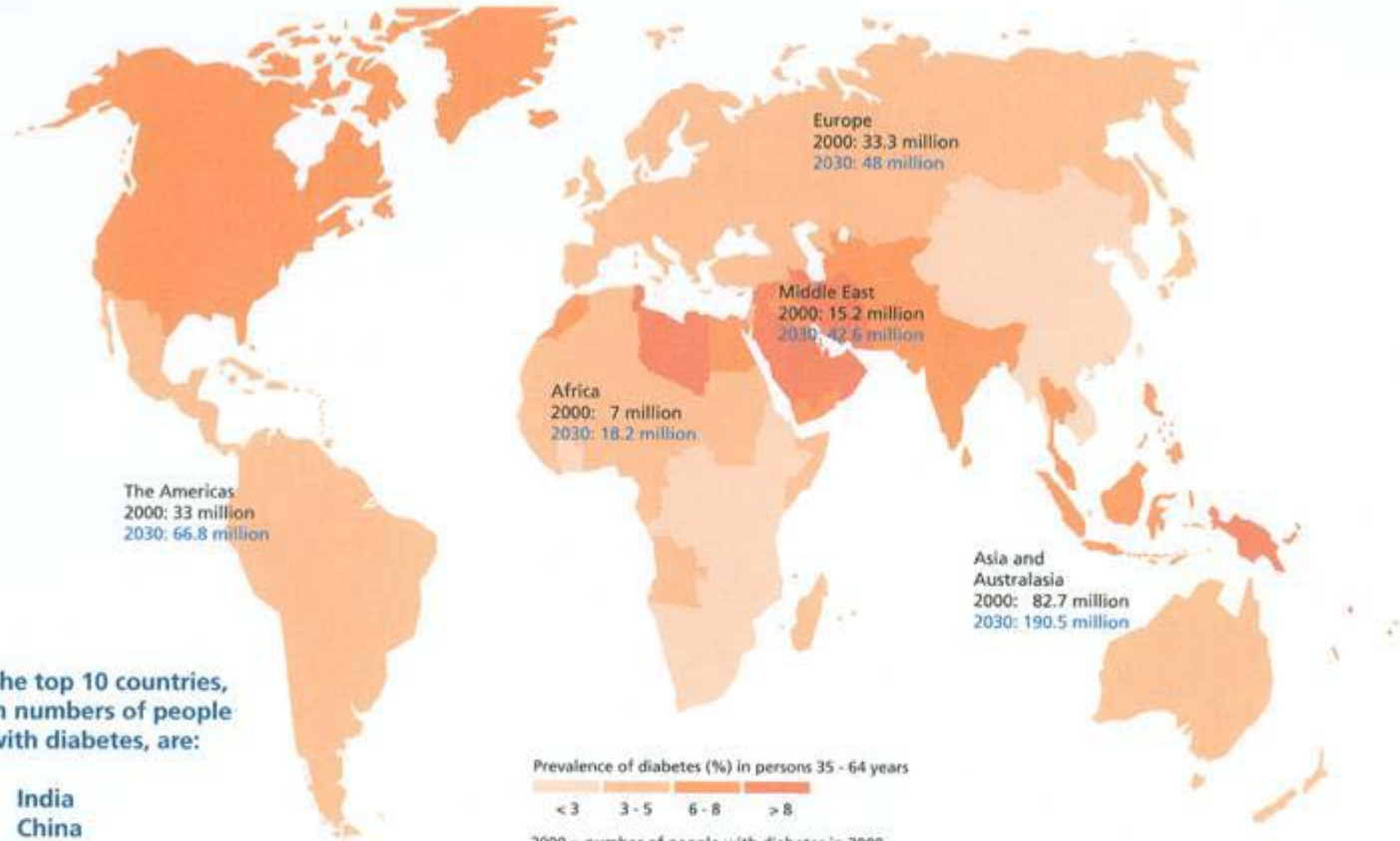
Prevalence of diabetes



Source: Wild et al, 2004

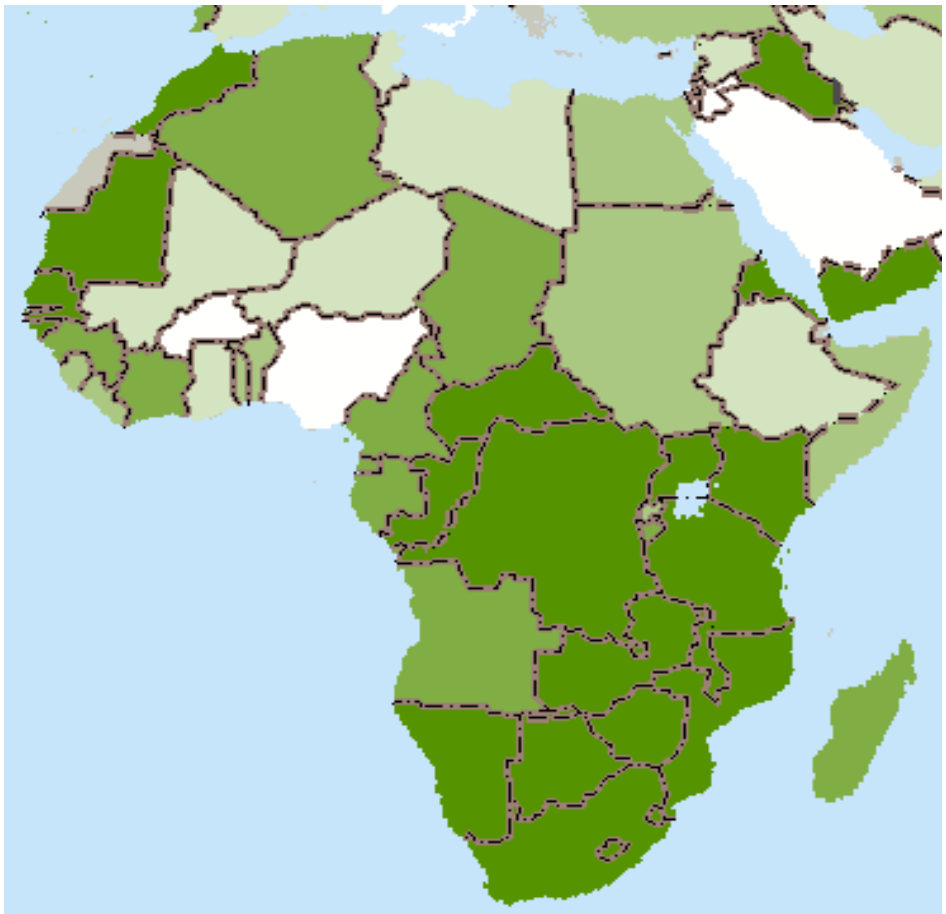
The top 10 countries, in numbers of people with diabetes, are:

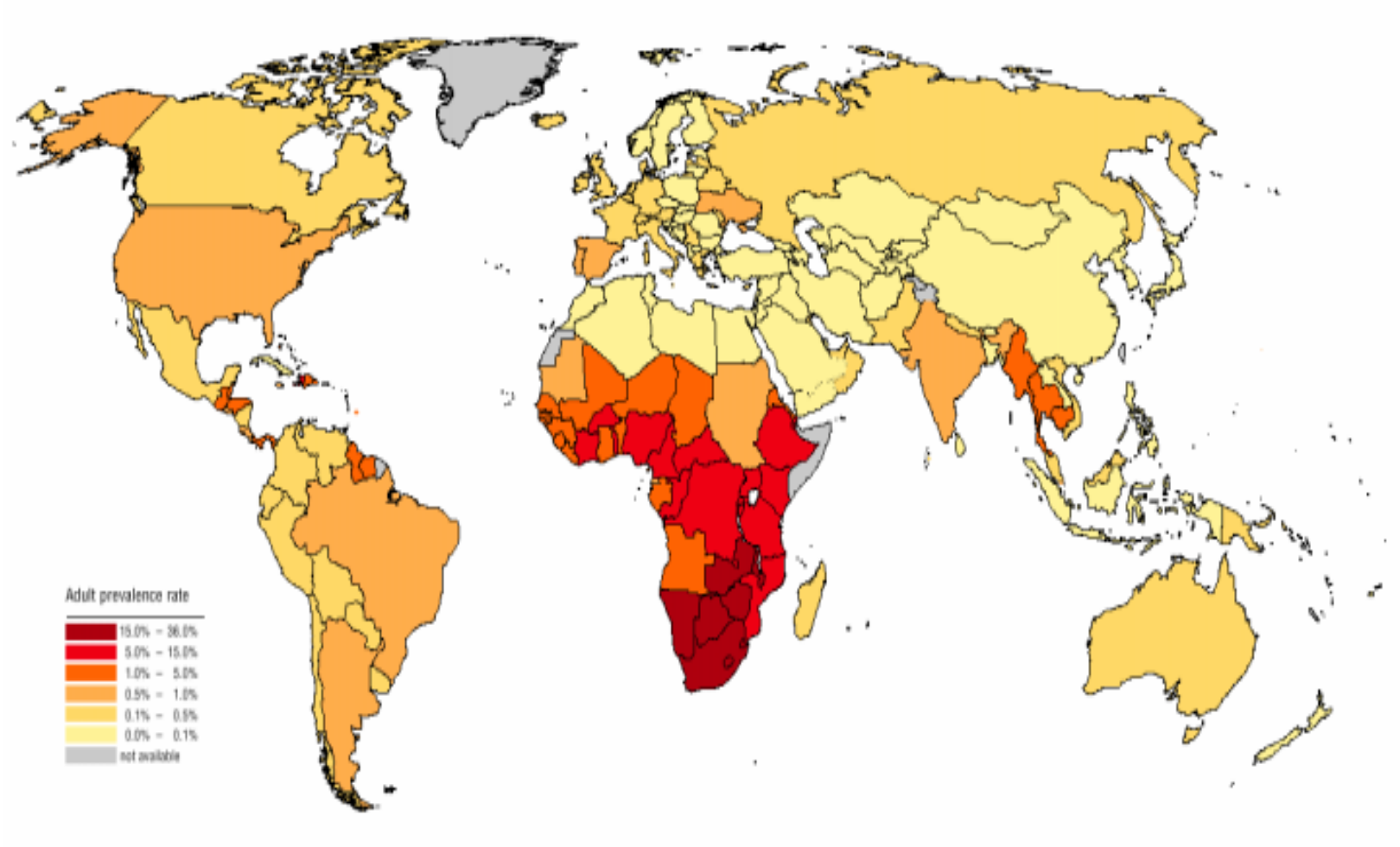
India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh

Year		2000	2030
Ranking	*Country*	*People with diabetes (millions)*	
1	India	31.7	79.4
2	China	20.8	42.3
3	United States of America	17.7	30.3

TB prevalence, cases of TB/100.000

Darkest green > 90, medium >=50, light > 30





HIV Prevalence with emphasis on Africa,

HIV in Africa brief

- MSF 90%, ♀:♂ > 1, MoToCh, unsafe b & i.
- P = > 30%: Botswana (cf. VDRL > 50% in 70'ies)
- P = 15 – 30%: S-Africa, Namibia, Malawi, Zambia, Zimbabwe
- P = 5 – 15%: Congo, Ethiopia,Kenya, Mocambique, Tanzania, Uganda (15 ->5%)
- P = 1 – 5%: Angola, much of W-Africa

Diabetes in central Kenya, recent study (KEMRI, Copenhagen)

(D.L.Christensen et al., 2006/07)

- 3 Tribes (Kamba, Luo, Masaii) 17->55 yrs

	Females	Males
Urban		
DM%	9.4	10.6
IGT	18.9	8.8
Rural		
DM	2.1	3.5
IGT	8.8	5.8

(Diabetes Atlas 2007 all Kenya: DM 3.5)

TB & Diabetes in Central Tanzania, Mwanza (NIMR, Copenhagen, Bergen)

(Friis et al., ongoing)

- Urban adult females and males with TB, +/-HIV
- DM 3.4 %
- IGT 18.3 %
- IFG 23.8%
- GI (IGT+DM) female OR 2.1
  HIV + OR1.9, HIV+ females OR4.2

Objectives (Friis et al.)

- To assess the role of diabetes
  - as a determinant of TB disease

- To assess the effect of diabetes on:
  - manifestations of TB disease
  - acute phase response, CD4 and HIV load
  - weight gain and body composition
  - grip strength, physical activity

  - treatment outcome

What we know: DM+TB+HIV may co-exist

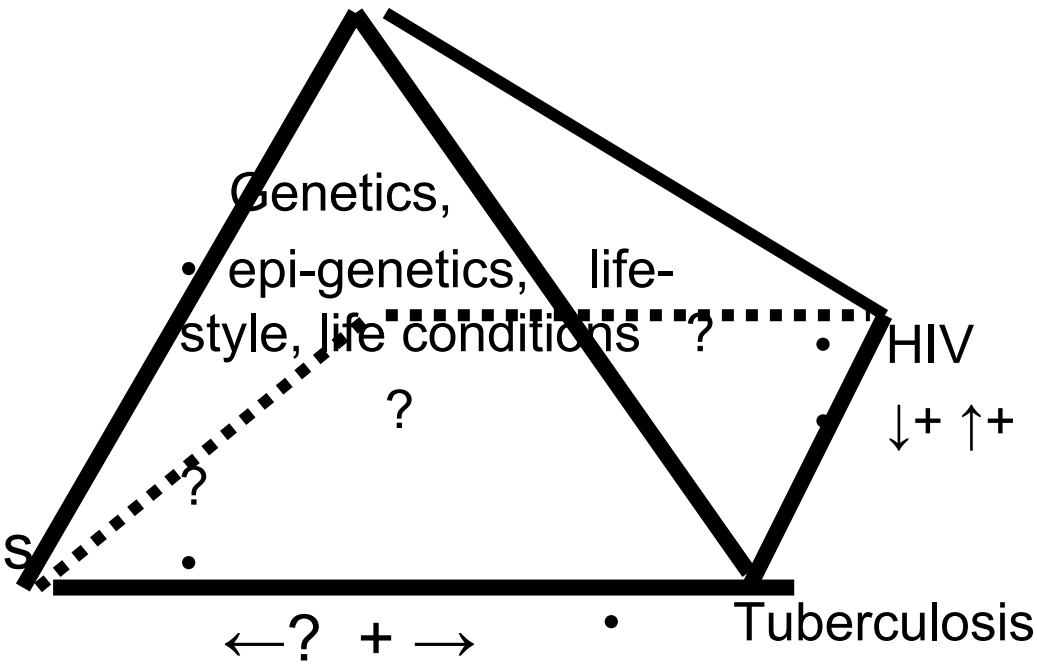
- Use standard TB treatment in DM, but
- Dose of oral hypoglycemic agents should be increased: interaction with Rifampicin
- Strict B-Glucose control indicated when co-morbidity
- Regular, life-long B-Glucose & B-Pressure control indicated when ARV-treatment

What we do not know

- Whether DM enhances HIV
- Whether HIV enhances DM
- Whether TB enhances DM
- How DM enhances TB, and how much
- How much TB enhances HIV
- How poor countries can control DM, TB and HIV
- How pathophysiology of interaction works

Potential and proven interactions between DM, TB and HIV

- ?=Not known; +=enhancing effect; -=antagonistic effect
  - Anti-diabetics, ← - anti-TB - → anti-Retrovirals.



Magnitude of increased risk of Tuberculosis in Diabetes by Risk (highest top, lowest down) and Country

(Author)	(Indicator)	(Country)
Feleke et al., 1999	Relative Risk 7-26 fold increased	(Ethiopia)
Ponce-De-Leon et al., 2004	Rate 5.7-8.2 fold increased	(Mexico)
Kim et al., 1995	Relative Risk 3.47-5.15 fold increased	(Korea)

For Comparison: Magnitude of increased Risk of Tuberculosis in HIV

WHO, 2005	Lifetime risk 50 % compared to 5-10% in HIV-neg., i.e. 5-7 fold increased	(SEAsia)

Anti**R**etro**V**irals, **H**ighly**A**ctive**A**nti**R**etroviral**T**herapy

- Antiretroviral agents:
- NRTI= analogues of nuceosides/tides (Adenine, Guanine, Cytosine, Thymidine f.ex. Azido-thymidine = AZT= Zidovudine =Retrovir®)
- NNRTI (non-nuclosideNRTI) f.ex. Nevirapine= Viramune®
- PI (protease inhibitors) f.ex. Indinavir= Crixivan®
- (Fusion-inhibitors,Entry-inhibitors f.ex. Enfurvitid= Fuzeon®)

Top 10-ARV individual side-effects

COMMON SIDE-EFFECTS OF COMMONLY USED ARV, TOP TEN LIST

Abbreviations: (N)NRTI (non-)nucleoside reverse transcriptase inhibitor
PI protease inhibitor

Generic name, nick name, Drug class, Side-effect,				Frequency/ Severity
Abacavir[3]	Ziagen®	NRTI	Hypersensitivity	5 % potentially fatal
Didanosine	DDI	NRTI	Neuropathy &	10 %, rarely optic
Stavudine	d4T	NRTI	Pancreatitis	5-10%, rarely fatal
Lamivudine[2,3]	3TC,Epivir®	NRTI	as above, but	< 10%, not severe
Zidovudine[2,3]	AZT	NRTI	Anaemia, myopathy	10-20%, rarely fatal
Efavirenz	Stocrin®	NNRTI	Rash	10 %, rarely fatal
Nevirapine	Viramune®	NNRTI	Rash, hepatotox	5-15%, sometimes fatal
Indinavir	Crixivan®	PI	Kidney stones	5-10%, preventable
Lopinavir/ritonavir, Kaletra		PI	Nausea, diarrhoea	5-15%, not severe
Nelfinavir	Viracept®, Invirase®	PI	Diarrhoea	10-30%, resolves
Saquinavir	Fortovase®	PI	Nausea, diarrhoea	10-20%, not severe

[2] in combination as Combivir® Ref. Scaling up ARV therapy in resource-limited settings, WHO 2001

[3] in combination as Trizivir®

P.S. Lactic acidosis may be seen with all NRTIs and the NNRTI Efavirenz
Lipid and glucose abnormalities may be seen with all PIs
These abnormalities may induce steatosis, lipoatrophy, lipodystrophy and possibly type 2 diabetes and cardiovascular diseases.
Haematological (bone-marrow suppression, including anaemia, leukocytopenia, thrombocytopenia) and hepatological (fat liver, toxic hepatitis) side-effects may be seen with virtually all drugs of all classes.
Resistance to all drugs of all classes may be induced; may occur after 1 single dose of Nevirapine, if used as mono therapy.

Top 10 diseases of referral hospital N-E-Tanzania, 2000.

No.	Disease	No. of Patients	Deaths
1	Malaria	761	77
2	Cataract	650	-
3	Chronic Dis	448	?
4	Diabetes*	398	41
5	Pneumonia	369	55
6	Hypertension*	347	35
7	Heart failure*	333	65
8	AIDS	322	91
9	Fibromyoma ut.	310	?
10	Anaemia	297	58
(*DM+CVD		1078	141)


DIABETES EDUCATION
Foot Care
DIABETES EDUCATION
Diabetes Complications

ARV-related DM, Hypertension, Dyslipidaemia (metabolic syndrome)

- Studies from US & Europe: 30-35% metablic side-effects, most with 1.st generation ARV
- Study from Rwanda: 34% dyslipidaemia, 1.st generation ARV

Recent study on interaction TB & DM

S-US & Mexico self-reported DM in TB in 6 years: Texan 27.8 %

Mexican 17.8 %

DM-TB comorbidity substantially exceeded that of HIV/AIDS-TB

Impact of T2DM on TB underappreciated

Recent added evidence outside Africa, II

Indonesia: DM is strongly associated with TB in Indonesisa

Alisjabana et al. Int J Tuberc Lung Dis 2006

Case-control study, recent diagn. TB, vs. Matched neighbour control

DM in 60 of 454 TB Ptts. = 13.2 %

DM in 16 of 556 controls = 3.2 % (OR 4.7)

NB! Young and non-obese subjects, urban

Brief thesis on available literature on DM & TB possible interactions by G. Ertner, 2006/07

- Many studies of relatively poor quality
- Few (6) studies of acceptable quality 1980-2006
- 4 on RR/OR, all showed significant increased risk of TB in DM – though none for Blacks
- 2 found increased risk of TB following DM diagnosis.

Is obesity them **main** factor for diabetes in Africa?

Figure 3.2

Proportion of diabetes (%) attributable to weight gain by region (30+ years)

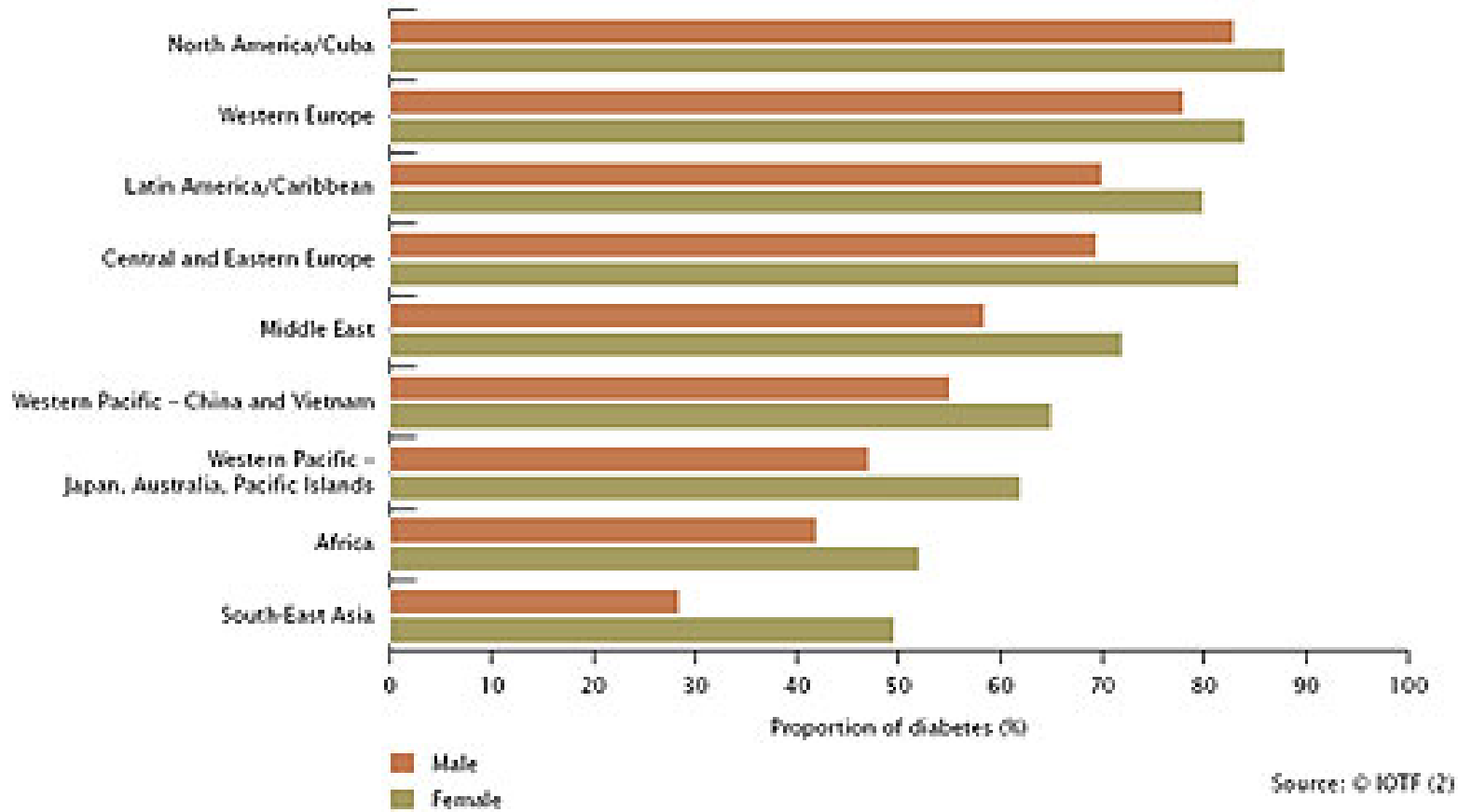
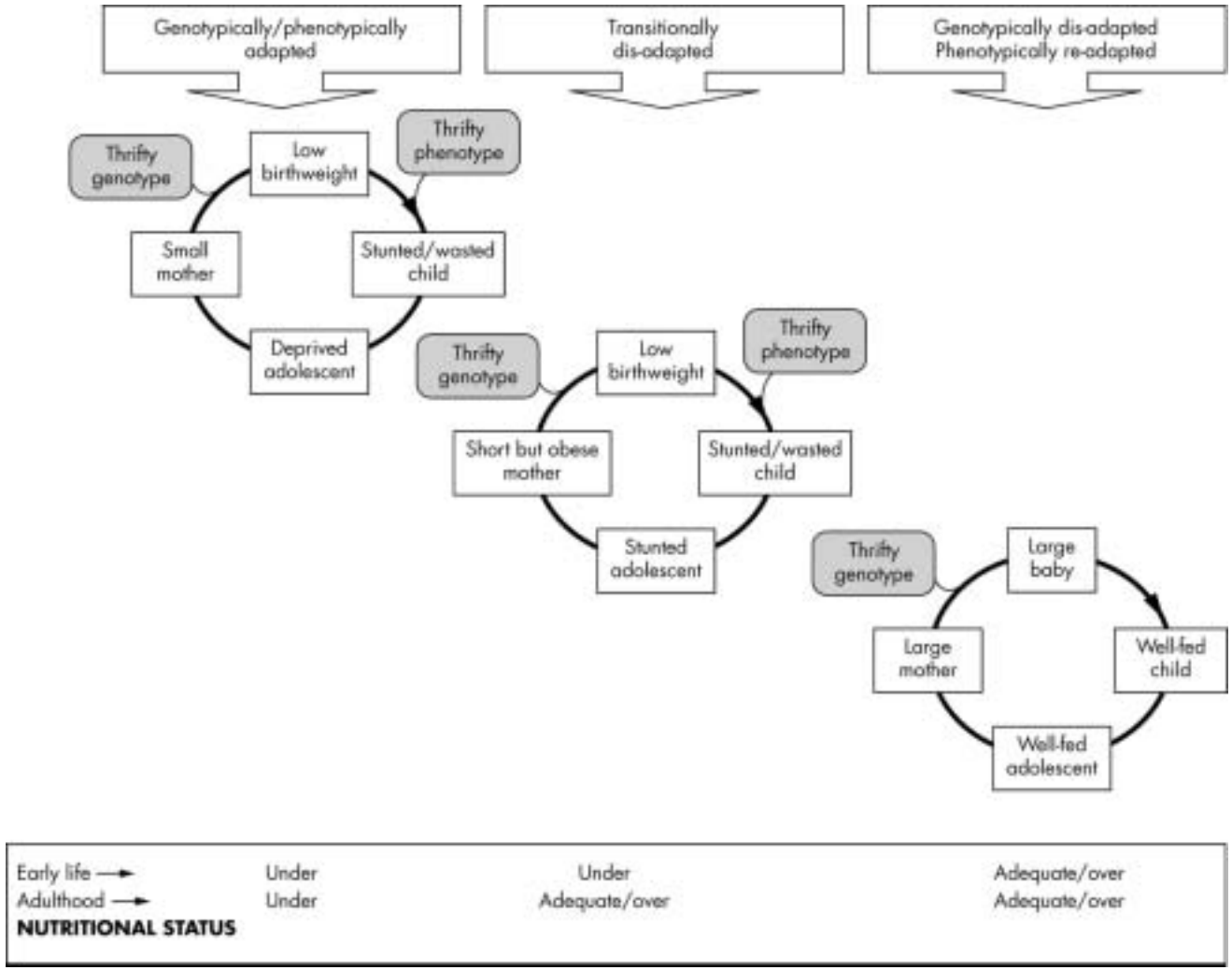


Figure 1 Schematic representation of the transitionally disadapted state affecting mothers and babies as populations make a rapid transition from nutritional poverty to affluence.



Prentice, A M et al. Arch Dis Child 2005;90:429-432

Main messages

- Non-Communicable Diseases (NCDs) and CDs often hit same populations (double burden)
- Cardio-vascular diseases CVD and diabetes (DM) interact in metabolic syndrome
- TB and HIV interact
- TB and DM interact
- HIV-treatment may induce CVD & DM
- DM, CVD, HIV and TB are all becoming chronic
- Resources for control are sparse
- Control of chronic diseases should be integrated