Persistent organic pollutants and diabetes:
epidemiological perspective

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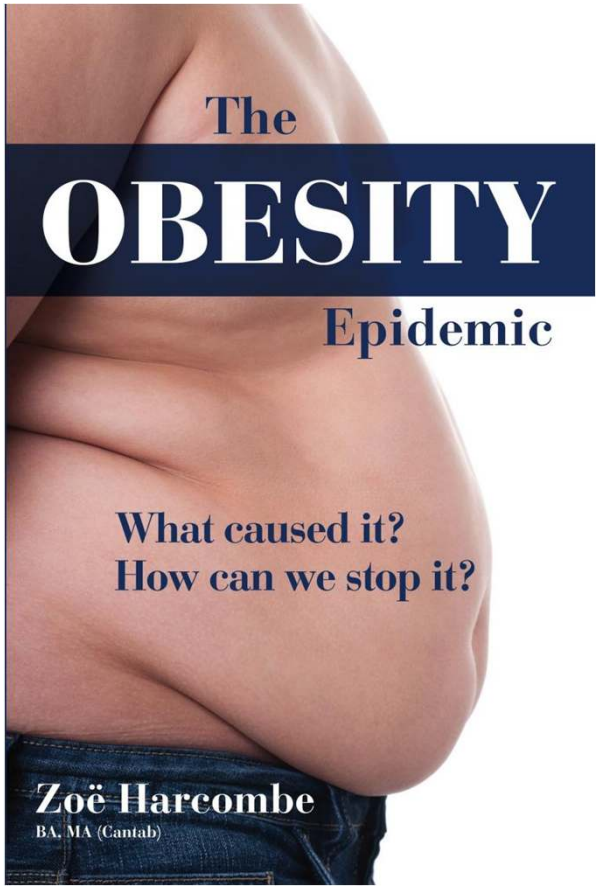
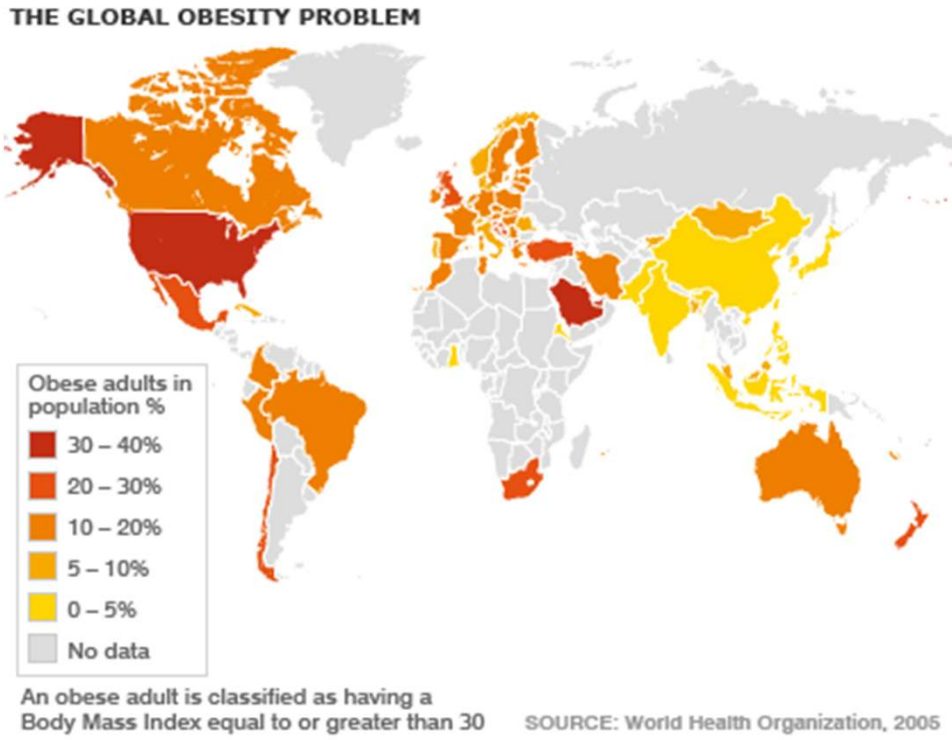
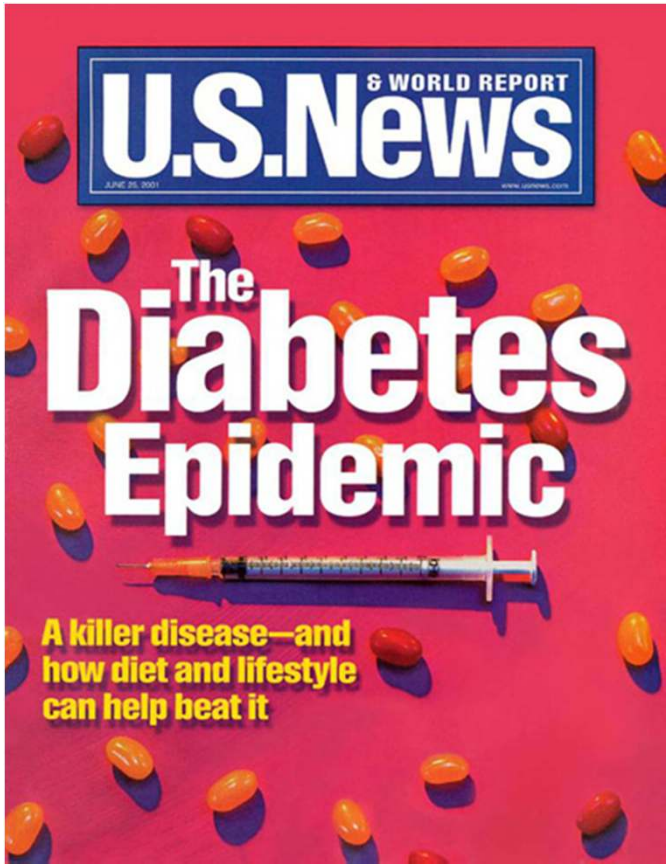
A world-wide epidemic of obesity





A world-wide epidemic of type 2 diabetes



환자 400만, '당뇨 대란' 오는가

[중앙일보 2005.05.24 09:48:47]

글자크기 | 이메일 | 프린트

[중앙일보 스폰서섹션] 당뇨병 환자가 크게 증가하고 있다. 의학계에서는 가까운 장래에 '당뇨대란'이 닥칠 것으로 우려하고 있다. 건강보험심사평가원의 자료에 따르면 현재 당뇨병으로 치료를 받고 있는 사람이 4백만명을 넘어섰다고 한다. 국민 100명 중 8명이 당뇨병 환자인 셈이다. 이미 우리나라에서는 한해 동안 50만명의 새로운 당뇨환자들이 생겨나고 있다. 이런 추세로 가면 2030년에는 당뇨병 환자가 7백만명을 넘어서고 국민 1백명 가운데 14.4명꼴로 당뇨병 환자가 생겨날 것으로 의학계는 예측하고 있다.당뇨병은 병 자체 보다 그로 인한 각종 합병증을 불러오기 때문에 더욱 무서운 것으로 알려져 있다. 또한 합병증이 발생할 때까지 특별한 증세를 보이지 않는 경우가 많아 '침묵의 살인자'라고도 불린다. 유전적인 영향도 있지만 최근 발생하는 당뇨병 환자들 대부분은 고지방식과 운동부족 때문인 경우가 많다. 적절한 음식섭취와 규칙적인 운동만 해주어도 당뇨병을 예방과 치료에 효과적이라는 것이 전문의들의 주장이다.

Current paradigm of type 2 diabetes

Calories intake >consumption

(diet & sedentary life style)

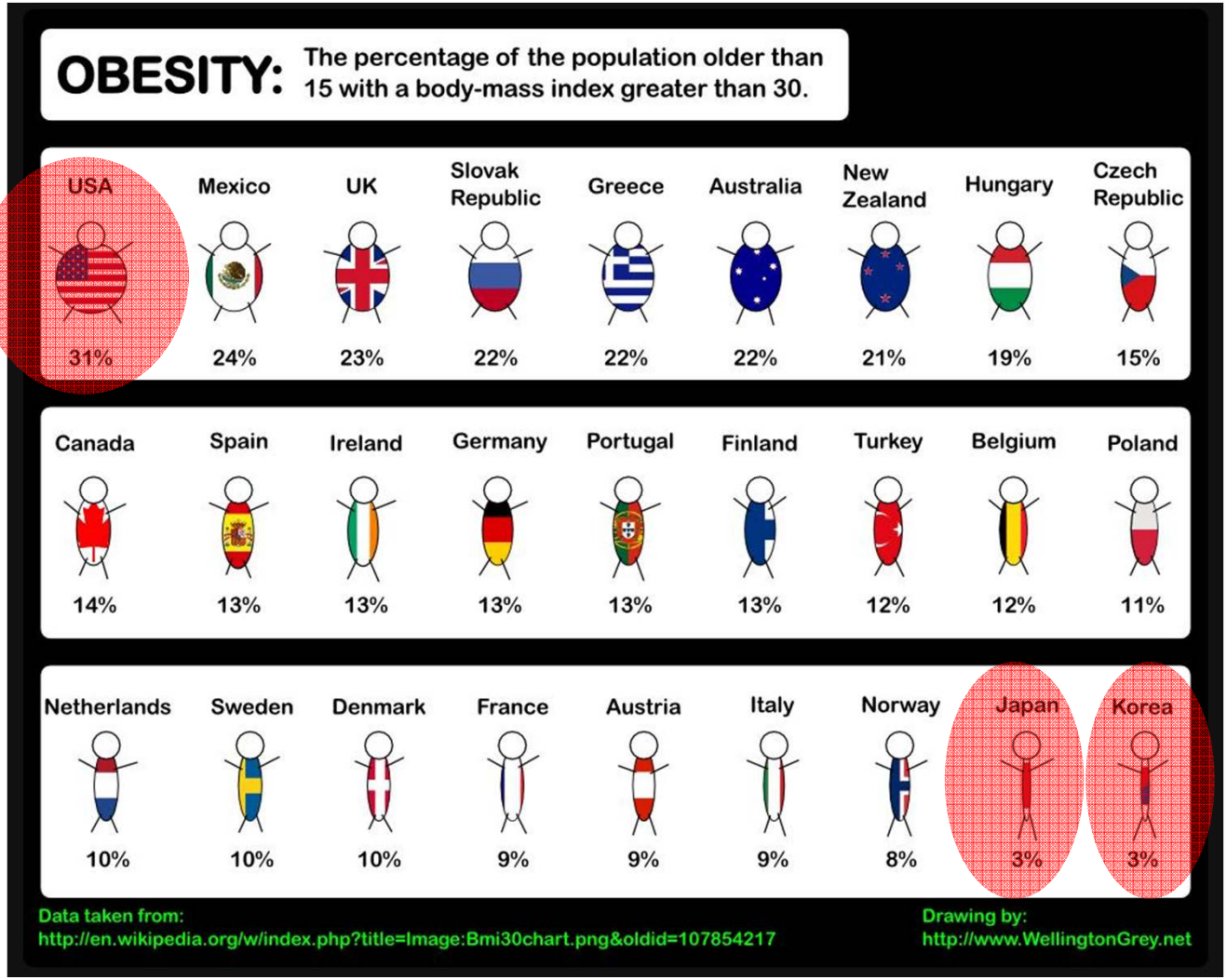
Insulin resistance:

Metabolic Syndrome

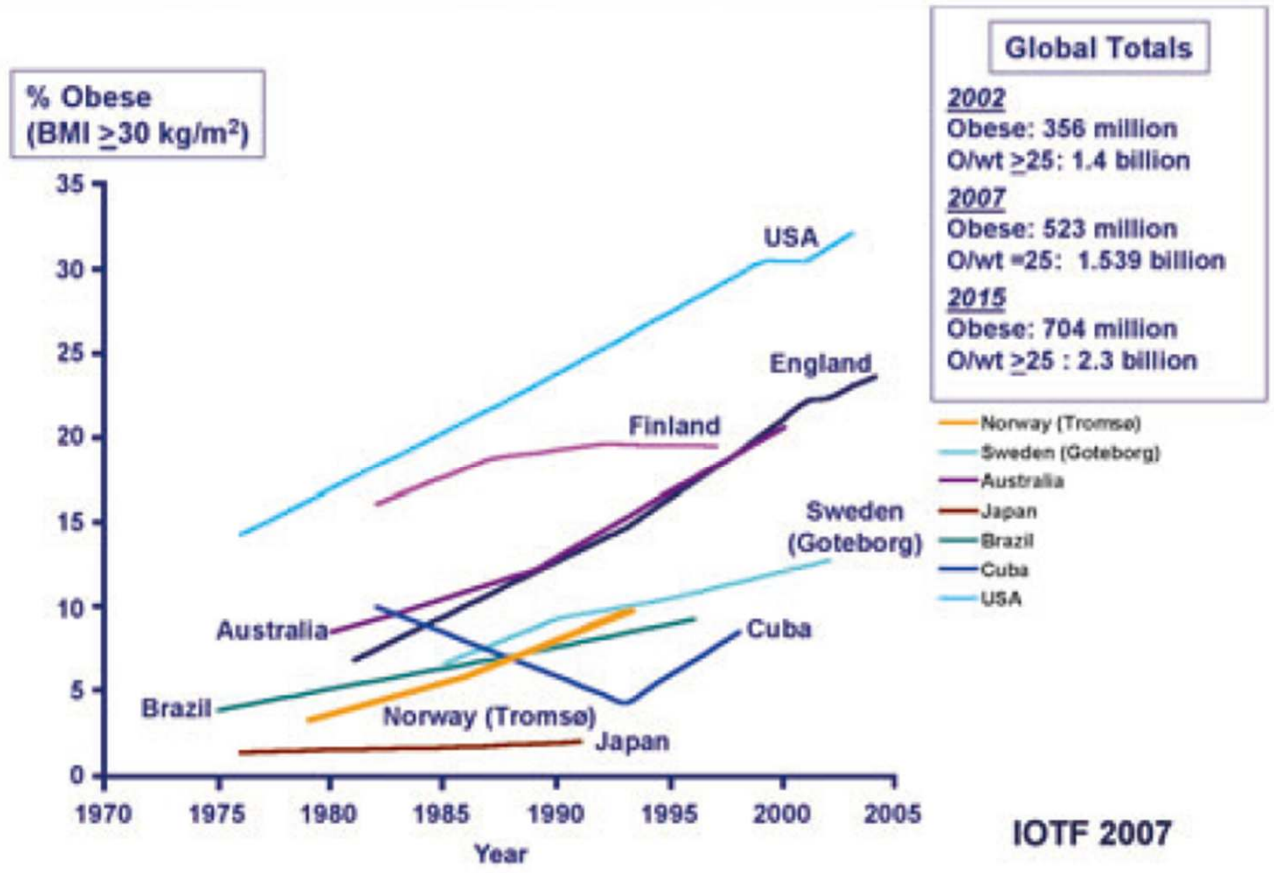
Pancreatic β cell insufficiency

Type 2 diabetes

Comparison of obesity prevalence



Comparison of increasing trend of obesity



James WPT. J Int Med 2008

Comparison of prevalence of type 2 diabetes

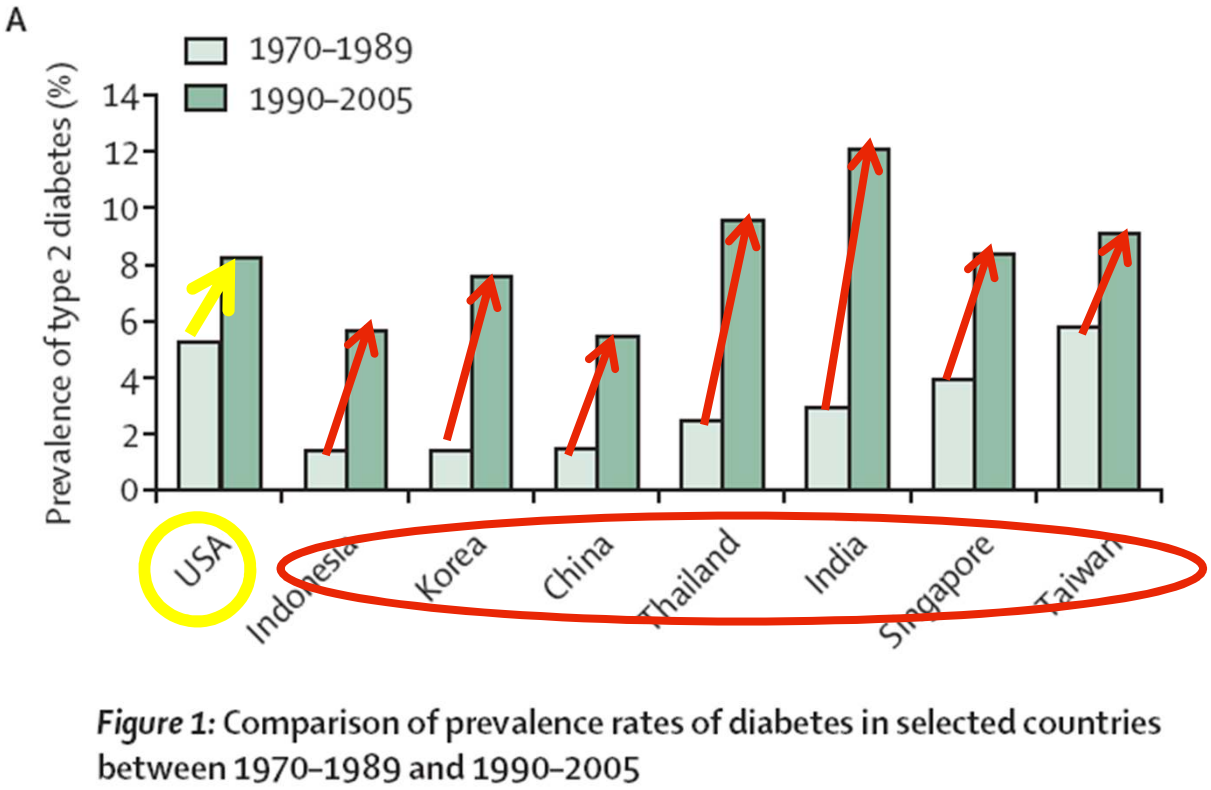


Figure 1: Comparison of prevalence rates of diabetes in selected countries between 1970–1989 and 1990–2005

Why??

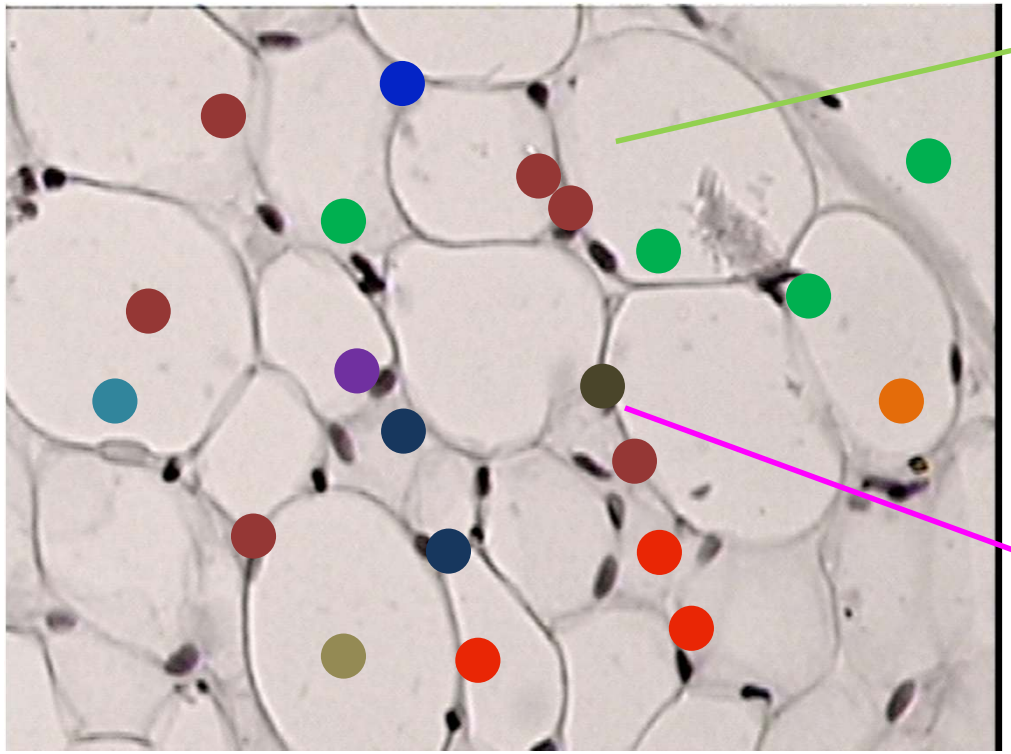
- Rapid changes in lifestyle
- Strong genetic susceptibility

  -Prominent central obesity
  -Early beta-cell failure

Really??

Yoon KH et al. Lancet 2006;368:1681-8

Adipose tissue is not a pure organ anymore in a modern chemical-contaminated society…



Lipophilic xenobiotics in adipose tissue, in particular Persistent Organic Pollutants (POPs), may be a key…

Not all of a sudden…

I was not a researcher in the field of environmental pollutants……

I had never heard of POPs before Nov 2005……

All hypotheses on POPs started with serum γ-glutamyltransferase

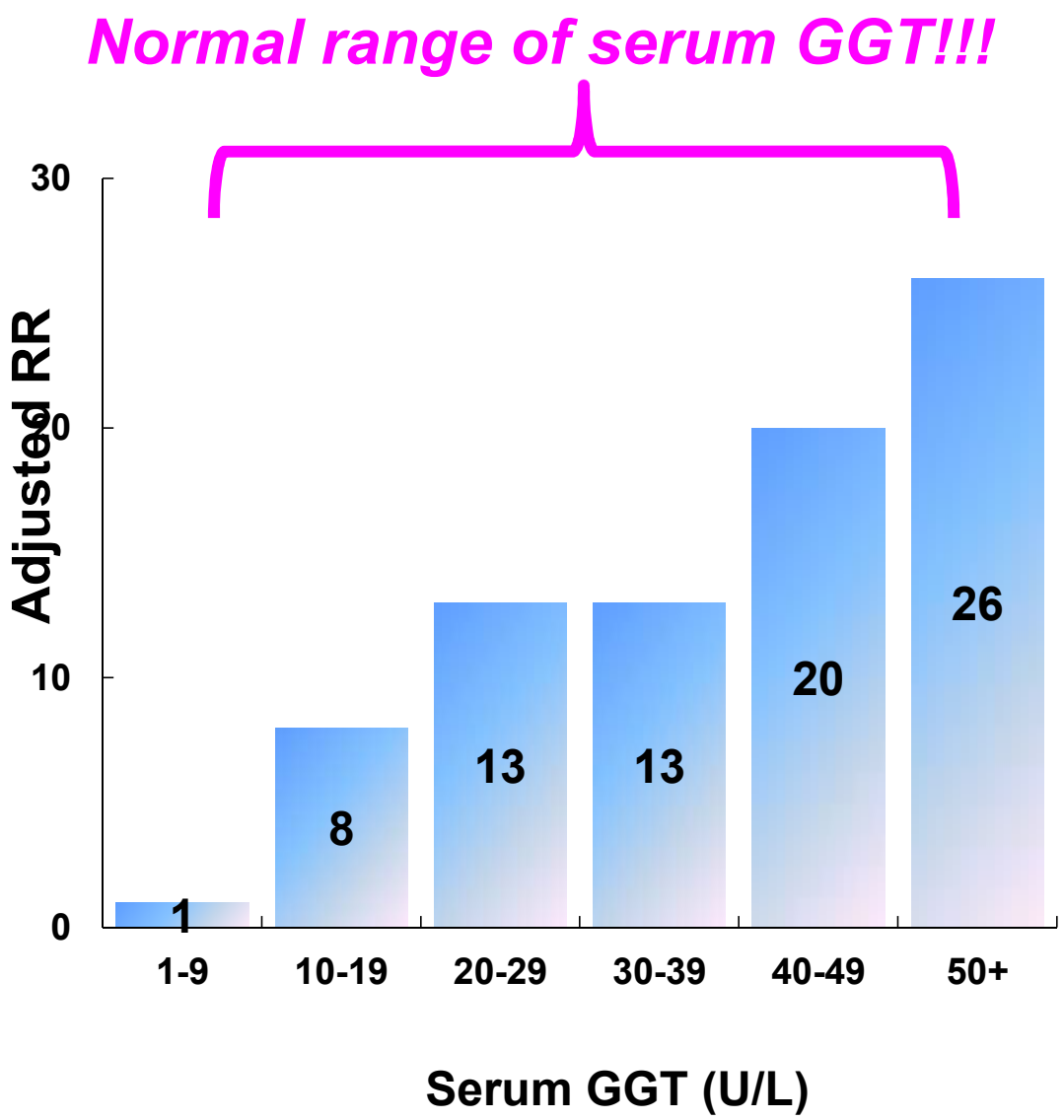
- **What's serum gamma glutamyltransferase (GGT)?**

  -Very well-known liver enzyme

  - Conventionally, used as a marker of alcohol consumption or hepatobiliary diseases

  - Easy and cheap measurement

Serum GGT strongly predicted type 2 diabetes in Korean men

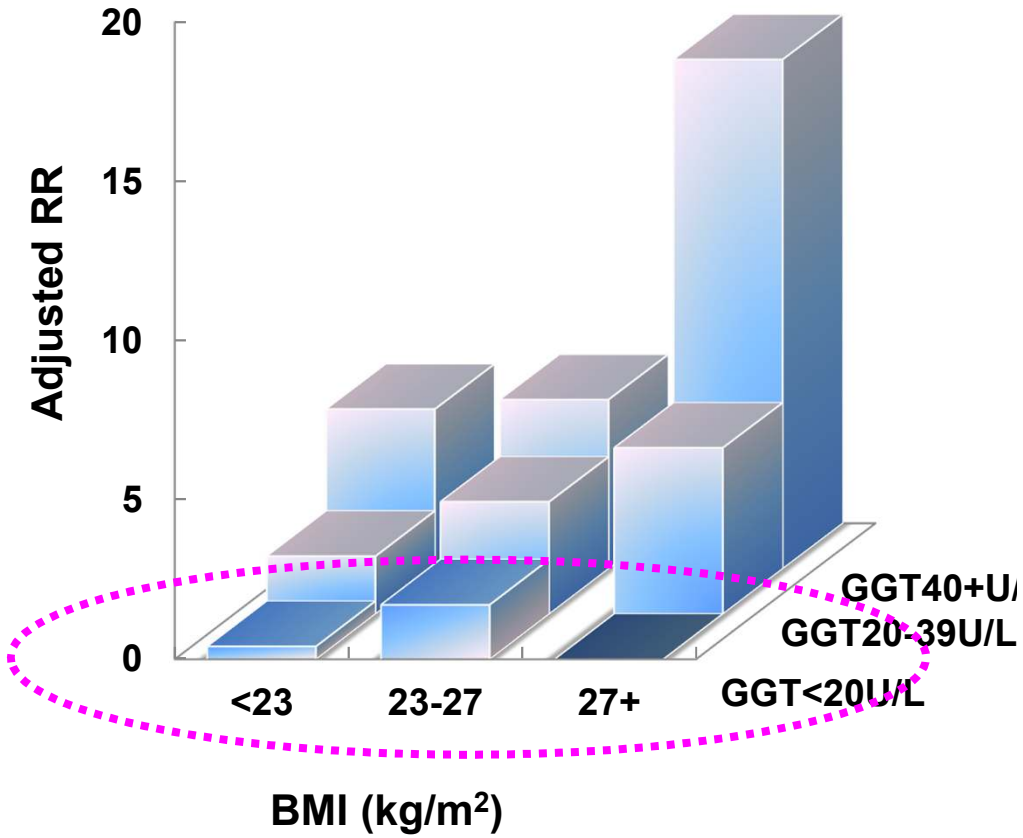


Conventional interpretation

-Alcohol consumption
-Liver dysfunction

Lee DH, et al. Diabetologia. 2003;46:359-64

Interaction between serum GGT and obesity on the risk of type 2 diabetes



Lee DH, et al. Diabetologia. 2003;46:359-64

Clinical Chemistry 49:8
1358–1366 (2003)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

γ-Glutamyltransferase Is a Predictor of Incident Diabetes and Hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

DUK-HEE LEE,[1,2] DAVID R. JACOBS, JR.,[3] MYRON GROSS,[4] CATARINA I. KIEFE,[5,6] JEFFREY ROSEMAN,[7] CORA E. LEWIS,[5] and MICHAEL STEFFES[4]

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The Journal of Clinical Endocrinology & Metabolism 89(11):5410–5414

doi: 10.1210/jc.2004-0505

γ-Glutamyltransferase, Obesity, and the Risk of Type 2 Diabetes: Observational Cohort Study among 20,158 Middle-Aged Men and Women

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Serum γ-glutamyltransferase (GGT) concentration within its ... ment for known risk factors of type 2 diabetes, relative risks

We were struck by these findings because…

- ***First, the strong dose-response relation !!***

  Serum GGT may be involved in a critical pathway of pathogenesis of type 2 diabetes

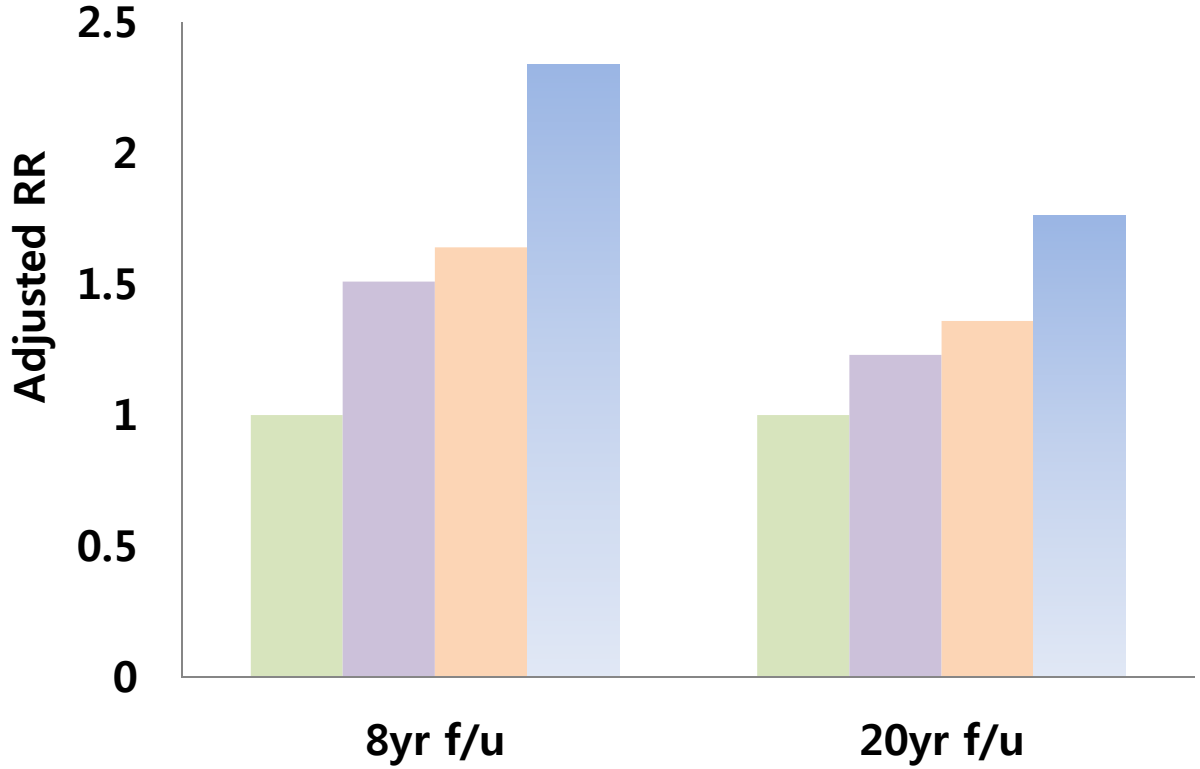
- ***Second, the reference range of serum GGT !!***

  Anything related to physiological function of serum GGT may be a key in the pathogenesis of type 2 diabetes

- ***Third, the interaction between obesity and serum GGT !!***

  Obesity may not be a true risk factor of diabetes. Something related to serum GGT may be more important

Serum GGT predict metabolic syndrome:
Framingham Heart Study



Within normal range

	Men	Women	
Q1	1-11	1-6	U/L
Q2	12-16	7-9	U/L
Q3	17-24	10-13	U/L
Q4	25+	14+	U/L

Lee DS, et al. Arterio Throm Vasc Biol 2007;27:127-133

Serum GGT predict coronary heart disease

Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28 838 middle-aged men and women

Within normal range

Duk-Hee Lee[1*], Karri Silventoinen[2], Gang Hu[2,3], David R. Jacobs Jr[4,5], Pekka Jousilahti[2,6], Jouko Sundvall[7], and Jaakko Tuomilehto[2,3,8]

[1]*Department of Preventive Medicine, School of Medicine, Kyungpook National University, 101 Dongin-dong, Jung-gu, Daegu, South Korea 700-422;* [2]*Department of Public Health, University of Helsinki, Finland;* [3] *Department of Epidemiology and Health Promotion, National Public Health Institute, Finland;* [4]*Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN, USA;* [5]*Department of Nutrition, University of Oslo, Oslo, Norway;* [6]*School of Public Health, University of Tampere, Finland;* [7]*Department of Health and Functional Capacity, National Public Health Institute, Finland; and* [8]*South Ostrobothnia Central Hospital, Seinäjoki, Finland*

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See page 2145 for the editorial comment on this article (doi:10.1093/eurheartj/ehl151)

KEYWORDS
Gamma-glutamyltransferase;
Myocardial infarction;
Coronary heart disease;
Diabetes;
Oxidative stress

Aims Serum gamma-glutamyltransferase (GGT) concentration may be involved in atherosclerosis. This study examined if serum GGT predicted coronary heart disease (CHD), especially differentiating non-fatal myocardial infarction (MI) and fatal CHD event, among the general population or participants with type-2 diabetes.

Methods and results A prospective study of 28 838 Finnish men and women aged 25–74 years was performed (1467 incident CHD cases; a median follow-up time of 11.9 years). Serum GGT cutpoints were the 25th, 50th, 75th, and 90th sex-specific percentiles. After adjustment for known cardiovascular risk factors, compared with the lowest GGT category, hazard ratios (HR) were 1.15, 1.25, 1.27, and 1.57 among men and 1.03, 1.22, 1.32, and 1.44 among women in other four GGT categories (P for trend <0.01, respectively). However, stronger associations were observed among subjects aged <60 and among alcohol drinkers. The strength of association was similar for non-fatal MI and for fatal CHD. Among subjects with type-2 diabetes, the corresponding adjusted HRs were 1.29, 1.57, 1.88, and 1.78 (P trend = 0.03, men and women combined).

Conclusion This study suggests an independent mechanism linking serum GGT to CHD among general population. Even though the strength of association appeared to be modest among all subjects, stronger associations were observed among subjects aged <60 and among alcohol drinkers. Especially, measurement of serum GGT among type-2 diabetics may be helpful to predict the future risk of CHD.

Lee DH, et al. Eur Heart J 2006;27:2170-6

Serum GGT predict stroke

RESEARCH REPORT

γ-Glutamyltransferase and risk of stroke: the EUROSTROKE project

Within normal range

M L Bots, J T Salonen, P C Elwood, Y Nikitin, A Freire de Concalves, D Inzitari, J Sivenius, A Trichopoulou, J Tuomilehto, P J Koudstaal, D E Grobbee

J Epidemiol Community Health 2002;56(Suppl I):i25–i29

See end of article for authors' affiliations

Correspondence to: Dr M L Bots, Julius Centre for Patient Oriented Research, Universtiy Medical Centre, Utrecht, room D01.335,

Background: Alcohol consumption has been implicated in the aetiology of stroke. As data on alcohol consumption obtained by questionnaire are susceptible to missclassification, this study evaluated the assocation between γ-glutamyltransferase (γ-GT), as a marker for alcohol consumption, and fatal, non-fatal, haemorrhagic and ischaemic stroke in three European cohort studies, participating in EUROSTROKE.

Methods: EUROSTROKE is a collaborative project among ongoing European cohort studies on incidence and risk factors of stroke. EUROSTROKE is designed as a nested case-control study. For each stroke case, two controls were sampled. Strokes were classified according to MONICA criteria or reviewed by a panel of four neurologists. At present, data on stroke and γ-GT were available from cohorts in Cardiff (57 cases), Kuopio (66 cases), and Rotterdam (108 cases).

Results: An increase in γ-GT of one standard deviation (28.7 IU/ml) was associated with an age and sex adjusted 26% (95% CI 5 to 53) increase in risk of stroke. Adjustment for confounding variables such as drug use, history of myocardial infarction, total cholesterol, and diabetes mellitus did not mater

Bots ML, et al. J Epidemiol Comm Health 2002;56:i25-9

Serum GGT predict hypertension

γ-Glutamyltransferase Is a Predictor of Incident Diabetes and Hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Within normal range

Duk-Hee Lee,[1,2] David R. Jacobs, Jr.,[2,3*] Myron Gross,[4] Catarina I. Kiefe,[5,6] Jeffrey Roseman,[7] Cora E. Lewis,[5] and Michael Steffes[4]

Background: γ-Glutamyltransferase (GGT), which maintains cellular concentrations of glutathione, may be a marker of oxidative stress, and GGT itself may produce oxidative stress. We performed a prospective study to examine whether serum GGT predicts diabetes and hypertension.

Methods: Study participants were 4844 black and white men and women 18–30 years of age in 1985–1986; they were reexamined 2, 5, 7, 10, and 15 years later. Year 0 GGT cutpoints were 12, 17, 25, and 36 U/L (overall 25th, 50th, 75th, and 90th percentiles; the laboratory cutpoints

index, cigarette smoking, and physical activity attenuated this relationship, but GGT remained a significant predictor.

Conclusions: Serum GGT within a range regarded as physiologically normal is associated with incident diabetes and hypertension. Considering known functionality of GGT, these associations are consistent with a role for oxidative stress in risk for diabetes and hypertension.

Lee DH, et al. Clin Chem 2003;49:1358-66

Serum GGT predict CVD incidence and total mortality:
Framingham Heart Study

Within normal range

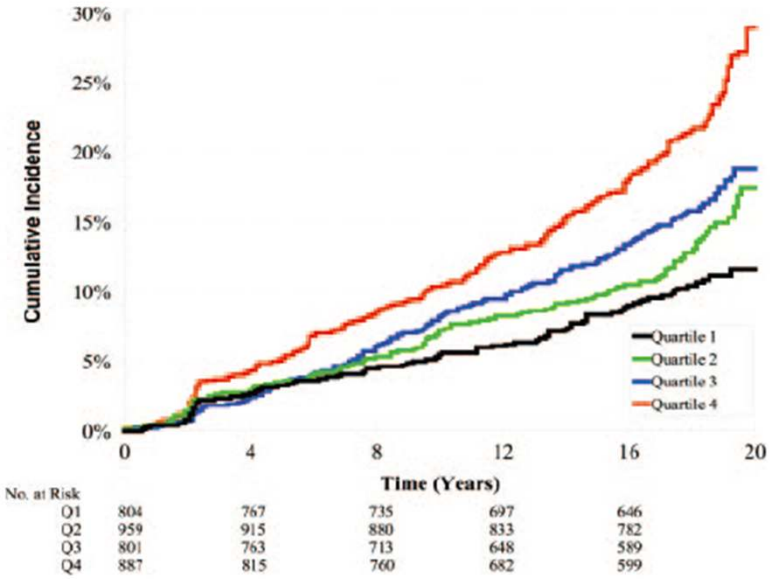


Figure 1. Age/sex-adjusted cumulative incidence of CVD by GGT quartile. Numbers at risk are not the same in each quartile because cut points were determined on all participants with available GGT data (before exclusions).

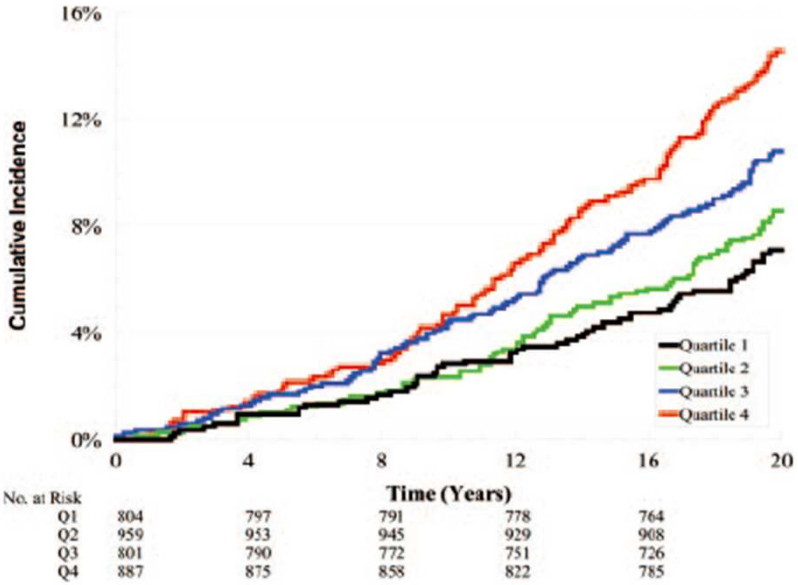
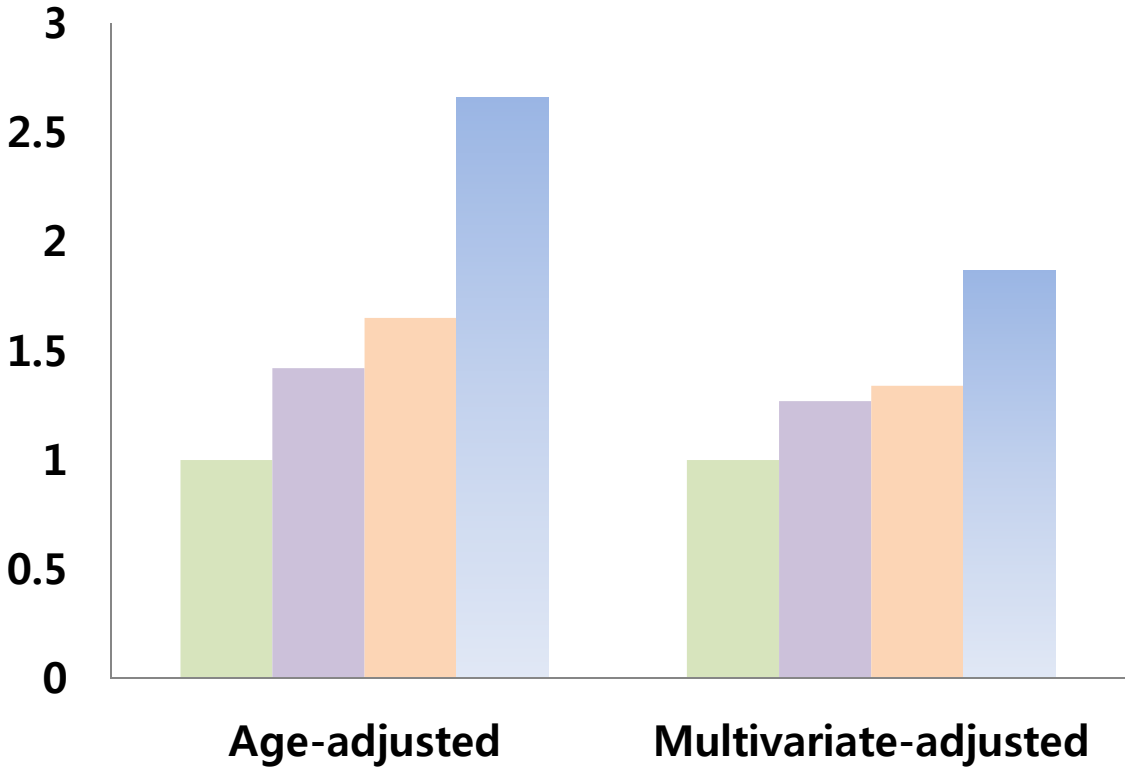


Figure 2. Age/sex-adjusted cumulative incidence of mortality by GGT quartile. Numbers at risk are not the same in each quartile because cut points were determined on all participants with available GGT data (before exclusions).

Lee DS, et al. Arterio Throm Vasc Biol 2007;27:127-133

Serum GGT predict chronic kidney disease
: nonhypertensive & nondiabetic Korean men

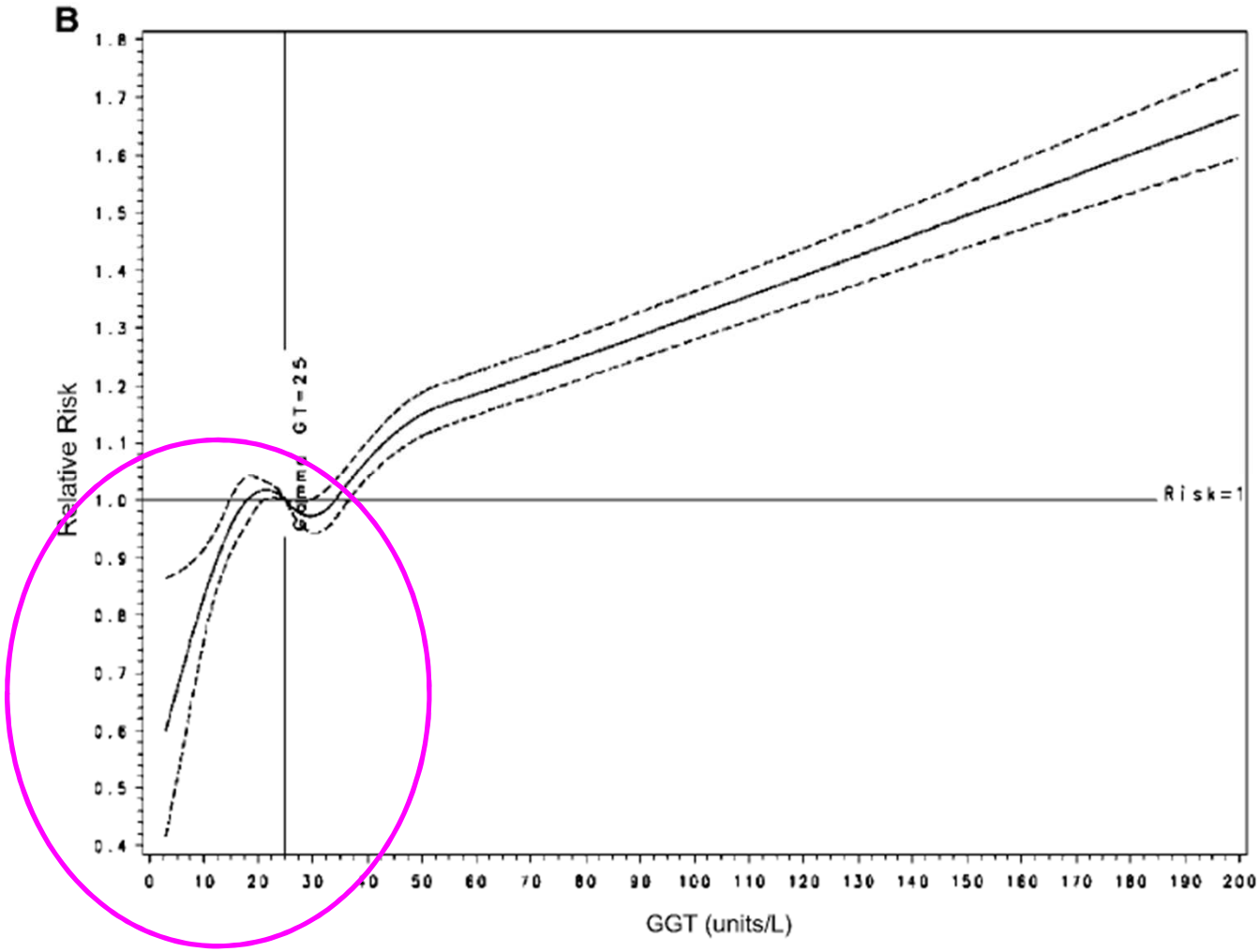


Within normal range

	Men
Q1	<18
Q2	19-25
Q3	26-39
Q4	40+

Ryu S, et al. Clin Chem 2007;53:71-7

Serum GGT predict cancer

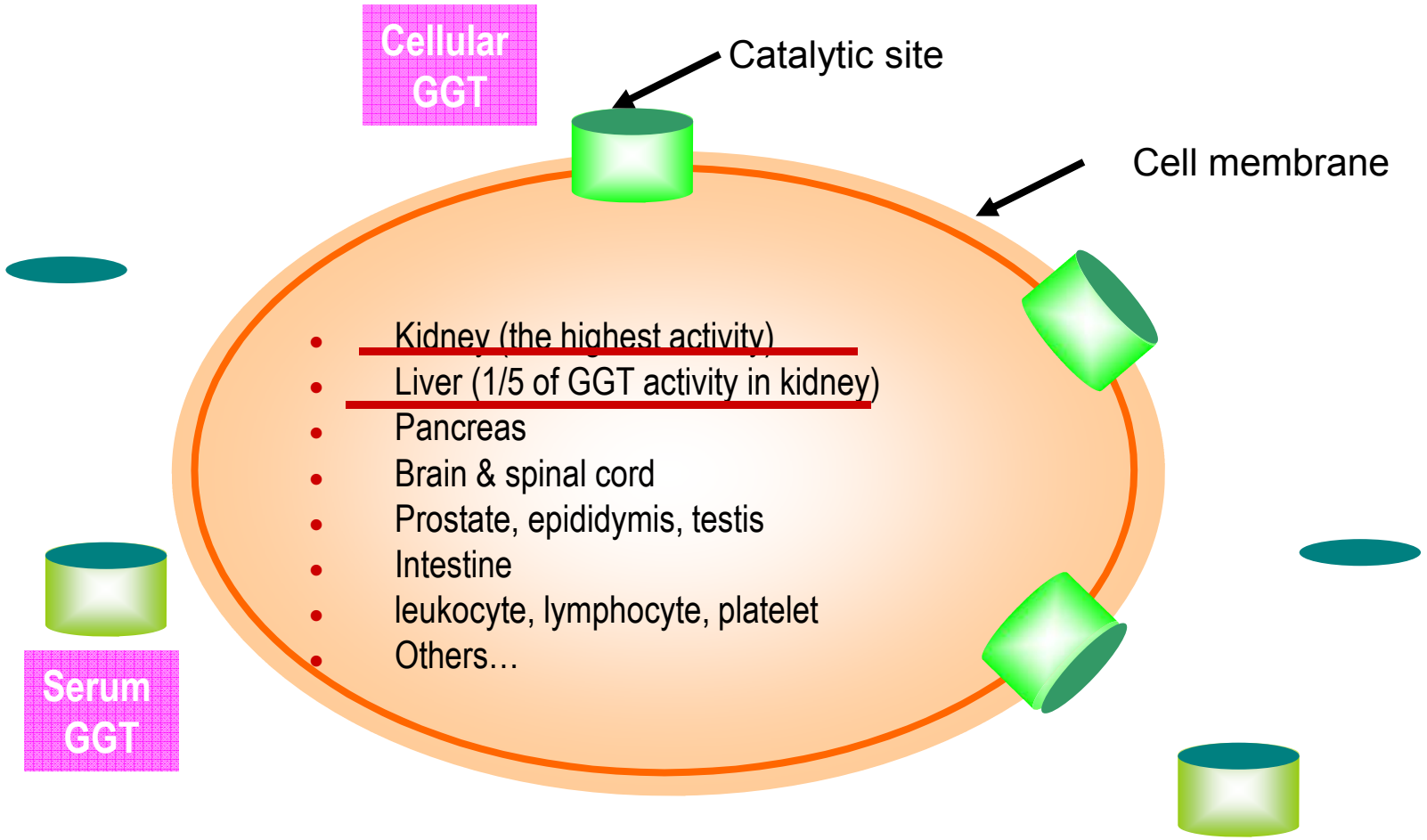


Within normal range

Strasak AM, et al. Cancer Res 2008;68:3970-7

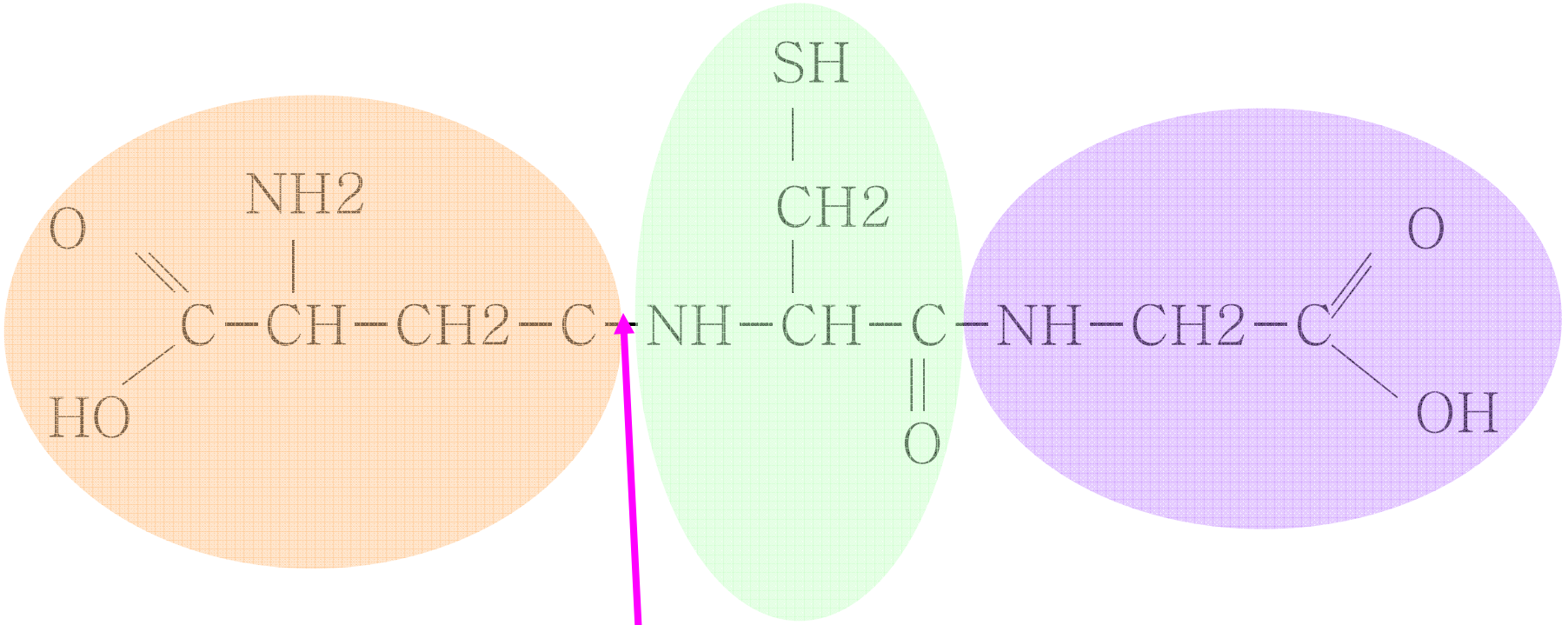
How can serum GGT within normal range predict various diseases with diverse pathophysiology in general population??

Back to an old biochemistry textbook: What is really GGT?



GGT is an critical enzyme for glutathione (GSH) metabolism

GSH: the most abundant and important intracellular antioxidant



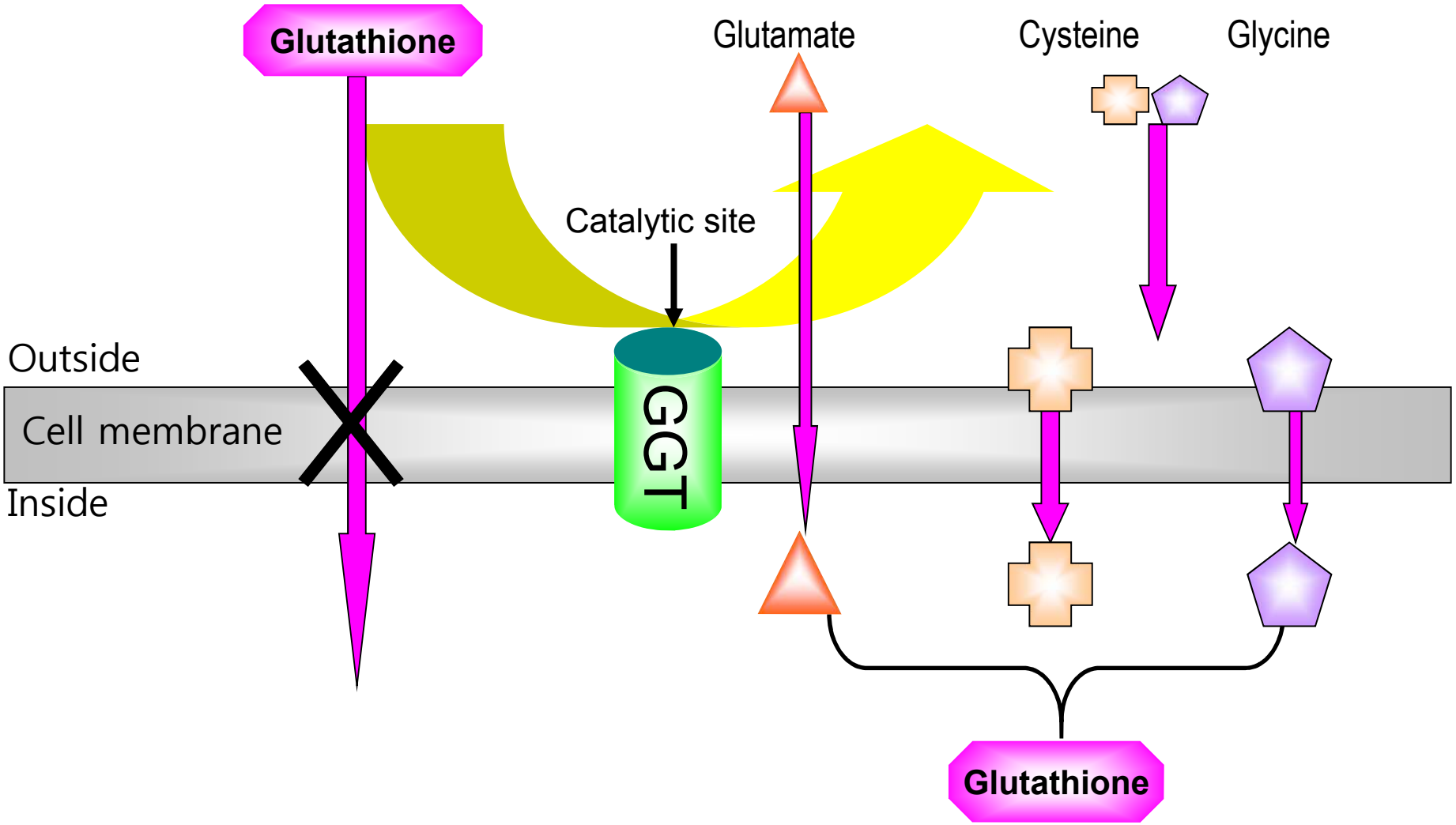
Glutamate Cysteine Glycine

<Gamma-carboxyl Linkage>

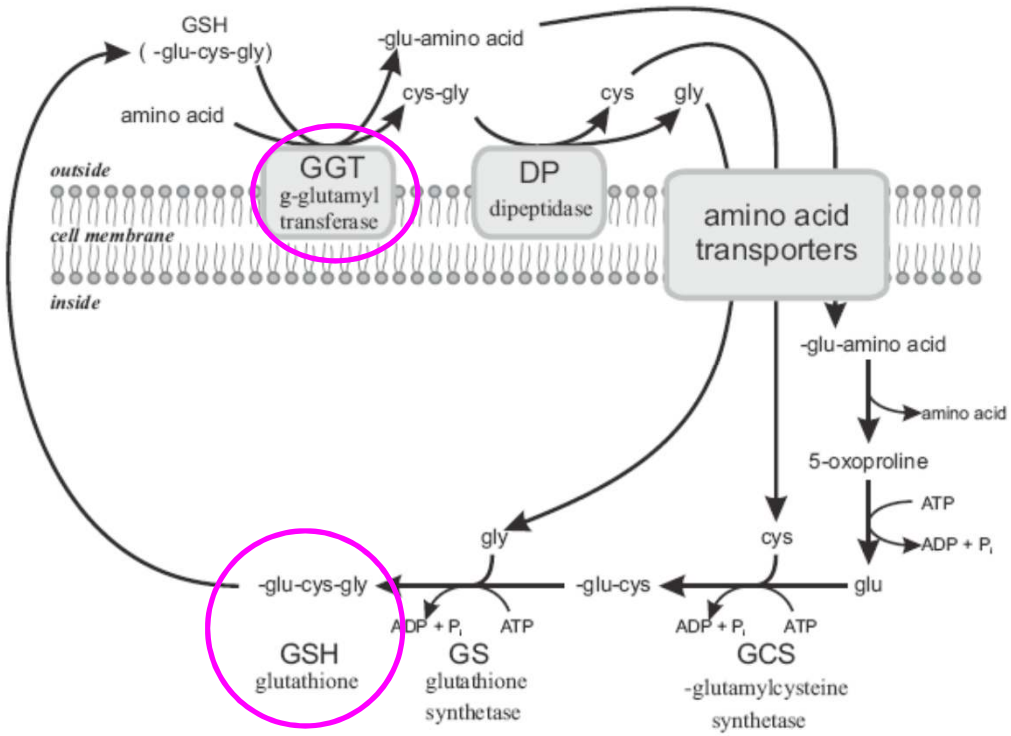
-Protect GSH from intracellular degradation by aminopeptidases

-Only GGT can break this linkage

GGT is essential for intracellular GSH de novo synthesis



Gamma-glutamyl cycling (from an old biochemistry textbook)



Association of Serum Carotenoids and Tocopherols with γ-Glutamyltransferase:

The Association between serum γ-glutamyltransferase and dietary factors: the Coronary Artery Risk Development in Young Adults (CARDIA) Study[1–3]

D

Duk-Hee Lee, Lyn M Steffen, and David R Jacobs Jr

Background: Our pr
γ-glutamyltransferas
oxidative stress, sup
studies. To further e
to oxidative stress, w
tween serum caroten
antioxidant propertie
Methods: Study parti
men and women 17–
carotenoids and toco
and 7, and serum GG
Results: Circulating

IS SERUM γ-GLUTAMYLTRANSFERASE INVERSELY ASSOCIATED WITH SERUM ANTIOXIDANTS AS A MARKER OF OXIDATIVE STRESS?

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Review

Free Radic Res 2004;38:535-9

Is Serum Gamma Glutamyltransferase a Marker of Oxidative Stress?

DUK-HEE LEE[a,*], RUNE BLOMHOFF[b] and DAVID R. JACOBS Jr.[b,c]

[a]*Department of Preventive Medicine and Health Promotion Research Center, School of Medicine, Kyungpook National University, Daegu, South Korea;* [b]*Institute for Nutrition Research, University of Oslo, Oslo, Norway;* [c]*Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis Minnesota, USA*

Accepted by Professor B. Halliwell

(Received 4 February 2004; In revised form 8 March 2004)

The primary role of cellular gamma glutamyltransferase (GGT) is to metabolize extracellular reduced glutathione (GSH), allowing for precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis. Paradoxically, recent experimental studies indicate that cellular GGT may also be involved in the generation of reactive oxygen species in the presence of iron or other transition metals. Although the relationship between cellular GGT and serum GGT is not known and serum GGT activity has been commonly used as a marker for excessive alcohol consumption or liver diseases, our series of epidemiological studies consistently suggest that serum

CELLULAR GAMMA GLUTAMYLTRANSFERASE (GGT) AND OXIDATIVE STRESS: EXPERIMENTAL EVIDENCE

There is evidence that cellular GGT plays an important role in antioxidant defense systems.[1–3] This enzyme is widely distributed in the human body, especially in kidney and liver, and is frequently localized to the plasma membrane with its active site directed into the extracellular space.[4]

A Strong Secular Trend in Serum Gamma-Glutamyltransferase from 1996 to 2003 among South Korean Men

Duk-Hee Lee[1], I
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Although oxidative stress has b
based on *in vitro* experiments c
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mium levels with oxidative s
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Nutrition Examination Survey.
the case of serum carotenoids

Letter to the Editor

Arterioscler Thromb Vasc Biol 2008;28:e26-8

Is Serum Gamma-Glutamyltransferase a Biomarker of Xenobiotics, Which Are Conjugated by Glutathione?

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Is serum gamma-glutamyltransferase a marker of exposure to various environmental pollutants?

Free Radic Res 2009;43:533-7

DUK-HEE LEE[1] & DAVID R. JACOBS JR[2,3]

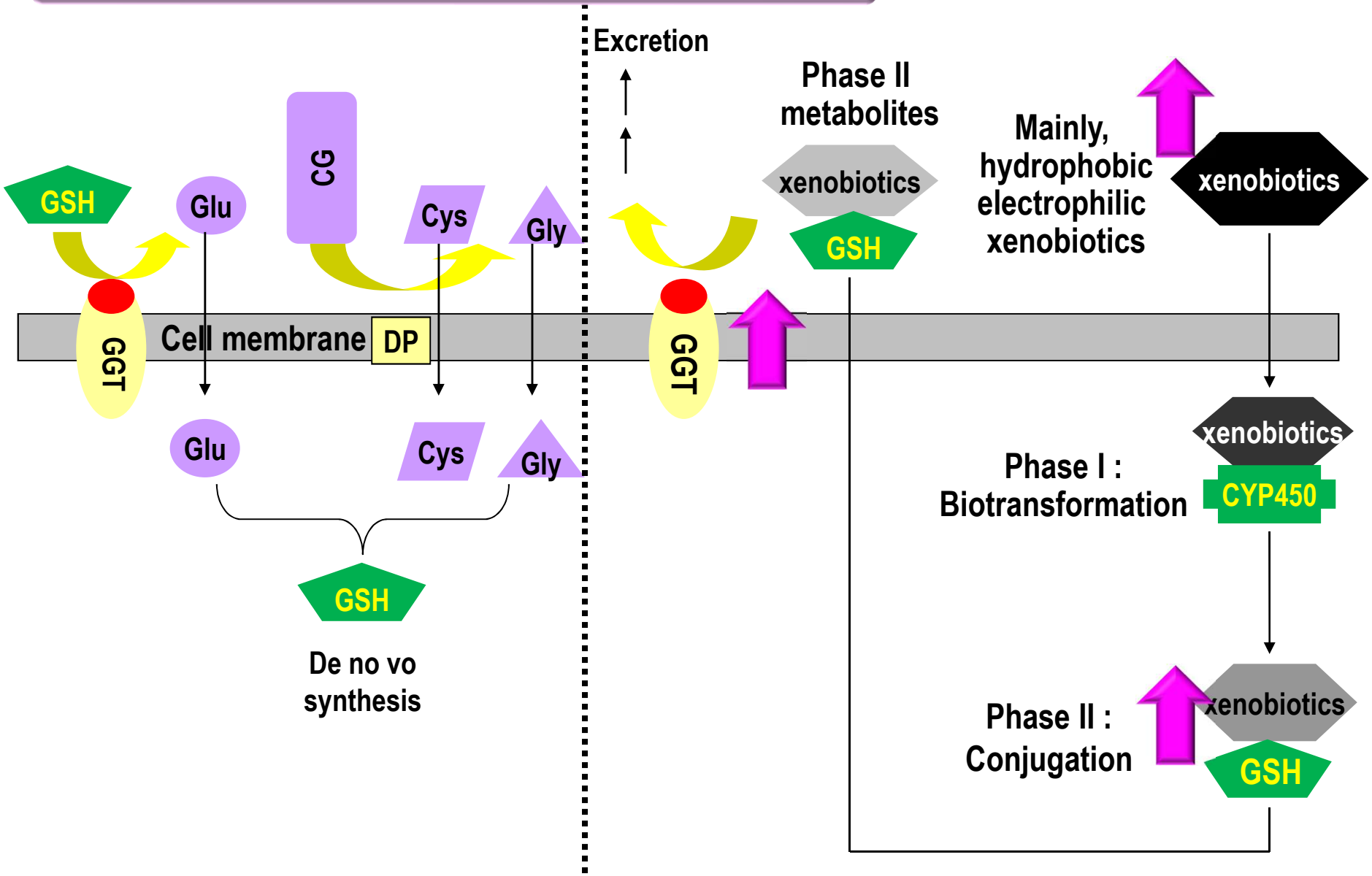
[1]*Department of Preventive Medicine, School of Medicine, Kyungpook National University, Daegu, Korea,* [2]*Division of Epidemiology, School of Public Health, University of Minnesota, Minnesota, USA, and* [3]*Department of Nutrition, University of Oslo, Oslo, Norway*

(Received 25 November 2008; revised 11 March 2009)

Abstract

It was previously hypothesized that serum gamma-glutamyltransferase (GGT) within its reference range predicts various clinical outcomes as a sensitive marker of oxidative stress in humans. This study further hypothesizes that serum GGT can mark exposure to various environmental pollutants, based both on recent epidemiological findings and on well-established biochemical features of cellular GGT. Cellular GGT is a prerequisite for metabolism of GSH conjugates that detoxify xenobiotics to mercapturic acid. Under this concept, serum GGT may increase with increasing exposure to environmental pollutants which need to be conjugated to GSH. Supporting this concept, it was recently reported that serum GGT within its reference range was linearly associated with important environmental pollutants, including lead, cadmium, dioxin and organochlorine pesticides. As a marker of the amount of conjugated xenobiotics, recent epidemiological findings about serum GGT imply the possibility of harmful effects of various environmental pollutants at background levels currently regarded as safe.

Comparison of two concepts on GGT



Lee DH, et al. Diabetologia 2008:51:402-7

The hypothesis on GGT and xenobiotics means... ★★★

- The induction of GGT due to the exposure to xenobiotics is *normal physiological response* of our body for the excretion of xenobiotics, *not any toxicity* due to xenobiotics

- The GGT induction occurs *at any dose of xenobiotics*

- Therefore, epidemiological findings on serum GGT within normal range suggest the *possible harmfulness of very low dose of mixed xenobiotics which we currently believe safe*

식품에서 발생하는 결합형 물질 위험한가?

[뉴스캔] 2009년 03월 23일(월) 오전 10:58 가 가 | 이메일 | 프린트

【아시아 데일리】 식품
로 일부 전환될 가능성이
에 따라 사전예방적 식품
니터링을 실시한 결과, 우

결합형 3-MCPD는 지방
며 결합형 3-MCPD의 우
환될 가능성이 있다.

3-MCPD(3-Monochlor
식품제조과정 중 생성되
등에서 검출된다.

아울러 결합형 3-MCPD
등 총 109건에 대하여 3
결과 3-MCPD는 식용유
가공품(3건), 수산물가공
간장의 허용기준인 0.3

국산 마늘·당근서 국제기준치 초과 납등 중금속 검출

[서울경제] 2009년 03월 16일(월) 오후 05:23 가 가 | 이메일 | 프린트

일부 국산 마늘과 당근에서 ㅎ

식품의약품안전청은 지난해
·참깨 등 7종류 450건에 대
당근 1건에서 국제식품규격위
고 16일 밝혔다.

마늘의 경우 0.055~0.063㎎/
섰으며 당근에서도 코덱스 기
재 이들 7종 농산물의 납
없고 EU 정도만이 코

식약청의 한 관계자는 "이번
으로 나타
물의 중
모니

고추장등 발효식품서 발암물질 '에틸카바메이트' 검출

[이투데이] 2009년 03월 09일(월) 오전 11:40 가 가 | 이메일 | 프린트

[이투데이] 조상희 기자(mo @e-today.co.kr)
고추장 등 발효식품에서 발암성 물질 '에틸카바메이트'가 검출됐다
식품의약품안전청은 발효식품 중 발효과정에서 자연적으로 생성되는 유해물질인 에틸카바메이트에 대한 안전성 확보를 위해 '발효식품 중 에틸카바 메이트 실태조사 및 위해평가' 를 실시한 결과 장류, 김치류, 젓갈류 등 발효식품 218건 중 29건에서 에틸카바메이트가 검출됐다고 9일 밝혔다. 다만 김치류, 젓갈류, 치즈에서는 검출되지 않았다.

식약청은 다른 날짜에 생산된 같은 회사 제품에 대해 추가검사를 실시한 결 에틸카바메이트가 검출되지 않았다고 밝혔다.

에틸카바메이트는 유방암과 대장암 관련 발암성 물질로, 국제암연구소(IARC) 발암물질 등급 가운데 두 번째인 '발암물질로 추정되는(probable)' 등급에 속한다.

식품별로는 고추장 등 장류가 16건으로 가장 많았으며 식초류가 11건, 빵류가 2건이었다.

지난해 식약청이 마련한 와인의 에틸카바메이트 허용기준안 30ppb와 비교할해보면 이번 조사에서 검출된 고추장의 에틸카바메이트량은 적지 않은 수준이다.

식약청 관계자는 "위해도 평가결과 유통중인 발효식품은 대부분 에틸카바메이트가 검출되지 않았고 존재하더라도 미미한 수준이므로 인체에 유해하지 않다"고 설명하고 "발효식품의 안전성을 확보하기 위해 지속적으로 모니터링을 실시할 것"이라고 밝혔다.

허용기준이내 OK??

What kinds of xenobiotics can explain the association between serum GGT and type 2 diabetes?

Considering previous epidemiological findings on serum GGT, they need to satisfy several conditions….

- Exposure through food consumption, especially meat intake
- Associated with adipose tissue
- Metabolism by glutathione conjugation
- Associated with an increase of serum GGT
- If any, it can be diabetogenic in *in*-vitro experiments

THEN…the answer is….

What are Persistent Organic Pollutants (POPs)?

- POPs include hundreds of different chemical compounds with common properties

  - long term persistence in the environment
  - bioaccumulation in fatty tissues of living organisms
  - travel long distances in global air and water current

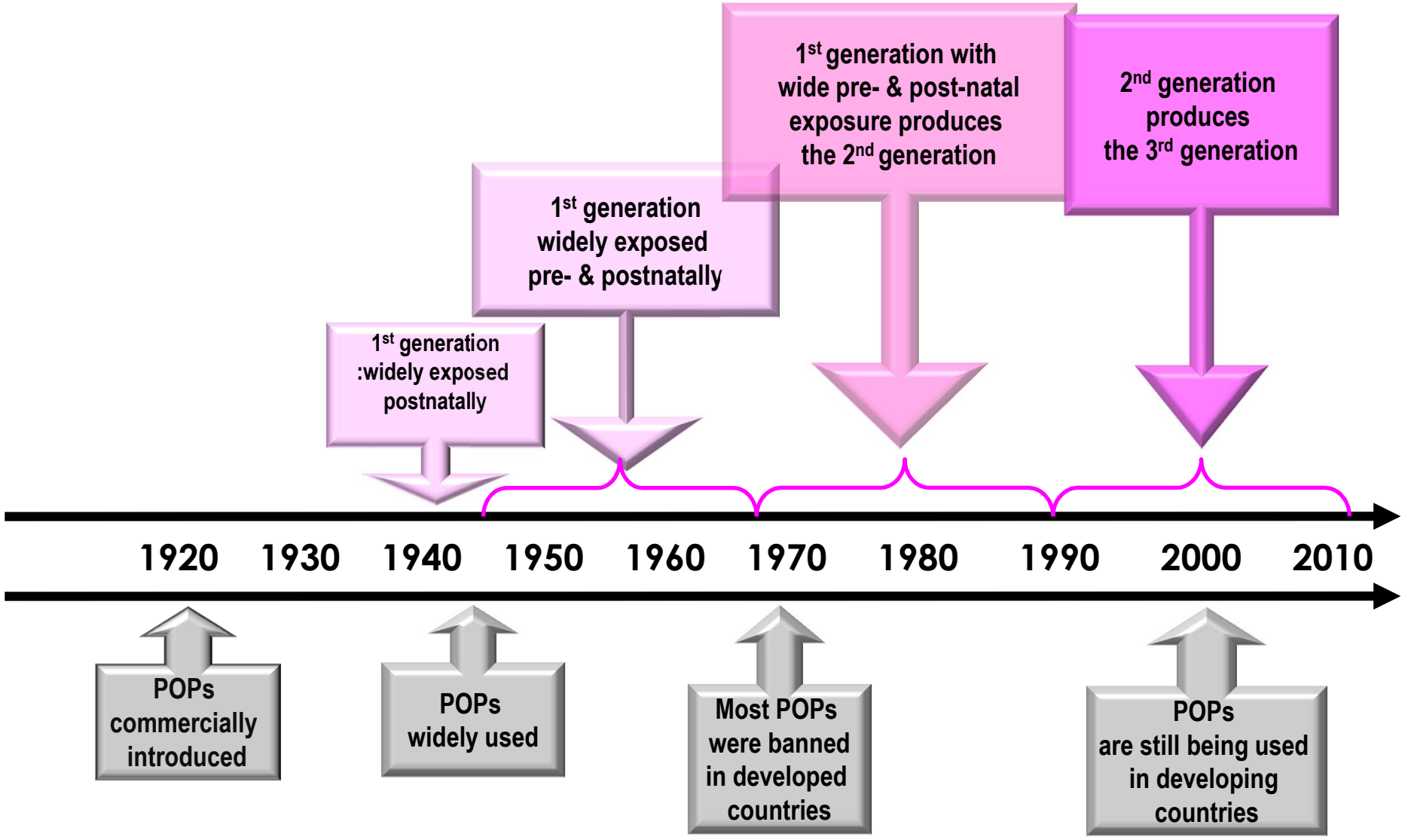
- Main groups of POPs

  - Organochlorine pes[Banned]C pesticides)
  - Polychlorinated biphenyls (PCBs)[Banned]
  - Polychlorinated dibenzo-p-dioxins and dibenzofurans ([Strictly regulated]CDFs)

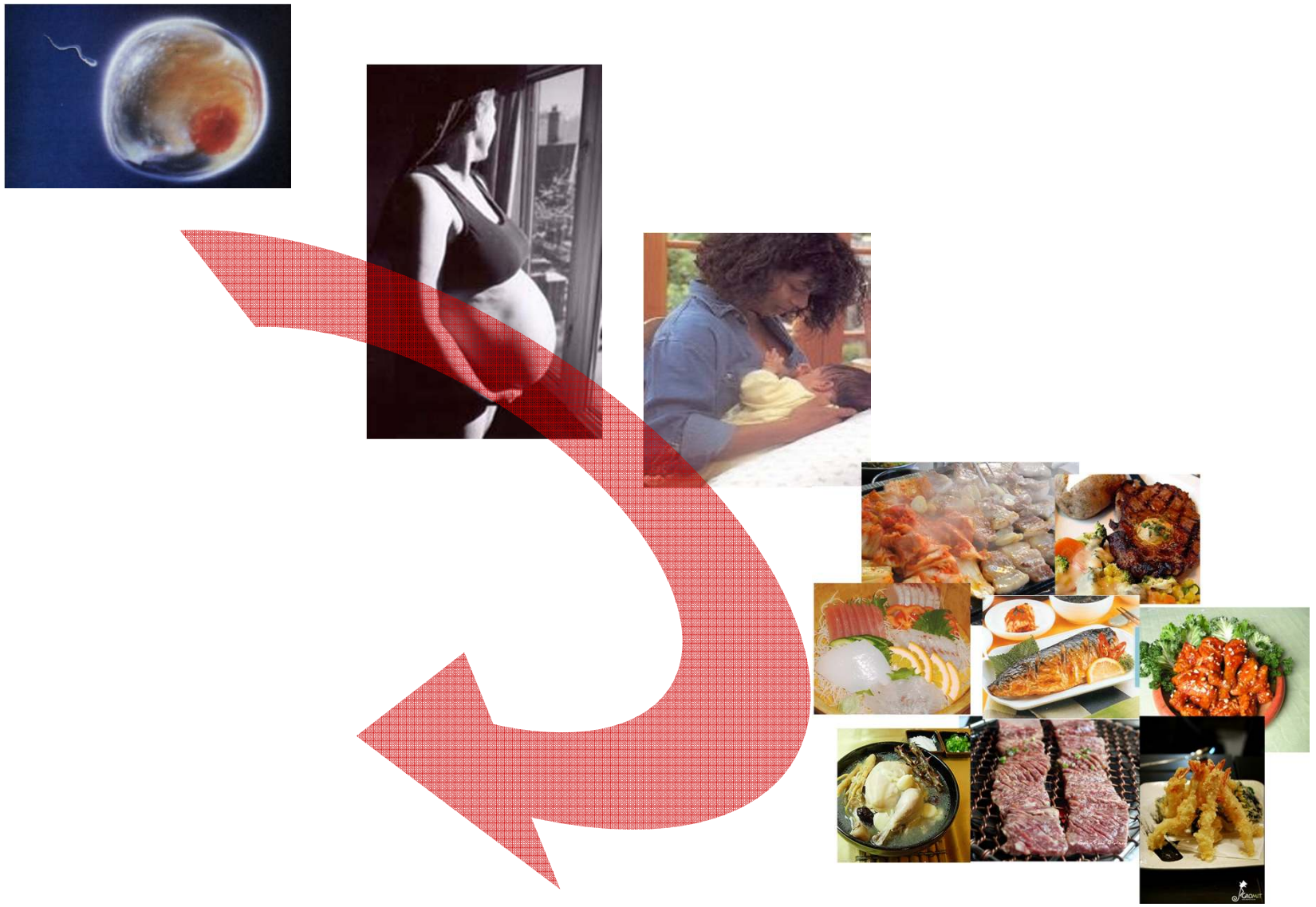
- POPs are detectable in virtually all of the general population

- Humans are generally exposed to POPs through their food consumption

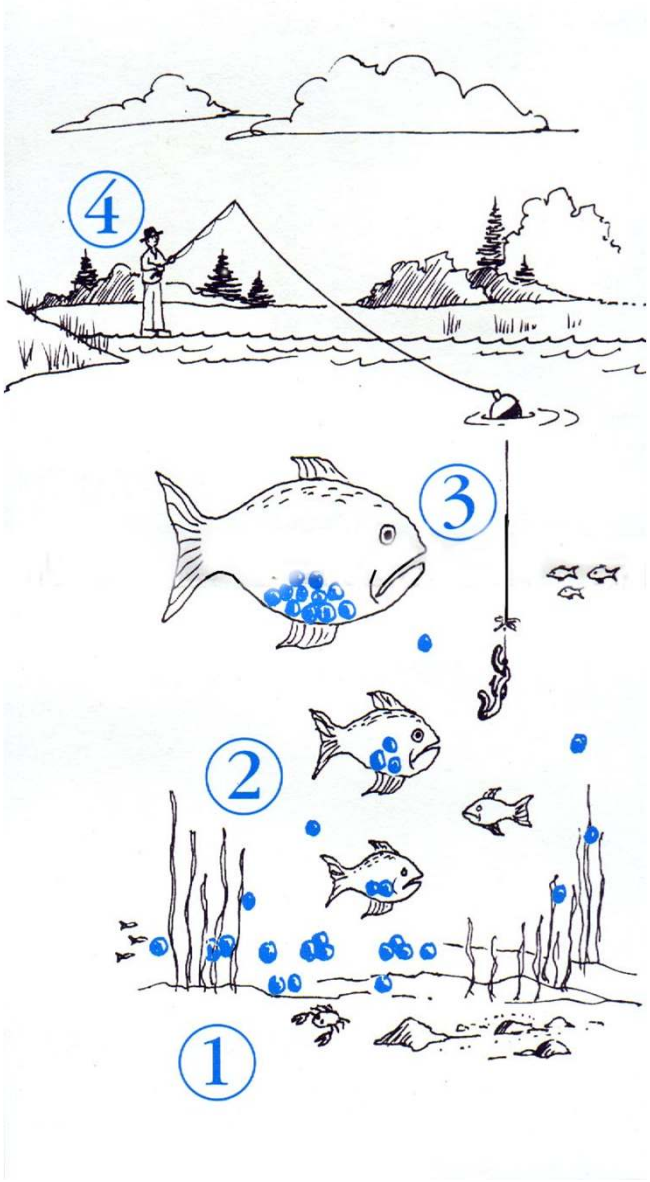
Chronology of human exposure to POPs

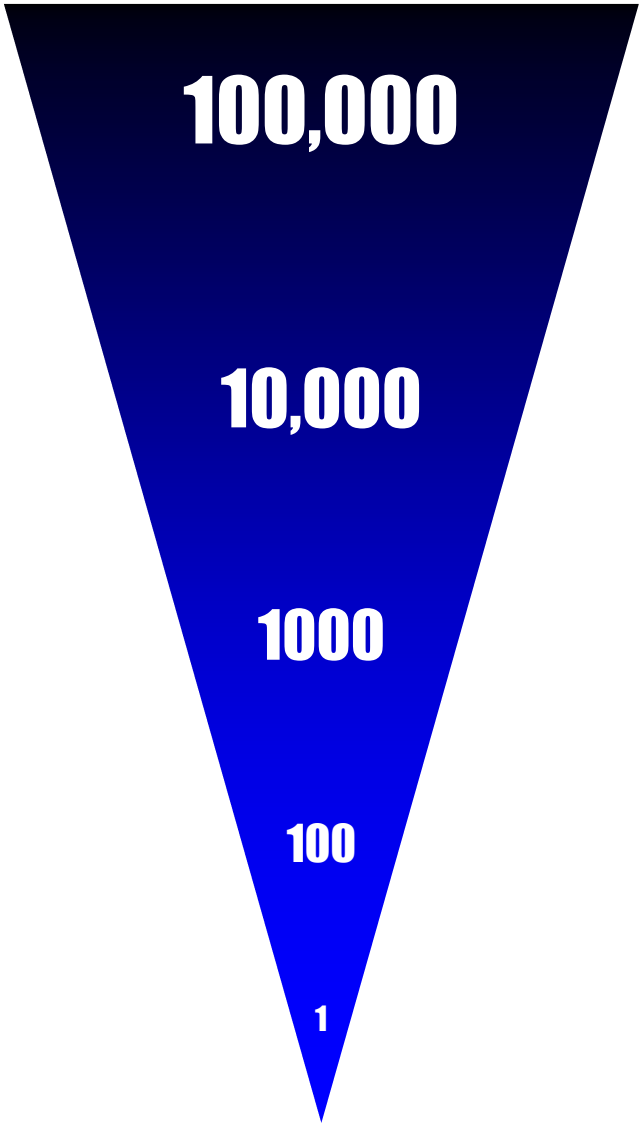


Exposure to POPs begins at conception and continued during gestation and breastfeeding……..

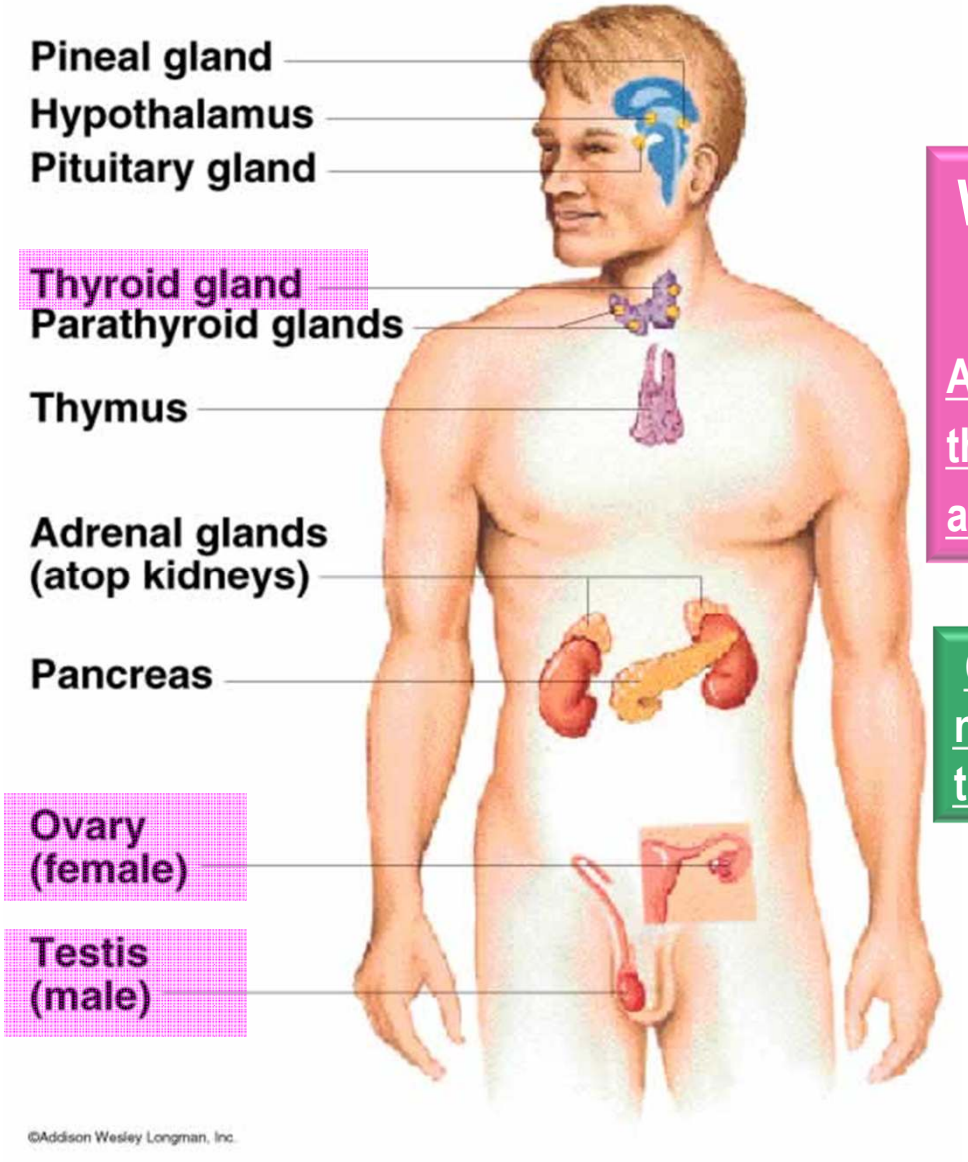


Bioaccumulation of POPs in food chains





POPs are endocrine disrupters



What are endocrine disrupters?

Any exogenous chemical which can interfere the synthesis, secretion, transport, binding, action, or elimination of any natural hormone

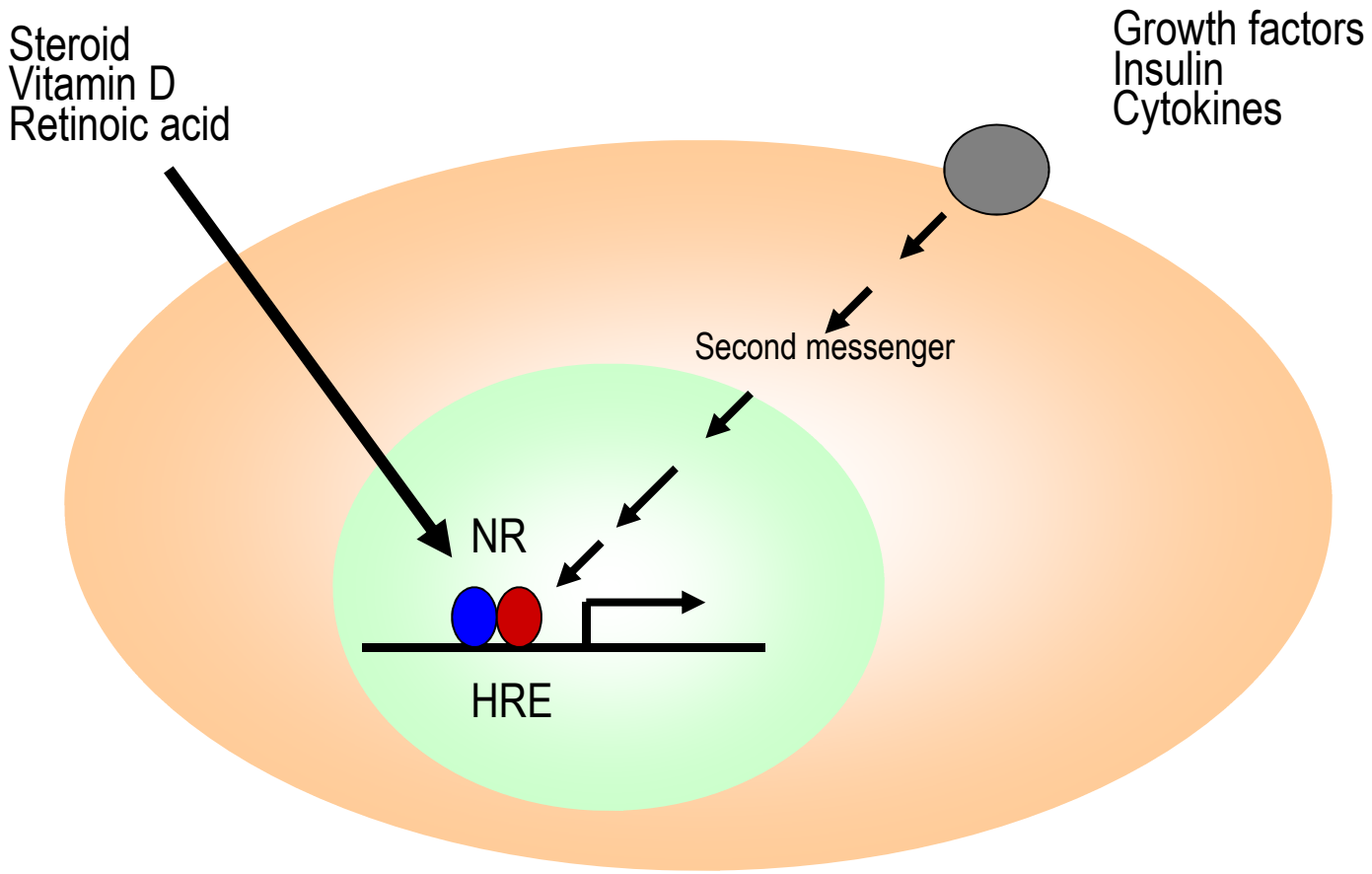
Our body is essentially a communication network that consists of hormones, the glands that produce them, and receptors

Endocrine system regulates..

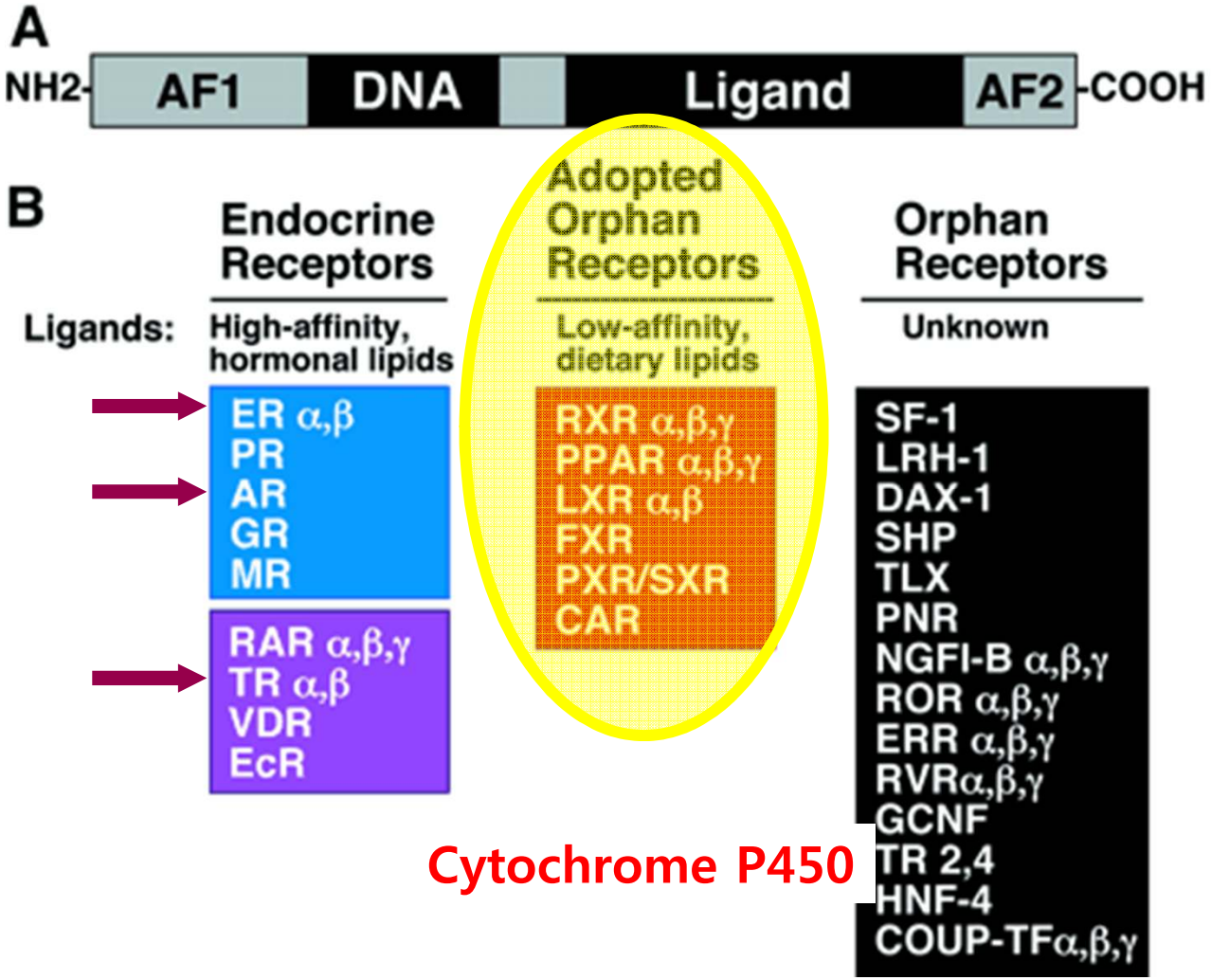
- **Reproduction**
- **Growth/development**
- **Metabolic function and equilibrium**
- **Immune system**

Development of many chronic diseases including metabolic syndrome, diabetes, autoimmune diseases, and cancer

Nuclear receptor vs. membrane receptor



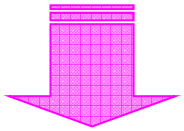
Nuclear receptor superfamily



Chawla A et al. Science 2001;294:1866-70

NHANES 1999-2002: measurement of 50 POPs in the U.S. general population

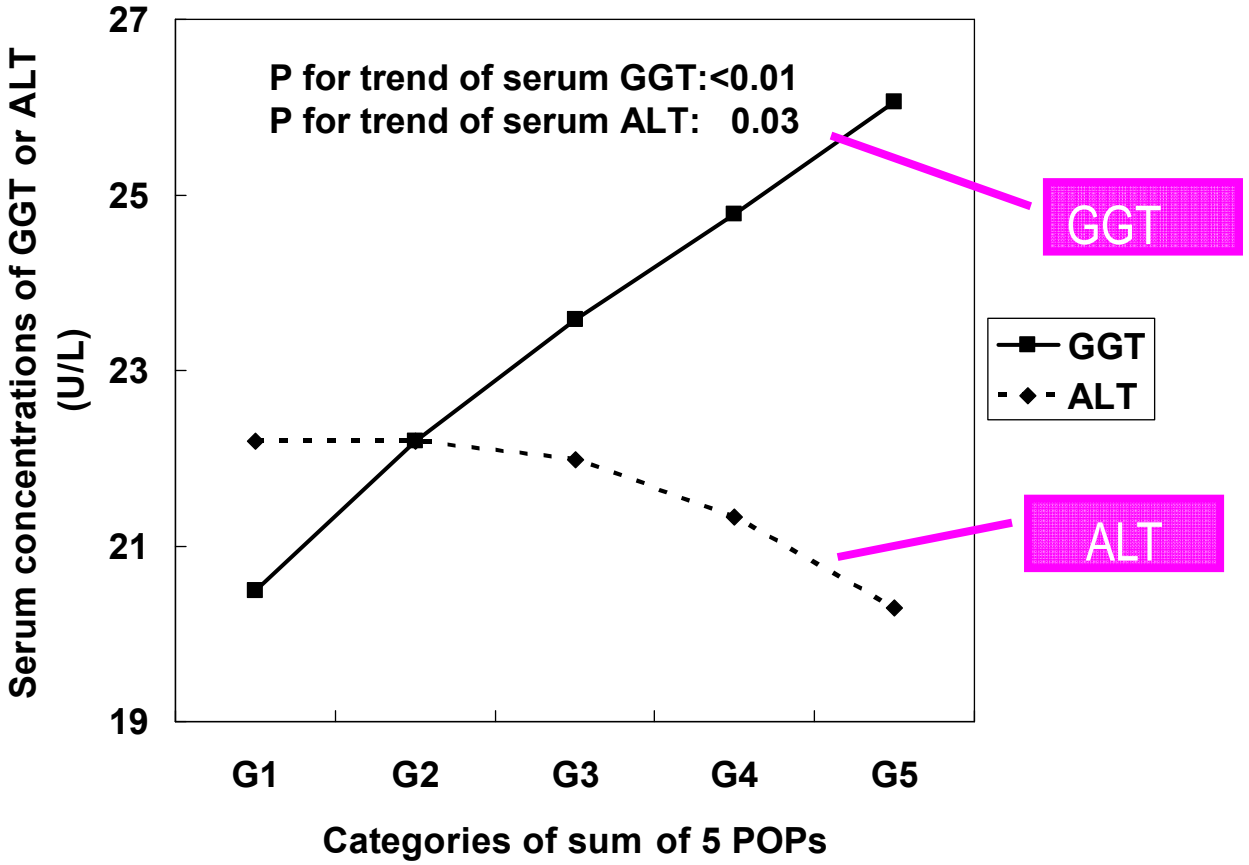
- Polychlorinated Dibenzo-p-dioxins (PCDDs)
- Polychlorinated Dibenzofurans (PCDFs)
- Dioxin-like PCBs
- Non-dioxin-like PCBs
- Organochlorine Pesticides



6 POPs which were detected among ≥ 80% of subjects

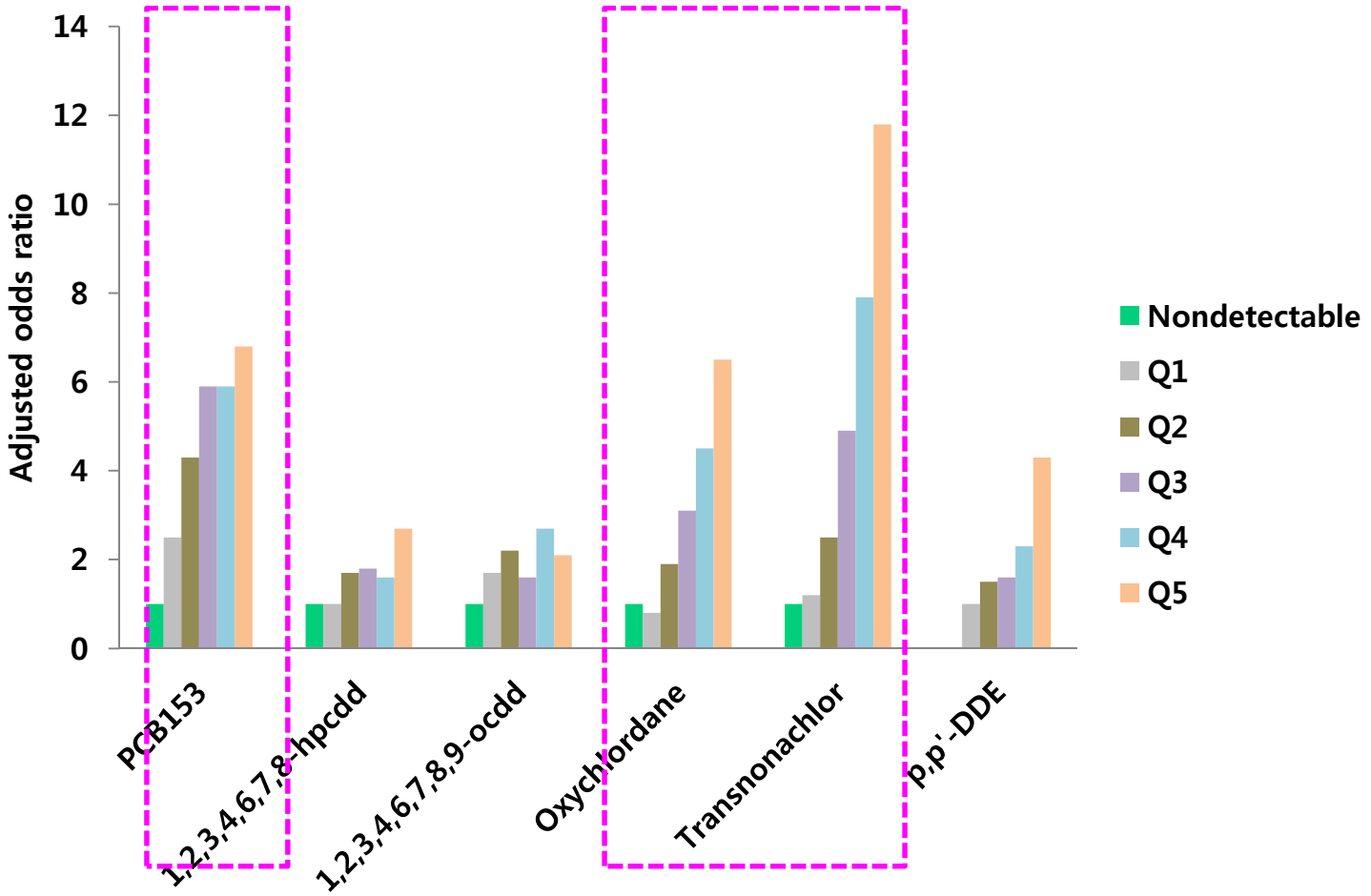
- 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) : banned in several decades ago
- 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin
- 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin
- oxychlordane : banned in several decades ago
- p,p'-DDE : banned in several decades ago
- trans-nonachlor : banned in several decades ago

Association of serum concentrations of POPs and GGT



Lee DH, et al. Clin Chem 2006;52:1825-6

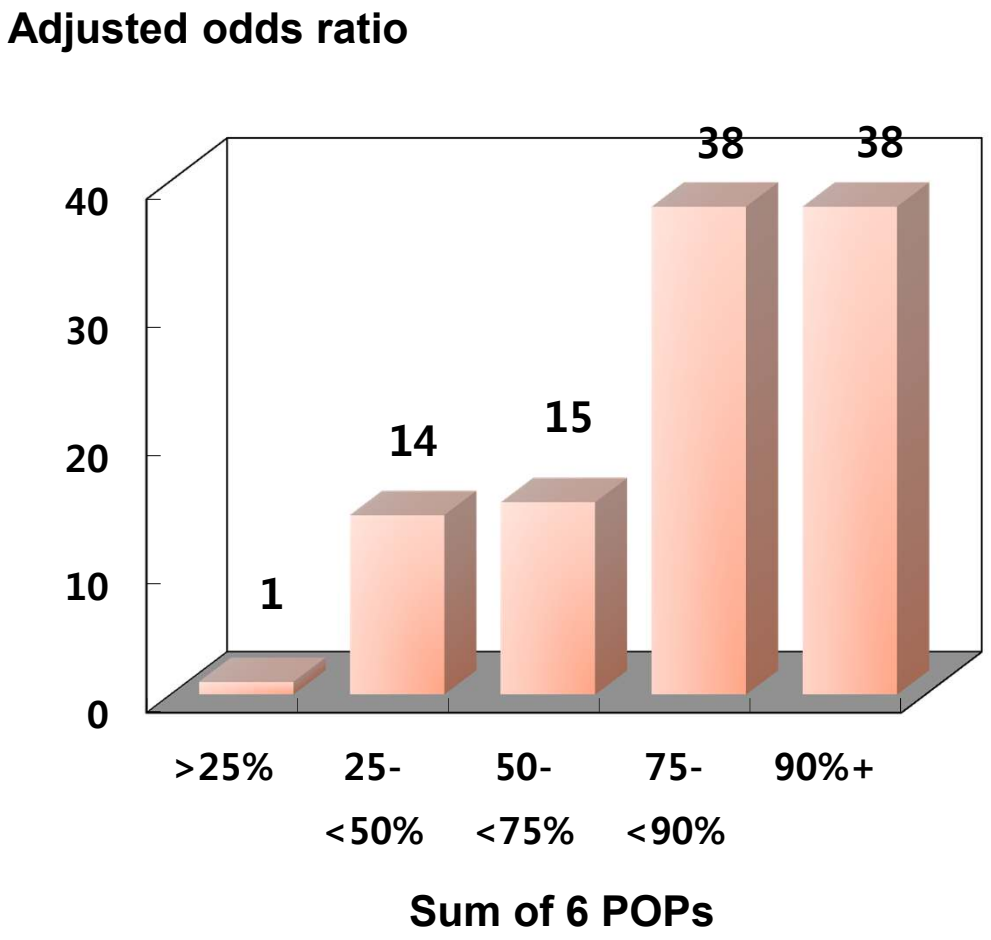
Associations between individual POPs and diabetes



† Adjusted for age, race, sex, poverty income ratio, body mass index, and waist circumference

Lee DH, et al. Diabetes Care 2006;29;1638-44

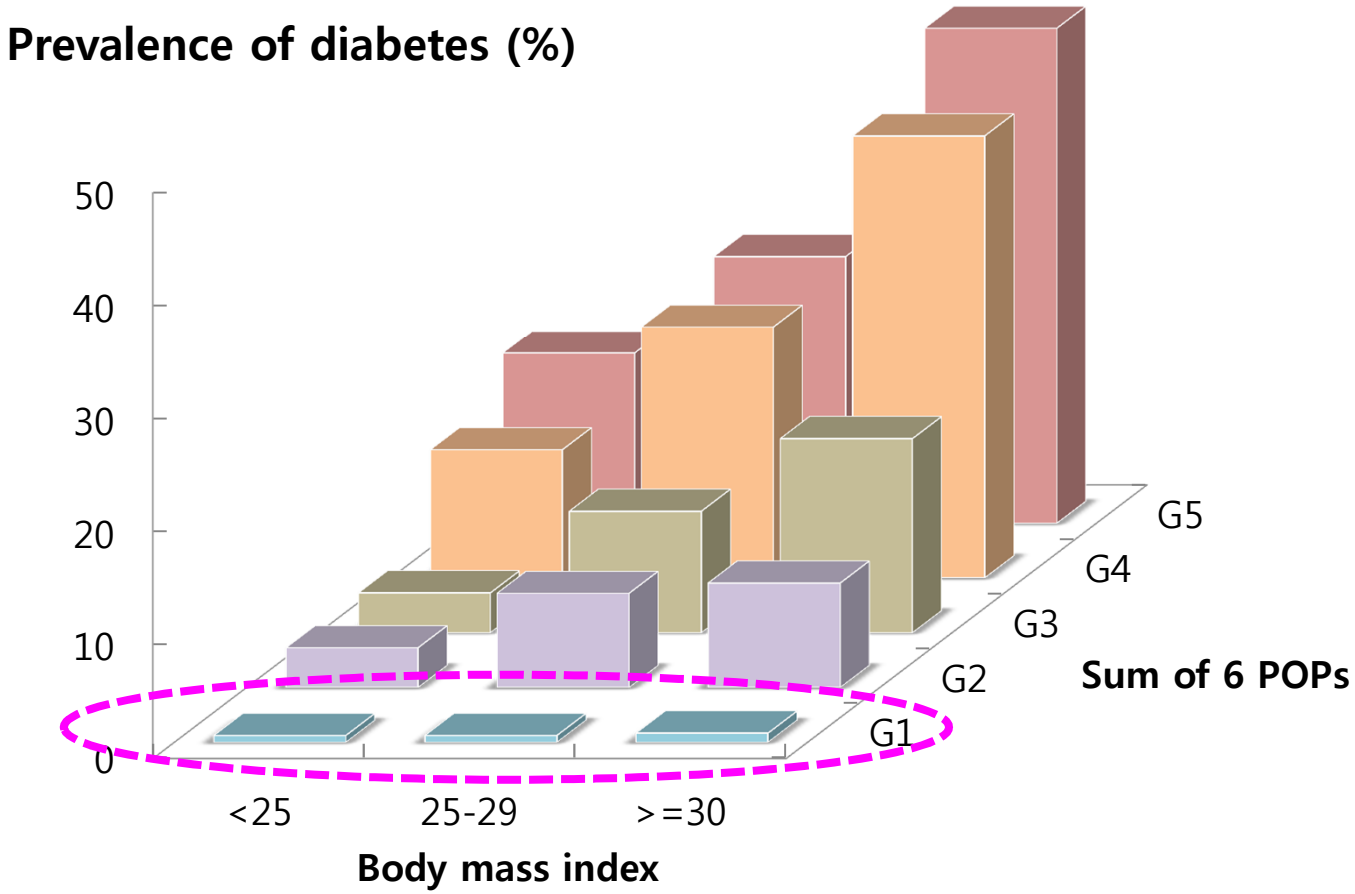
Summary measure of 6 POPs and diabetes



† Adjusted for age, race, sex, poverty income ratio, body mass index, and waist circumference

Lee DH, et al. Diabetes Care 2006;29;1638-44

Interaction between POPs and obesity on the risk of diabetes



† Adjusted for age, race, sex, poverty income ratio, body mass index, and waist circumference

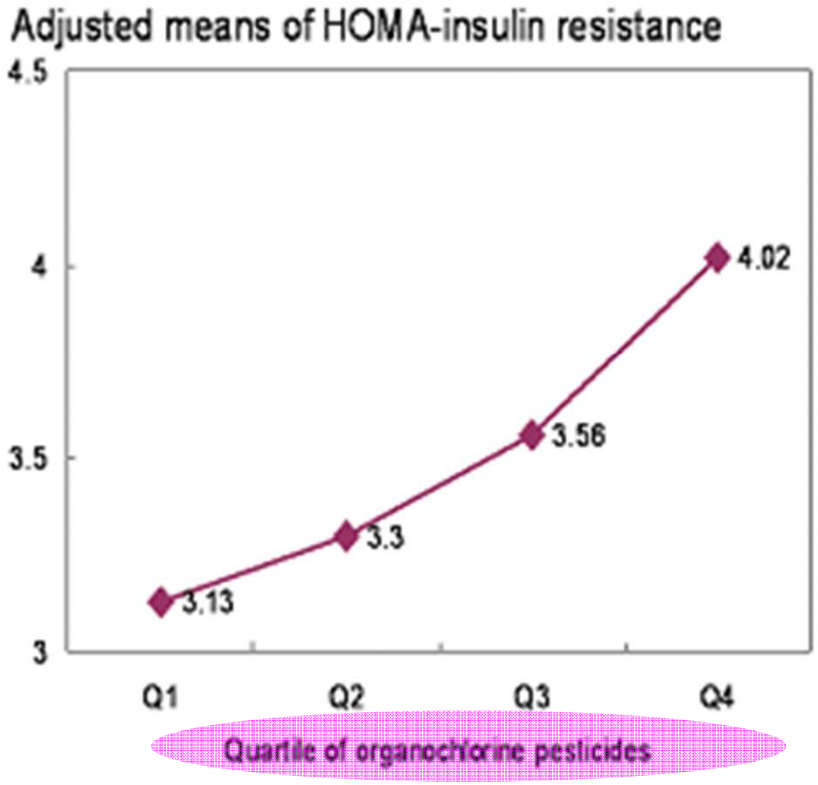
Lee DH, et al. Diabetes Care 2006;29;1638-44

Commentary in Lancet :
Persistent organic pollutants and the burden of diabetes

Another striking finding in Lee and co-workers' study is that there was no association between obesity and diabetes in individuals with non-detectable levels of persistent organic pollutants. Obesity was a risk factor for diabetes only if people had blood concentrations of these pollutants above a certain level. This finding might imply that virtually all the risk of diabetes conferred by obesity is attributable to persistent organic pollutants, and that obesity is only a vehicle for such chemicals. This possibility is shocking. '

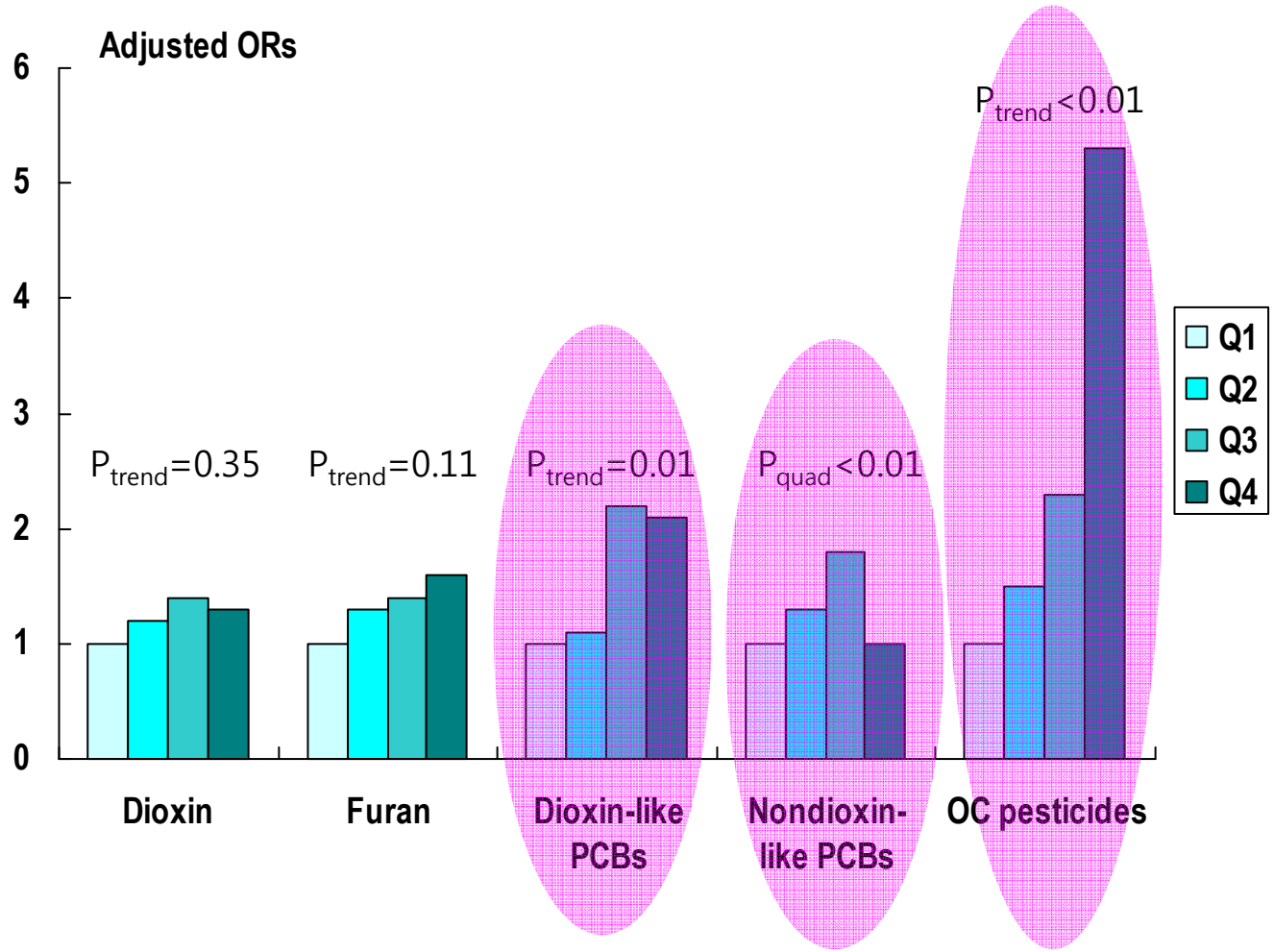
Porta M. Lancet 2006;368:558-9

POPs and insulin resistance among non-diabetes



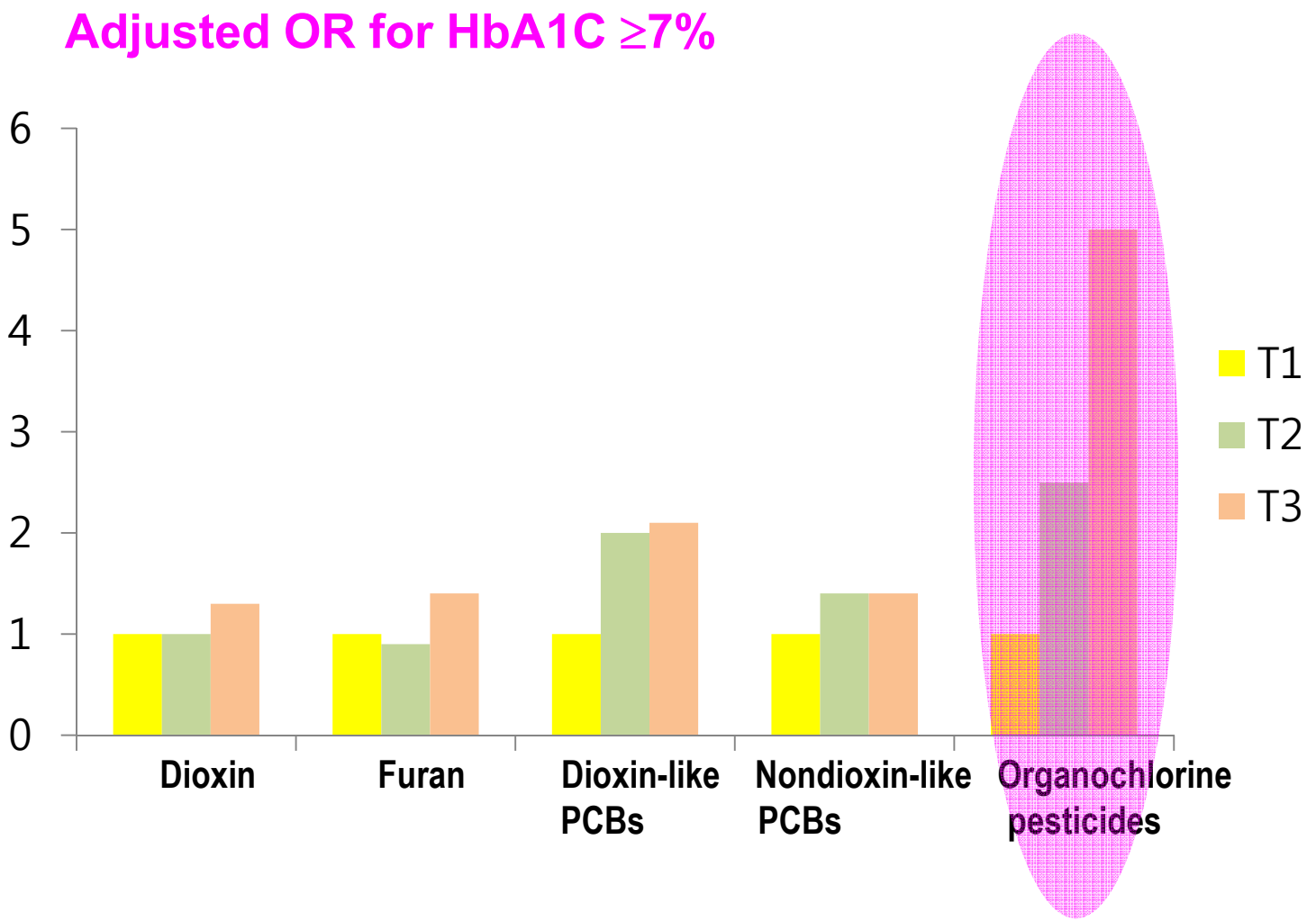
Lee DH, et al. Diabetes Care 2007;30;622-8

POPs and metabolic syndrome among non-diabetes



Lee DH, et al. Diabetologia 2007;50:1841-51

POPs and glycemic control in diabetic patients



Lee DH, et al. Diabetes 2008;57:3108-11

Critiques

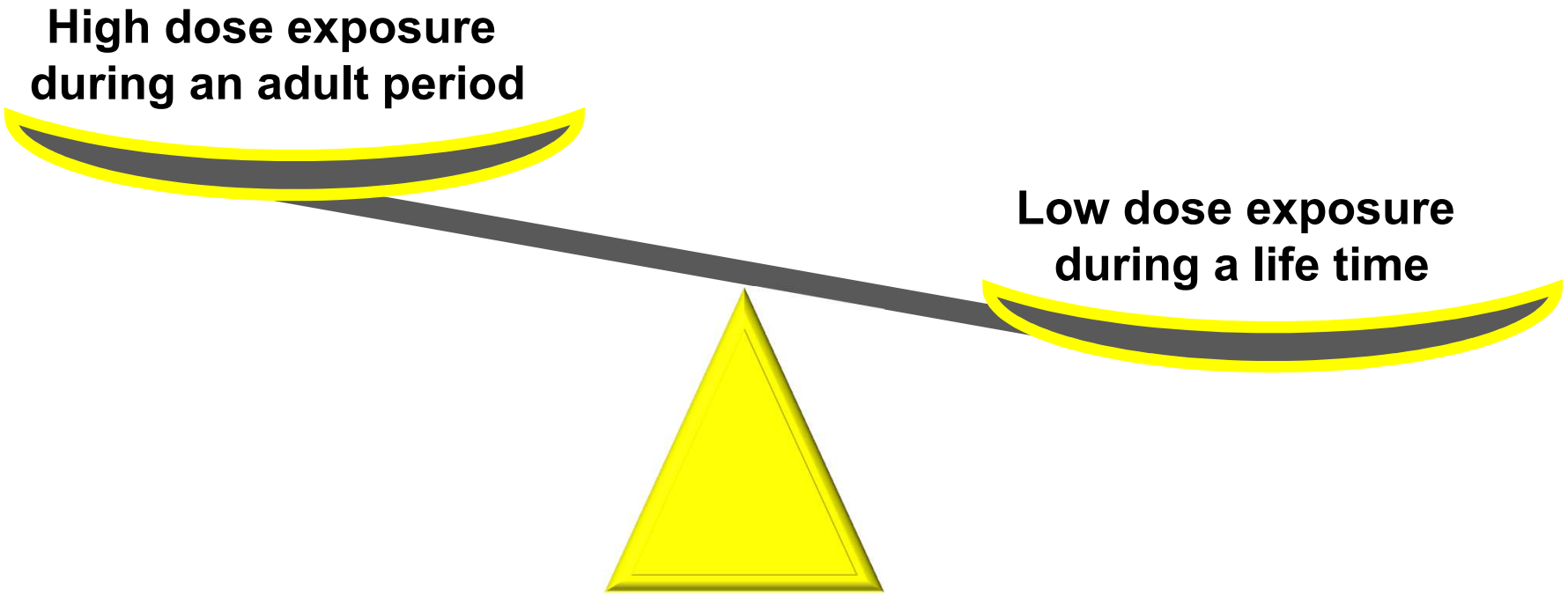
Q1 : Previous studies with high exposure to several selected POPs in occupational or accidental settings showed inconsistent or only weak associations.

When high dose exposure did not show clear associations, how could low dose exposure show such strong associations?

Q2 : Body burden of chlorinated POPs in human has been decreasing during recent several decades, but type 2 diabetes is currently epidemic

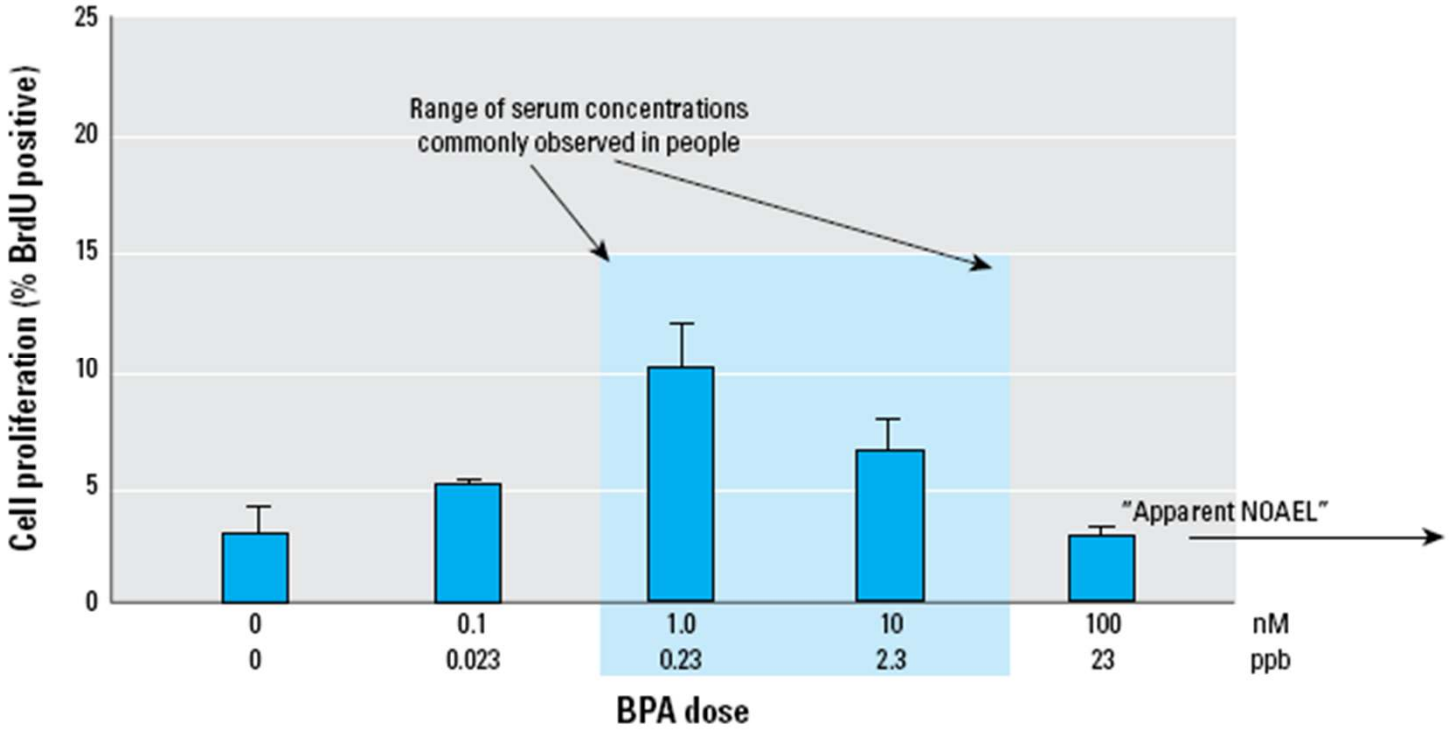
How this kind of discrepancy of time trend is possible, if chlorinated POPs are really important in the pathogenesis of type 2 diabetes?

First explanation: Dose? Duration? Time?



First explanation: Dose? Duration? Time?

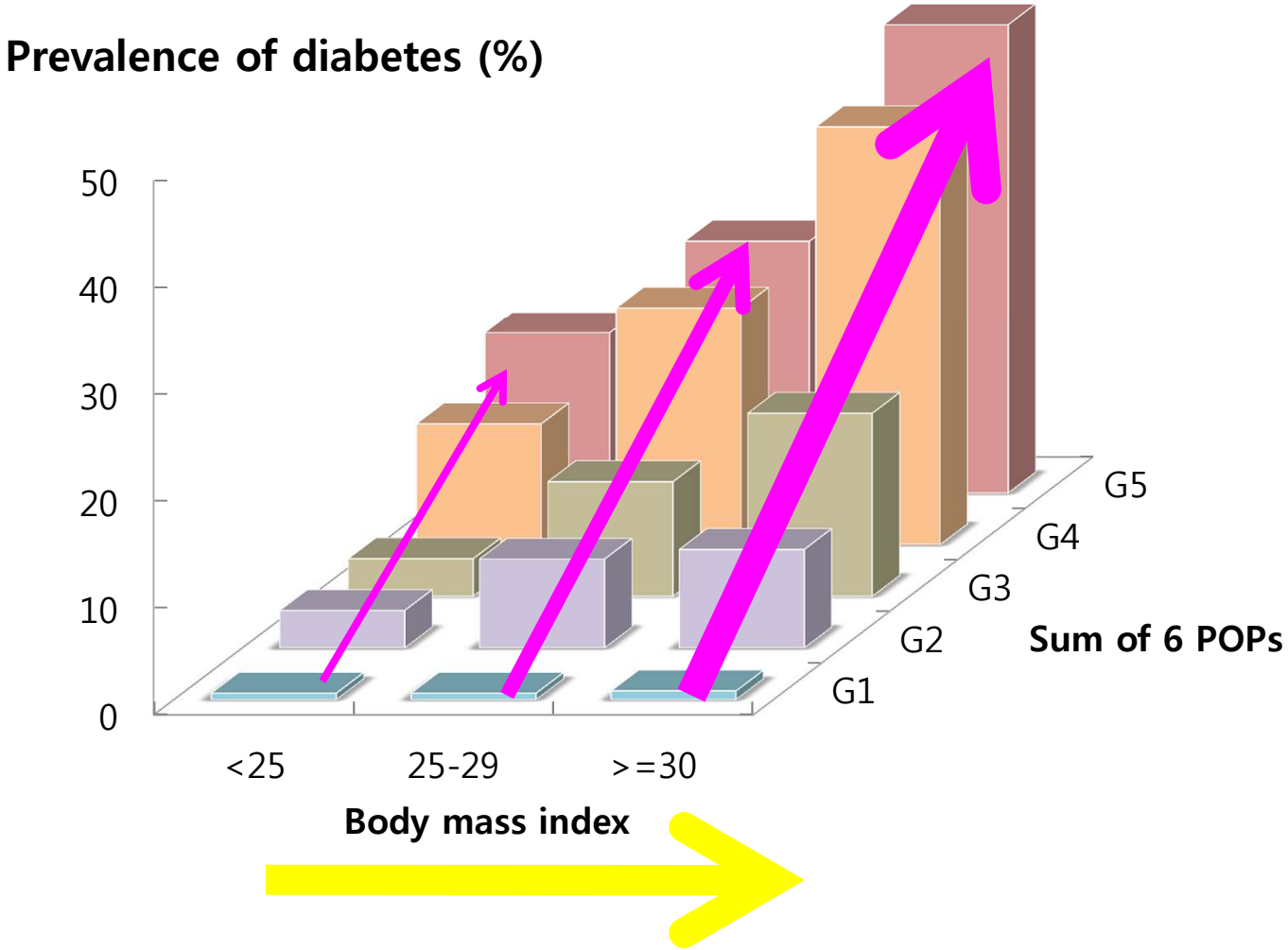
Low dose effects of POPs as endocrine disruptors??



Below NOAEL
(허용기준)

Myers JP, et al. Environ Health Perspect 2009;117:1652-5

Second explanation: Interaction with obesity??



Lee DH, et al. Diabetes Care 2006;29;1638-44

Second explanation: Interaction with obesity??

+

Proinflammatory status of adipose tissue

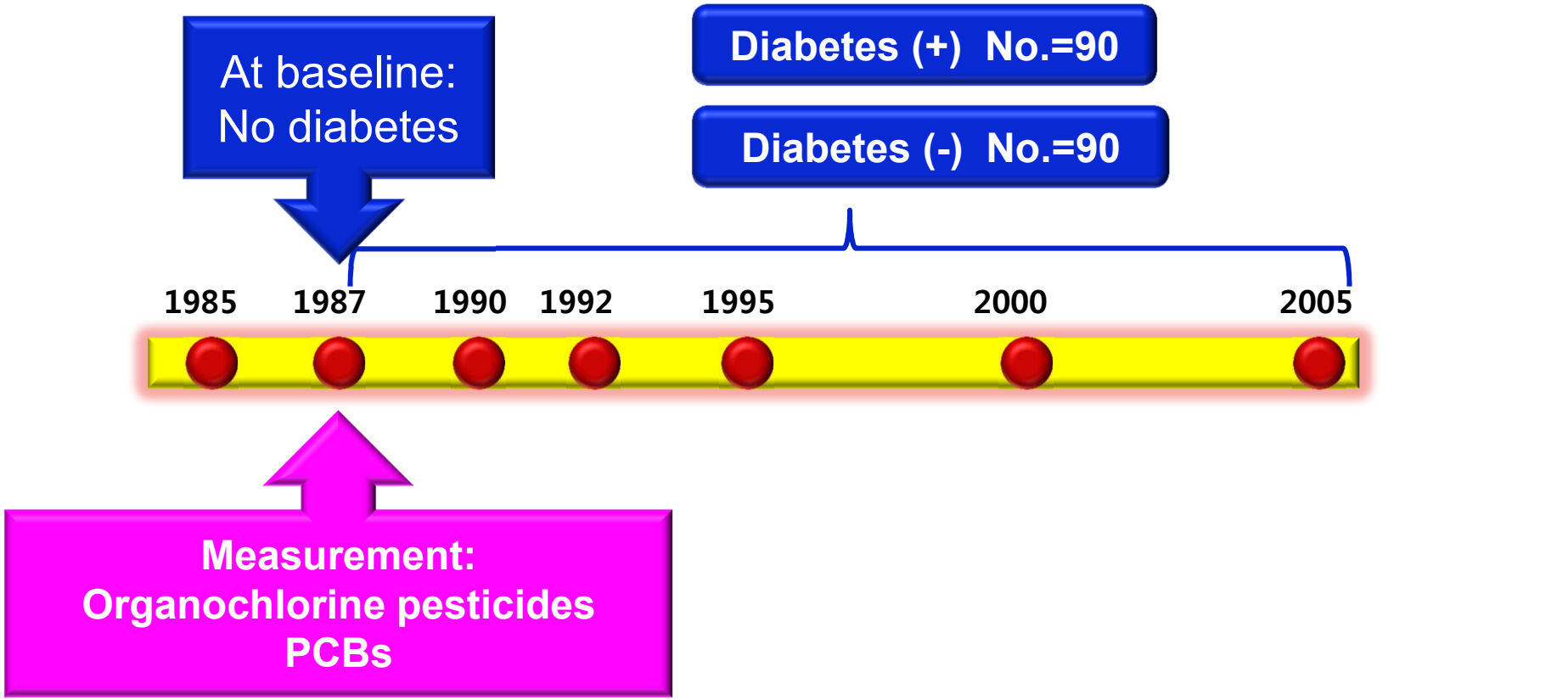
Inflammation is host **Protective** response to **xenobiotics**

Evidence from recent prospective studies : a nested case control CARDIA study

In collaboration with

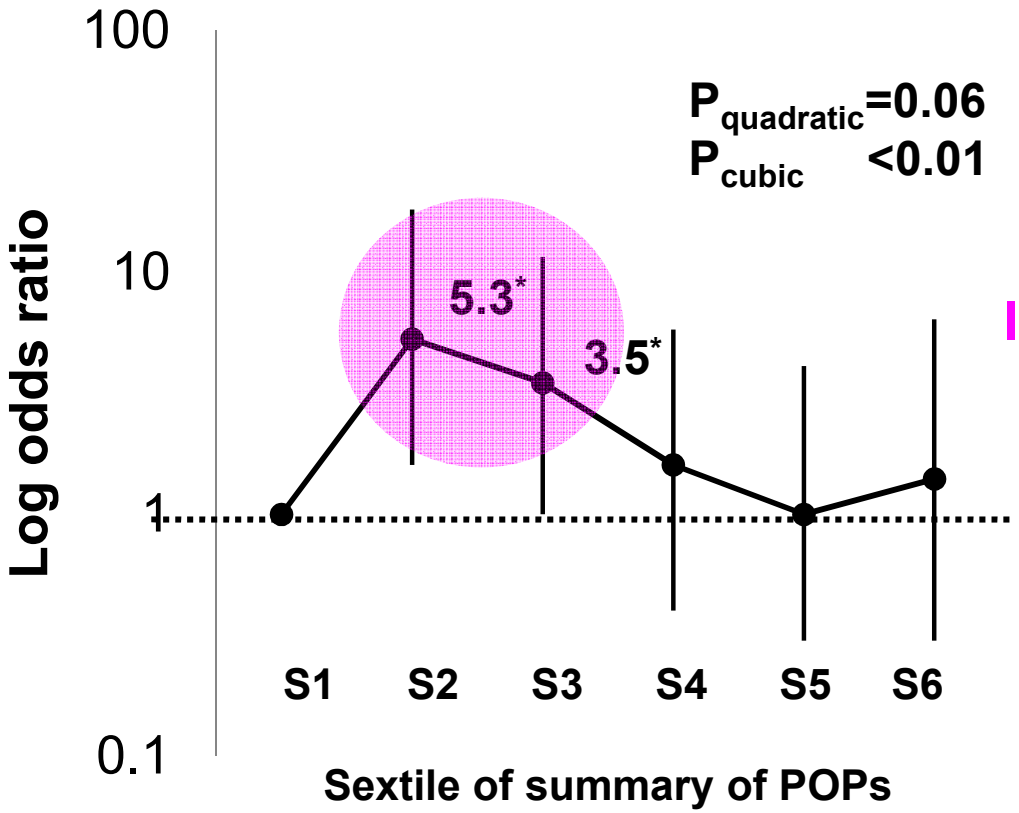
University of Minnesota: Jacobs DR, Steffes M

National Center for Environmental Health, CDC: Sjodin A, Jones RS, Needham LL



Lee DH et al. Environ Health Perspectives 2010

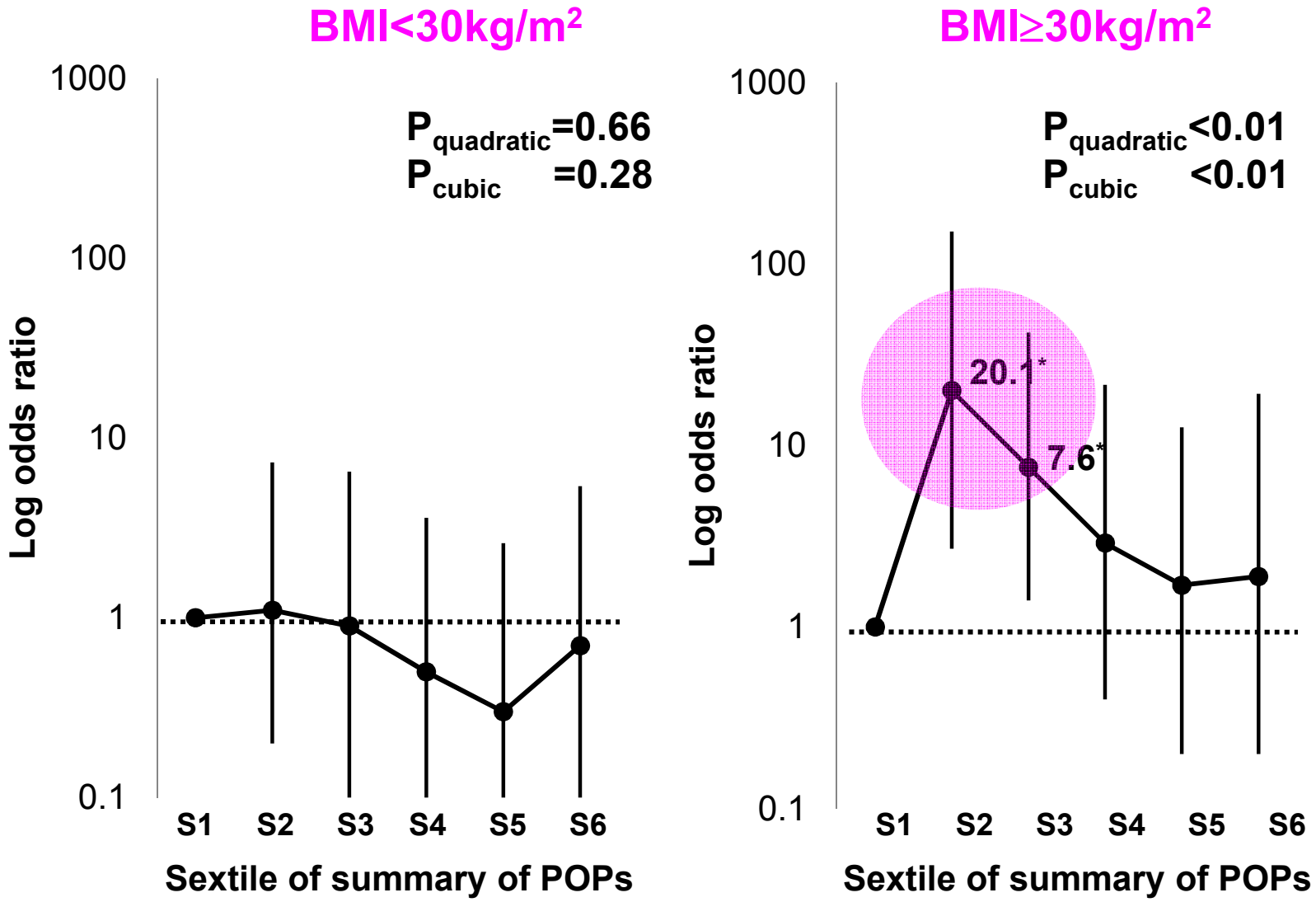
POPs and incident diabetes



Inverted U-shaped

Lee DH et al. Environ Health Perspectives 2010

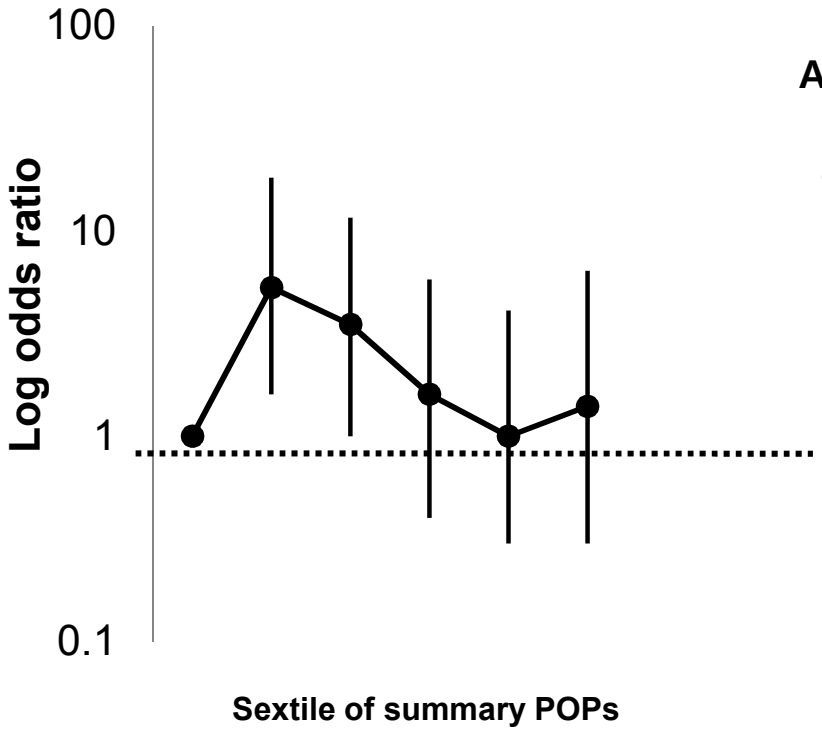
POPs, BMI, and incident diabetes



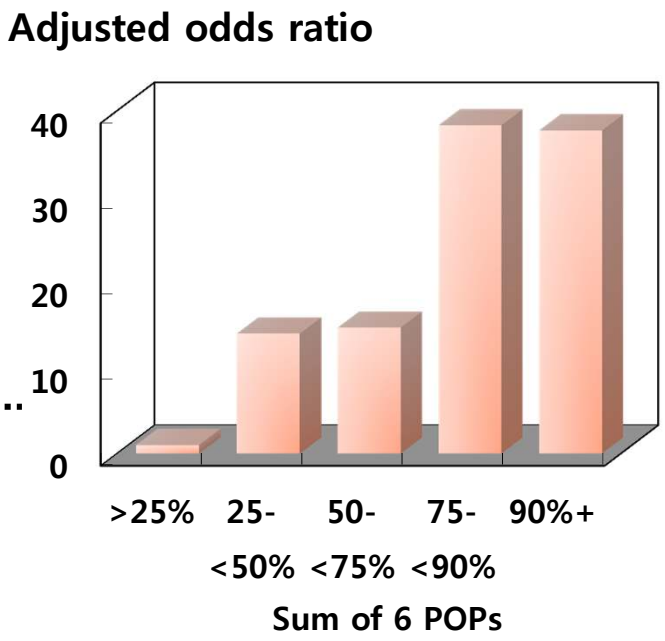
Lee DH et al. Environ Health Perspectives 2010

Why different dose response curves between the two studies?

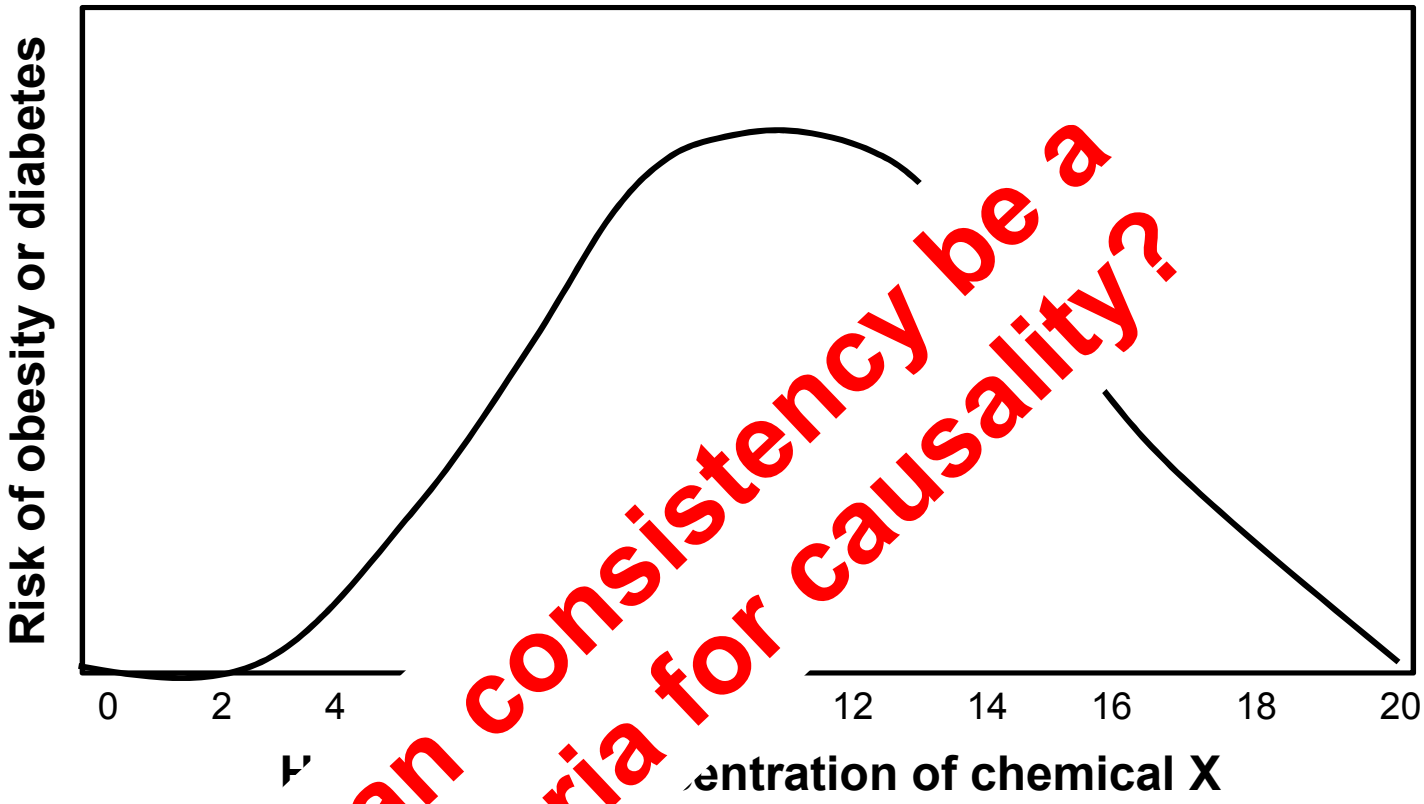
CARDIA study



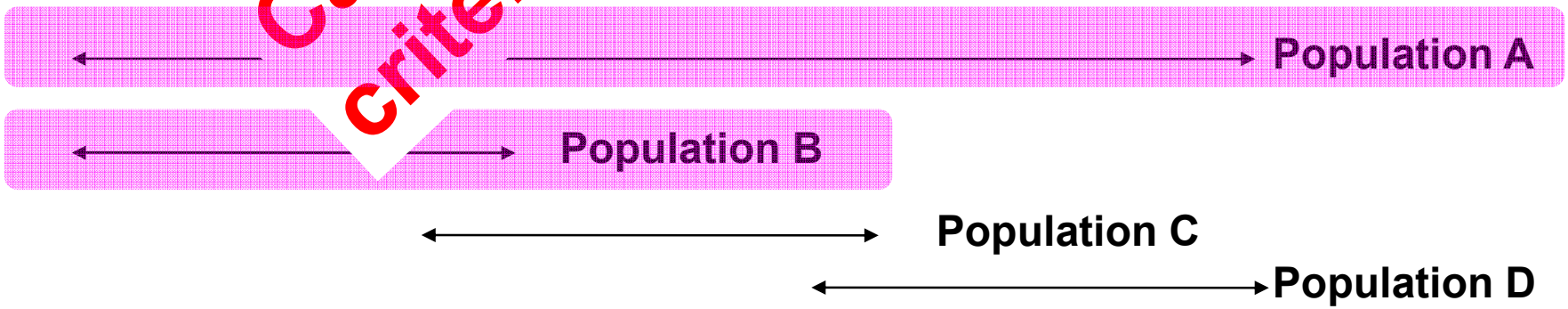
NHANES study



Different dose response curves in human studies



Can consistency be a criteria for causality?



Possible mechanisms??

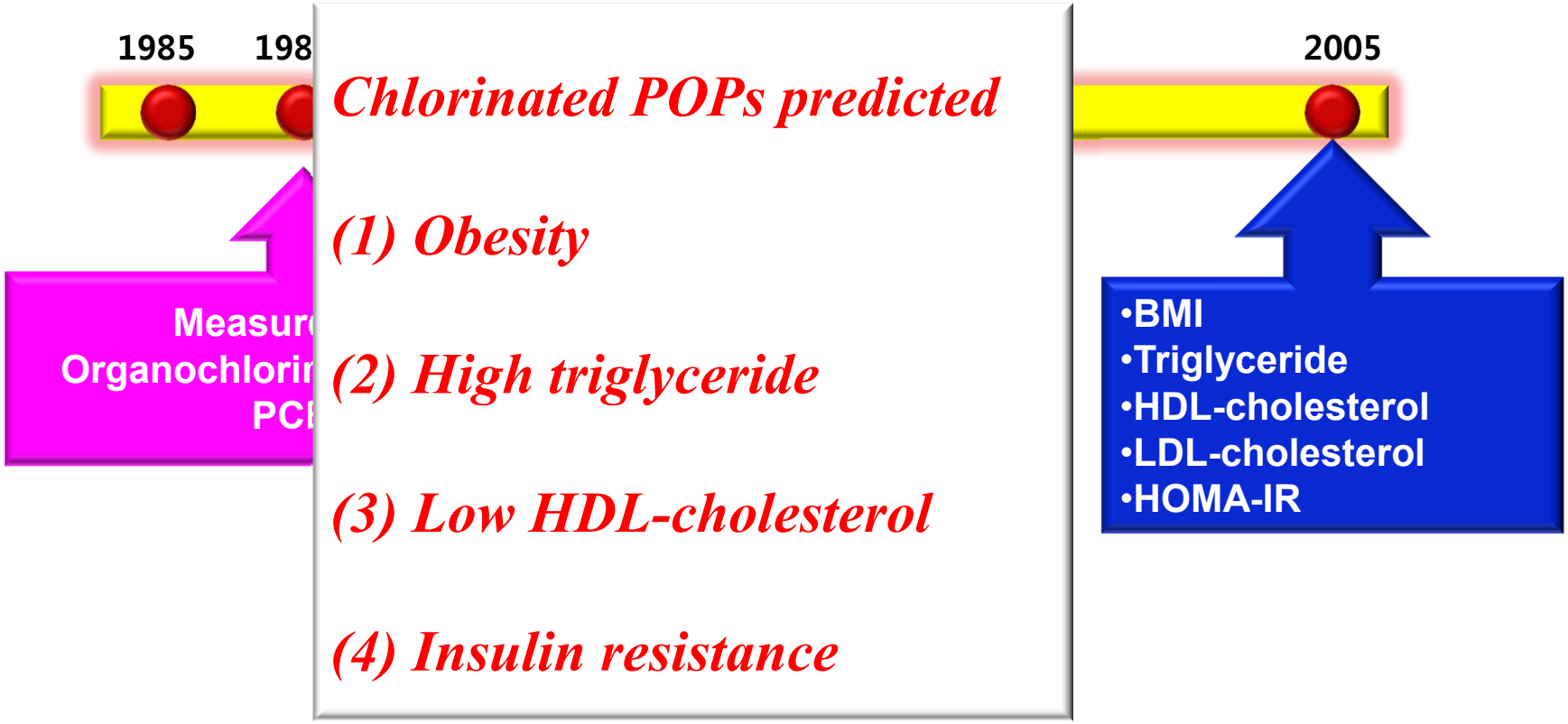
Wolff et al. classification of PCBs	
Group 1A	Weak PB-type inducers, not persistent
Group 1B	Estrogenic, weak PB-type inducers, persistent:
Group 2A	Antiestrogenic, immunotoxic, dioxin-like, moderately persistent
Group 2B	Antiestrogenic and immunotoxic, dioxin-like, persistent
Group 3	PB-type inducers, persistent:

Key common property: Persistency

Lee DH et al. Environ Health Perspectives 2010

POPs and obesity, dyslipidemia, and insulin resistance

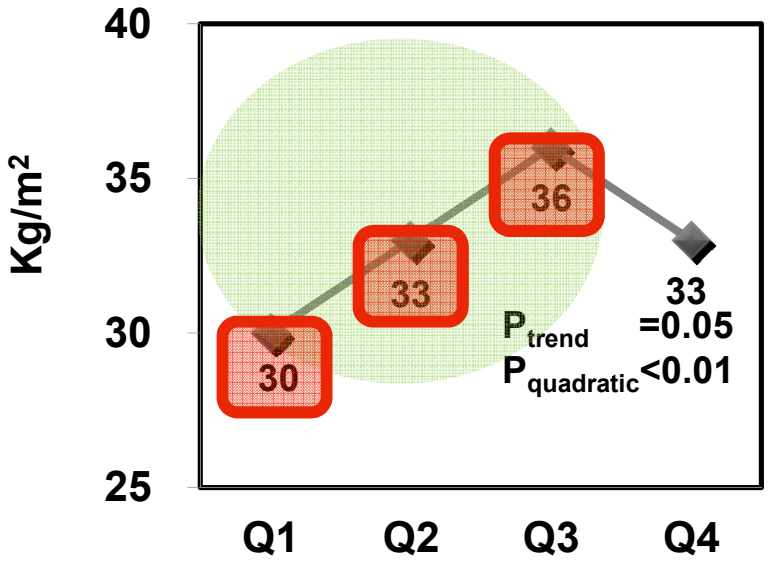
Study subjects: 90 subjects without diabetes
(controls of the nested case control study)



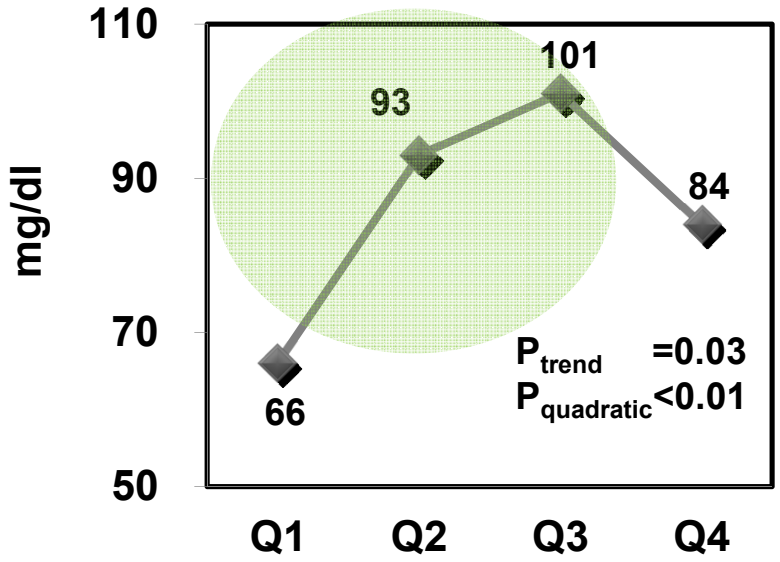
Lee DH et al. PLoS One 2011;6:e15977

BMI 18yrs later

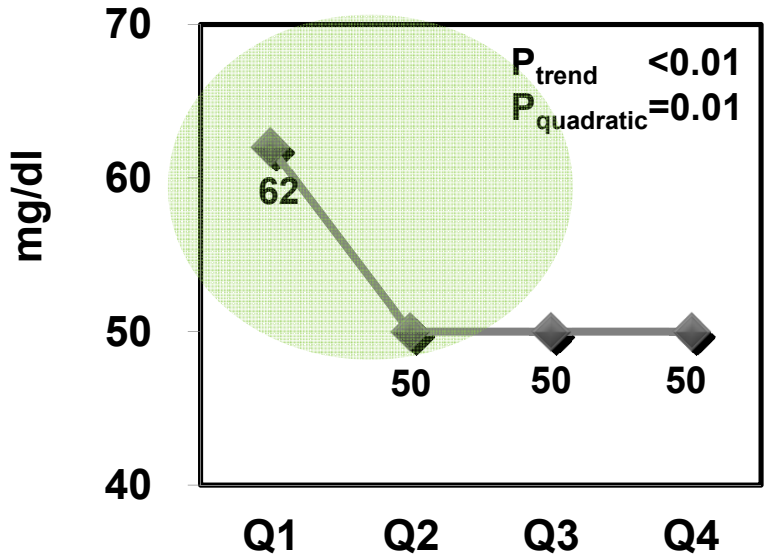
Example:P,p'-DDE



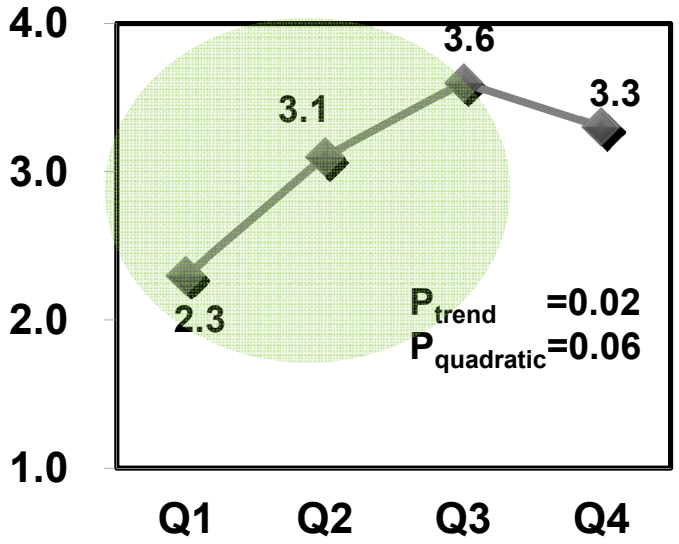
Triglycerides 18yrs later



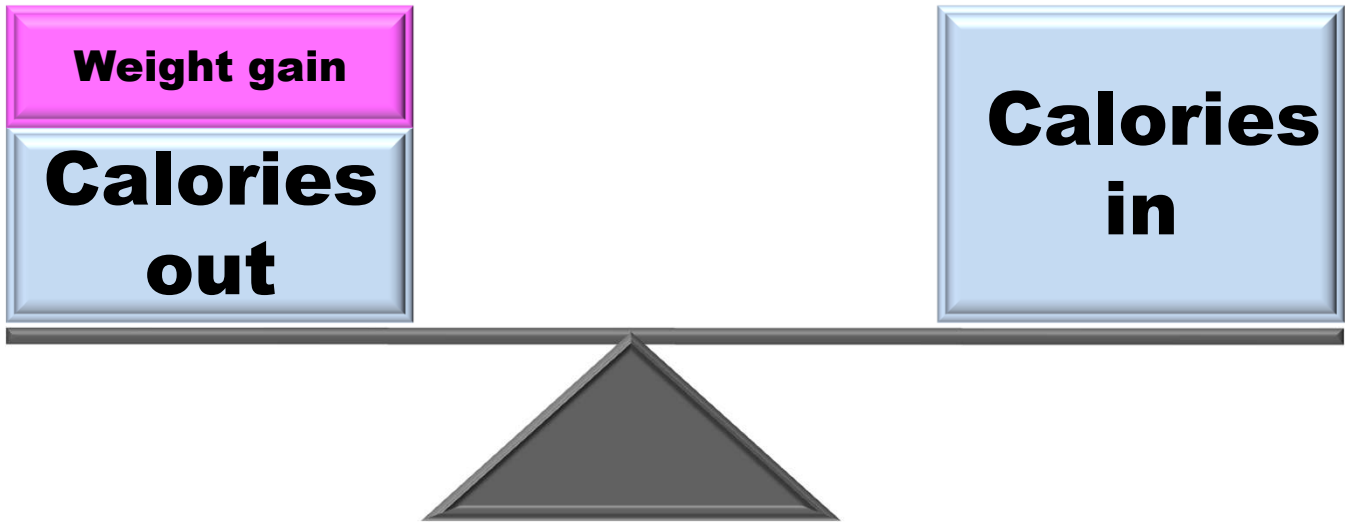
HDL-cholesterol 18yrs later



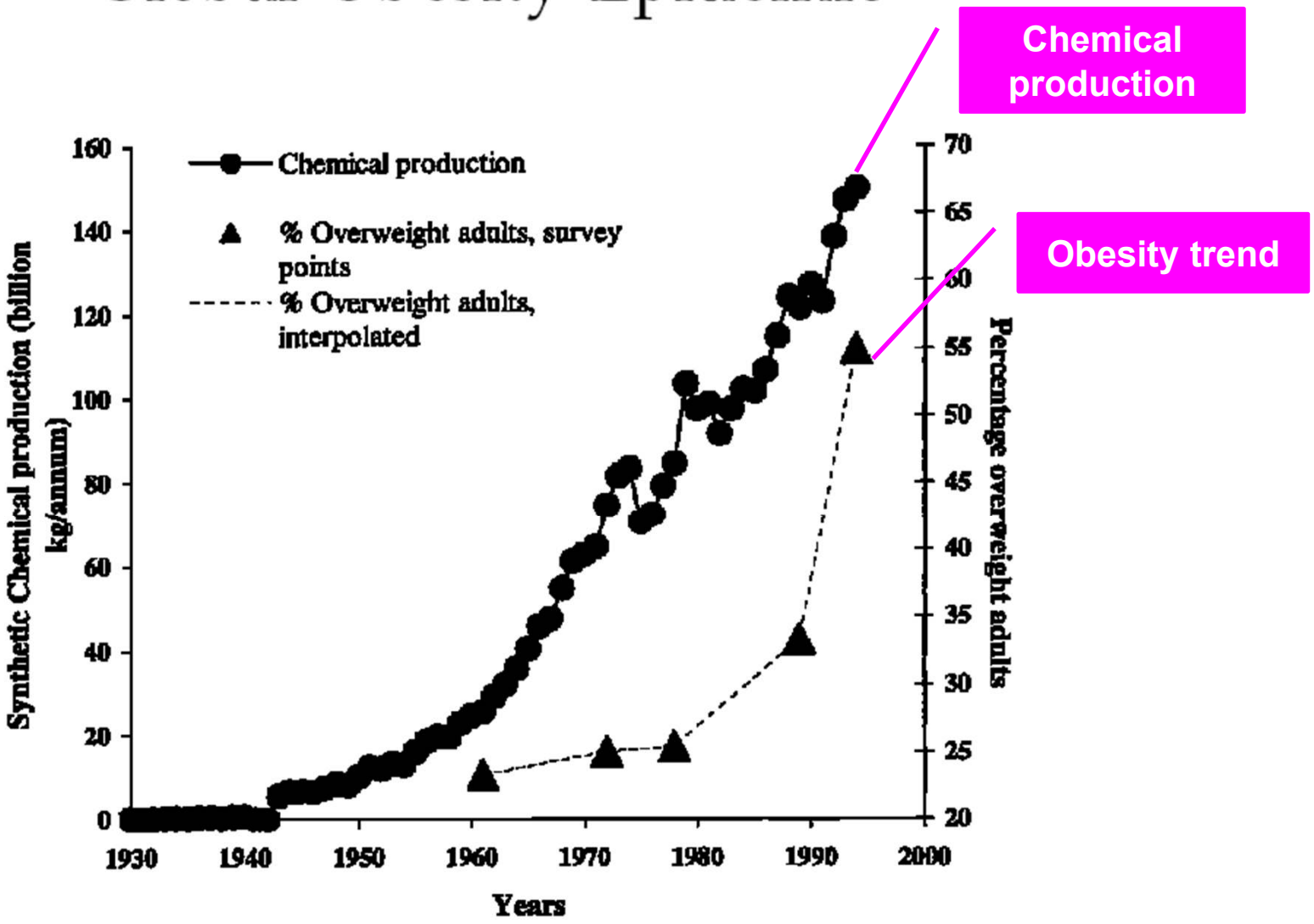
HOMA-IR 18yrs later



Current paradigm on obesity



Chemical Toxins: A Hypothesis to Explain the Global Obesity Epidemic



Baillie-Hamilton PF. J Altern Complement Med 2002;8:185-192

Old toxicological studies already observed..

- ***Low dose exposure to chemicals → weight gain***
- ***High dose exposure to chemicals → weight loss***

- **Organochlorine pesticides: DDT, Lindane, Hexachlorobenzene, Atrazine**
  (Chadwick et al, 1988; Deichmann et al, 1972; Deichmann et al, 1975; Dorgan et al, 1999; Hovinga et al, 1972; Stellman et al, 1997; Takahama et al, 1972; Villeneuve et al, 1977)
- **Organophosphates**
  (Breslin et al, 1996; Cranmer et al, 1978; Nicolau et al, 1983; Trankina et al, 1985)
- **Carbamates**
  (Walker et al, 1994; Yen et al, 1984)
- **PCBs**
  (Clark, 1981; Dar et al, 1992; Hovinga et al, 1993)
- **Xenoestrogens: DES, Bisphenol A, Genistine**
  (Ashby et al, 1999;Howdeshell et al, 1999)
- **Phthalates**
  (Ema et al, 1990; Field et al, 1993;Lamb et al, 1987)
- **Heavy metals: Cadmium, Lead**
  (Antonio et al, 1999; Hovinga et al, 1993)
- **Solvents**
  (Chu et al, 1986; Gaworski et al, 1985; Hardin et al, 1987; Moser et al, 1995; Wahlberg and Boman, 1979)

Obesogen hypothesis

Chemicals that inappropriately stimulate adipogenesis and fat storage

Bruce Blumberg, Ph.D.

University of California, Irvine

Grun F & Blumberg B. Endocrinology 2006;147:S50-5

NTP Workshop:

Role of Environmental Chemicals in the Development of Diabetes and Obesity

January 11-13, 2011

Raleigh Marriott Crabtree Valley • 4500 Marriott Drive

There has been increasing interest in the concept that environmental chemicals may be contributing factors to the epidemics of diabetes and obesity. The National Toxicology Program (NTP) is holding a workshop to evaluate the science associating exposure to certain chemicals or chemical classes with the development of diabetes and obesity in humans. Participants at the workshop will:

- Evaluate strength/weaknesses, consistency, and biological plausibility of findings reported in humans and experimental animals for certain environmental chemicals including arsenic and cadmium, PCBs, DDT/DDE, other organohalogens, bisphenol A, phthalates, and organotins
- Identify the most useful and relevant endpoints in experimental animals and *in vitro* models
- Identify relevant pathways and biological targets for assays for the Toxicology Testing in the 21st Century high throughput screening initiative ("Tox21")
- Identify data gaps and areas for future evaluation/research

The format of the workshop includes both plenary talks and breakout groups. The workshop is open to the public with time set aside in the agenda for public comments during the plenary session on the first day. The public can attend the breakout groups as observers. A literature review document will be prepared prior to the meeting. Information about the workshop and on-line registration are available from the NTP website. Registration is on a first come basis and is limited to 100 people. For additional information, contact Dr. Kristina Thayer (thayer@niehs.nih.gov or 919-541-5021).

This workshop is sponsored by the National Institute of Environmental Health Sciences/NTP, U.S. Environmental Protection Agency, and the FDA National Center for Toxicological Research.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
NATIONAL INSTITUTES OF HEALTH
NIEHS National Institute of Environmental Health Sciences
NTP National Toxicology Program
U.S. Department of Health and Human Services
FDA
NCTR

Target chemicals in the NTP workshop

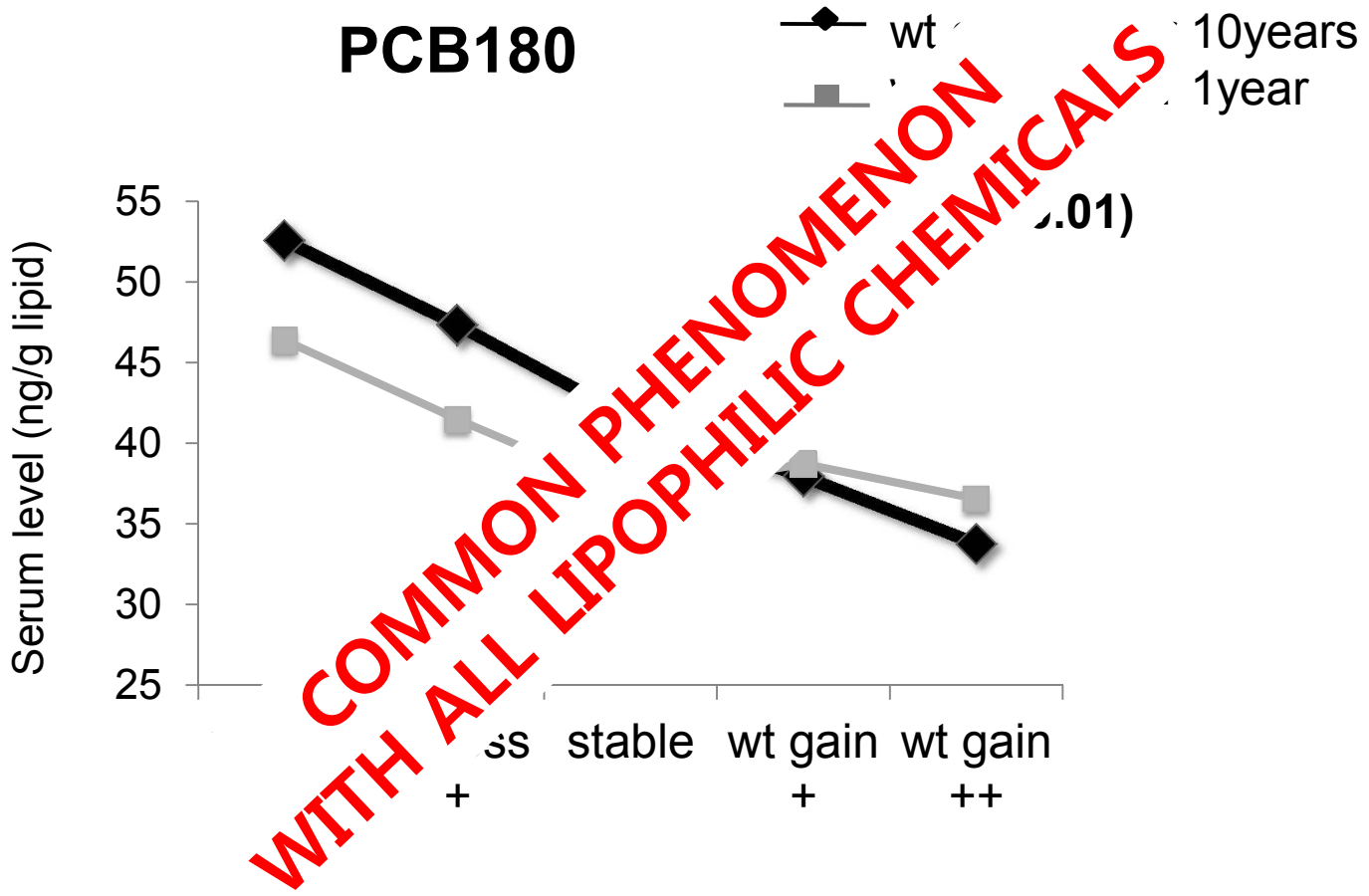
- Arsenic
- Bisphenol A
- Organotins and Phthalates
- Maternal smoking during pregnancy / Nicotine
- Pesticides
- **Persistent Organic Pollutants: the clearest human evidence**

However, from the perspective of chemicals, more fat tissue can be beneficial..

If the same amount of lipophilic chemicals present…

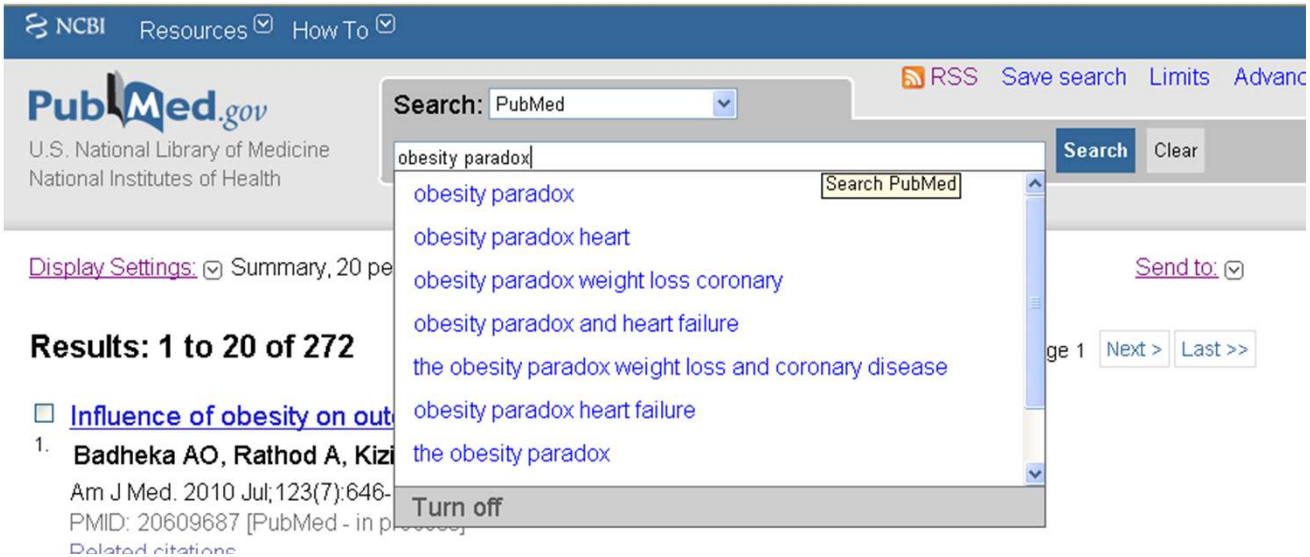
More capacity which can store lipophilic chemicals in a relatively safe way

Weight change affects serum POPs levels



Lim JS et al. Int J Obesity 2011;35:744-7

Obesity paradox??

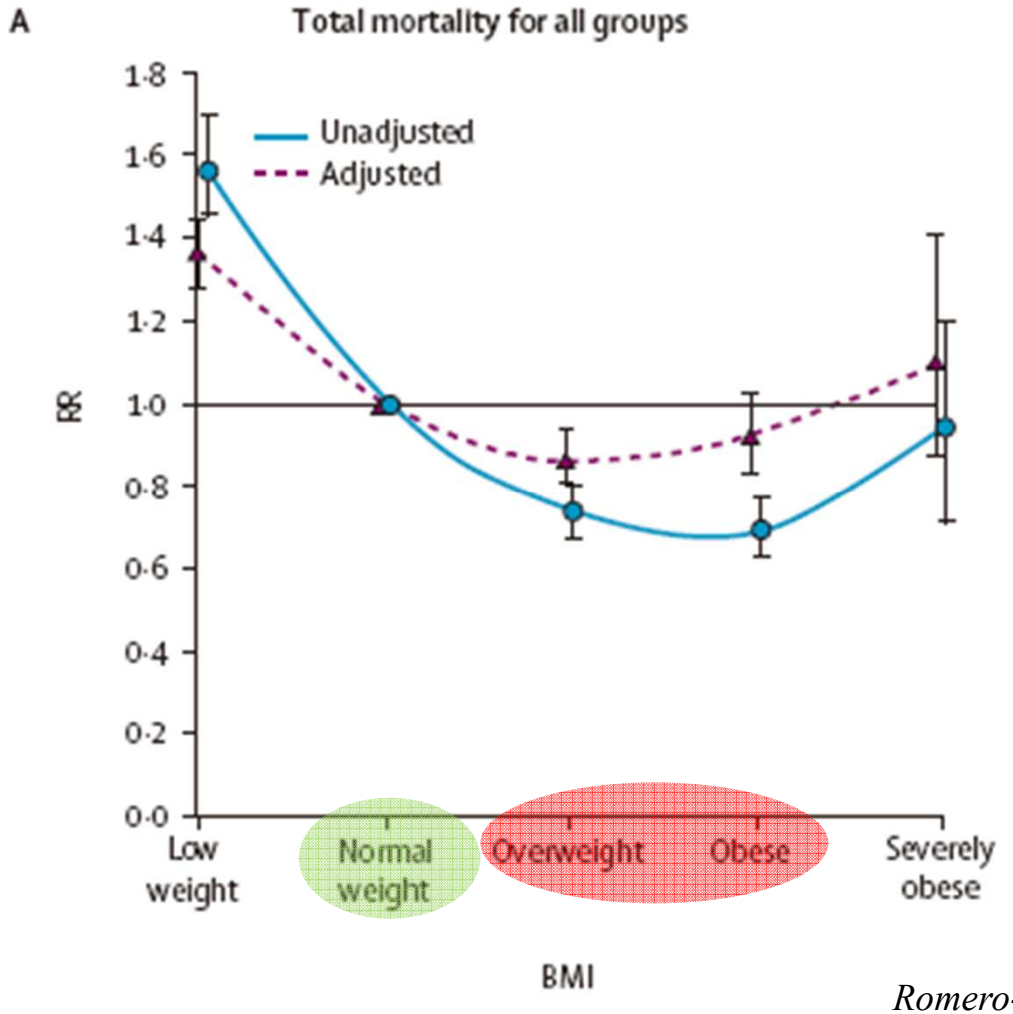


Better survival among overweight or obese patients

- Coronary heart disease
- Congestive heart failure
- Chronic kidney disease
- Hemodialysis
- Cancer
- Chronic lung disease
- Hypertension
- AIDS
- Elderly..

Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies

- 40 cohort studies: 250,152 CHD patients



Romero-Corral A et al. Lancet 2006;368:666-78

The Obesity Paradox, Weight Loss, and Coronary Disease

- 529 CHD patients in cardiac rehabilitation and exercise training program

Weight loss (+)

Table 5 Impact of Cardiac Rehabilitation and Exercise Traini… …oronary Risk Factors in Overweight and Obese Patients with Significant W…

Characteristics	Before Rehab		P Value
BMI, kg/m²	31.2 ± 4.(		.001
% Fat	32.9 ±		<.0001
Total cholesterol, mg/dL	16(		.070
Triglycerides, mg/dL			<.0001
HDL cholesterol, mg/dL		…%	<.0001
LDL cholesterol, mg/dL		−5%	.025
C-reactive protein, mg/dL		−40%	<.0001

Weight loss (-)

Table 4 Impact of Ca… …ing Programs on Coronary Risk Factors in Overw… …nificant Weight Loss (n = 197)

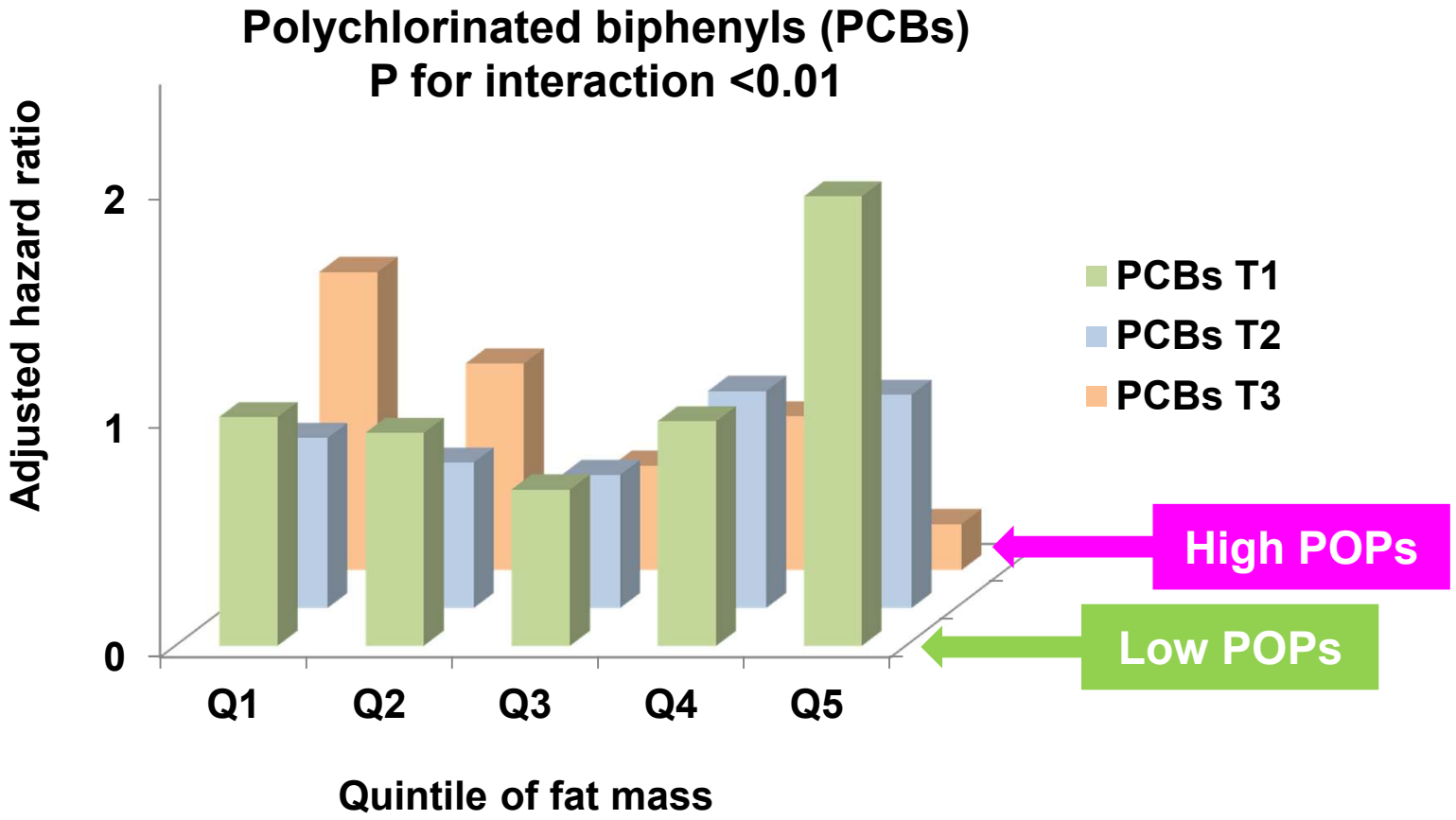
Characteristics		After Rehab	% Change	P Value
BMI, kg/m²	….0	30.3 ± 4.1	+2%	<.0001
% Fat	± 7.2	29.8 ± 7.2	−1%	.95
Total chole…	…68 ± 35	171 ± 34	+2%	.14
Triglycerides, …	157 ± 89	147 ± 75	−6%	.08
HDL cholesterol, …	40.3 ± 11.6	42.7 ± 11.8	+6%	<.0001
LDL cholesterol, mg/…	98.1 ± 36.1	101 ± 36	+2%	.52
C-reactive protein, mg/…	4.9 ± 6.2	4.6 ± 7.0	−6%	.28

WHY?? UNKNOWN BAD THINGS IN WEIGHT LOSS GROUP??

Lavie CJ et al. The American Journal of Medicine 2009;122:1106-14

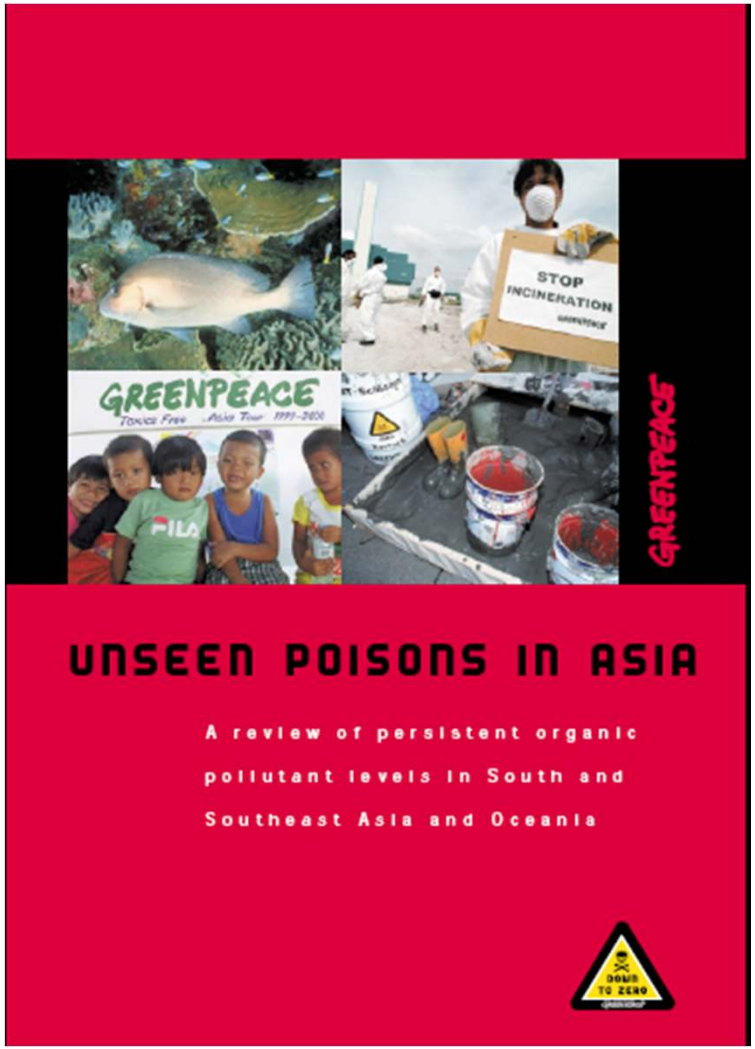
POPs can explain obesity paradox!!

Associations fat mass and mortality are different depending on POPs levels



Hong NS et al. Int J Obe (in submission)

Some OC pesticides are still used or had recently used in in developing countries

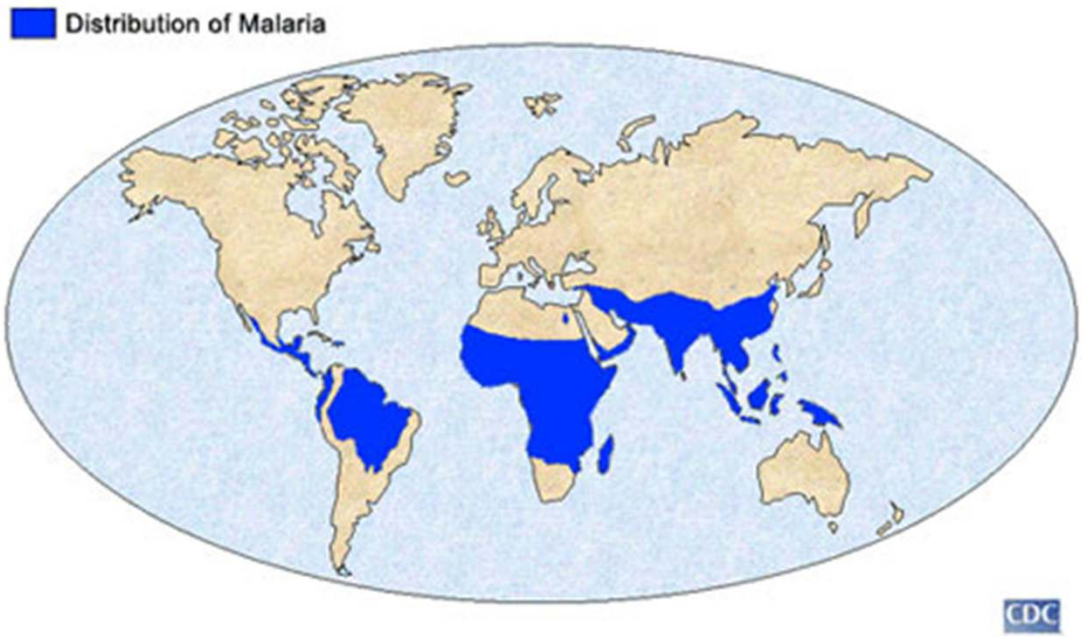


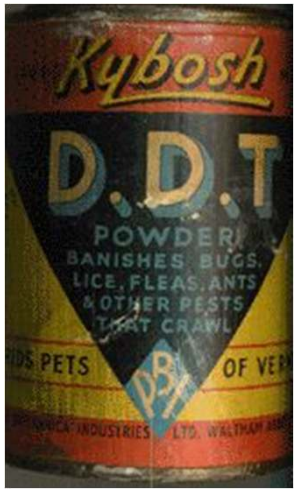
by Greenpeace

- For example, two big countries where still produce DDT in the world or very recently banned

1. India
2. China

DDT is currently used for the control of malaria in tropical and subtropical areas

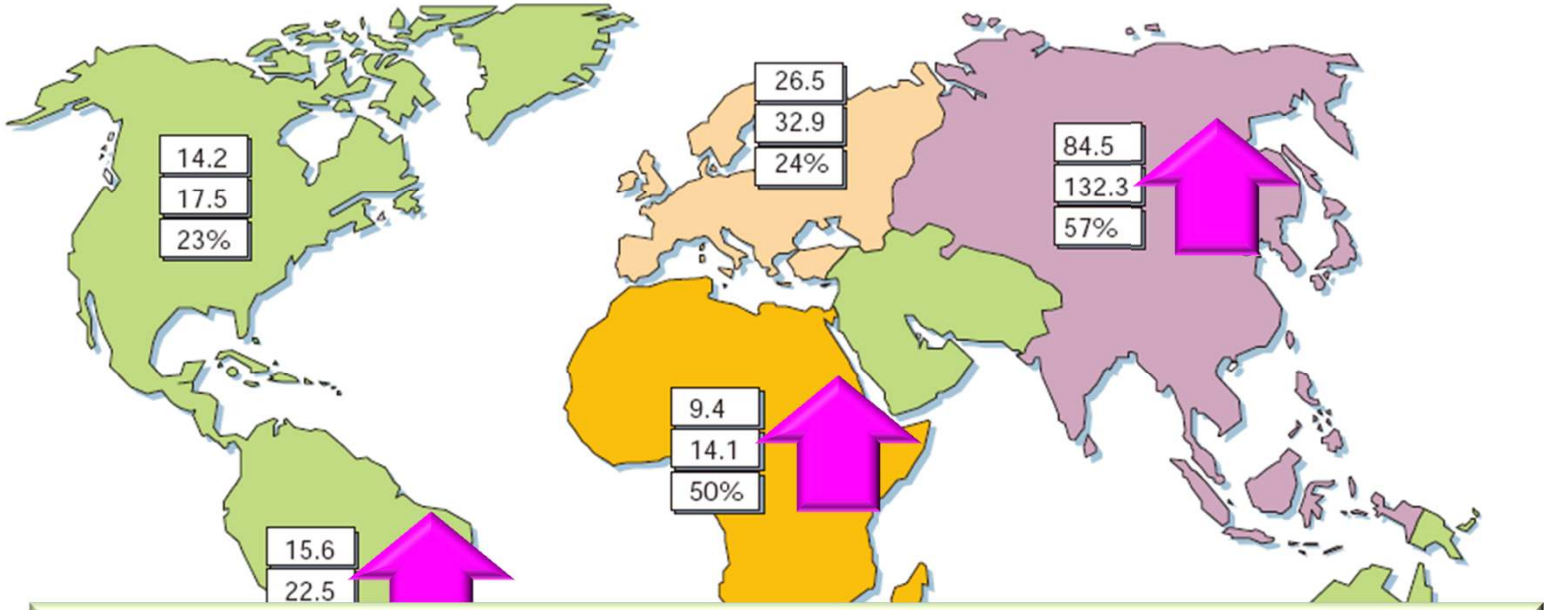




PCBs and dioxin-like compounds are being dumped or produced in developing countries through e-wastes

Areas with a more salient epidemic of type 2 diabetes

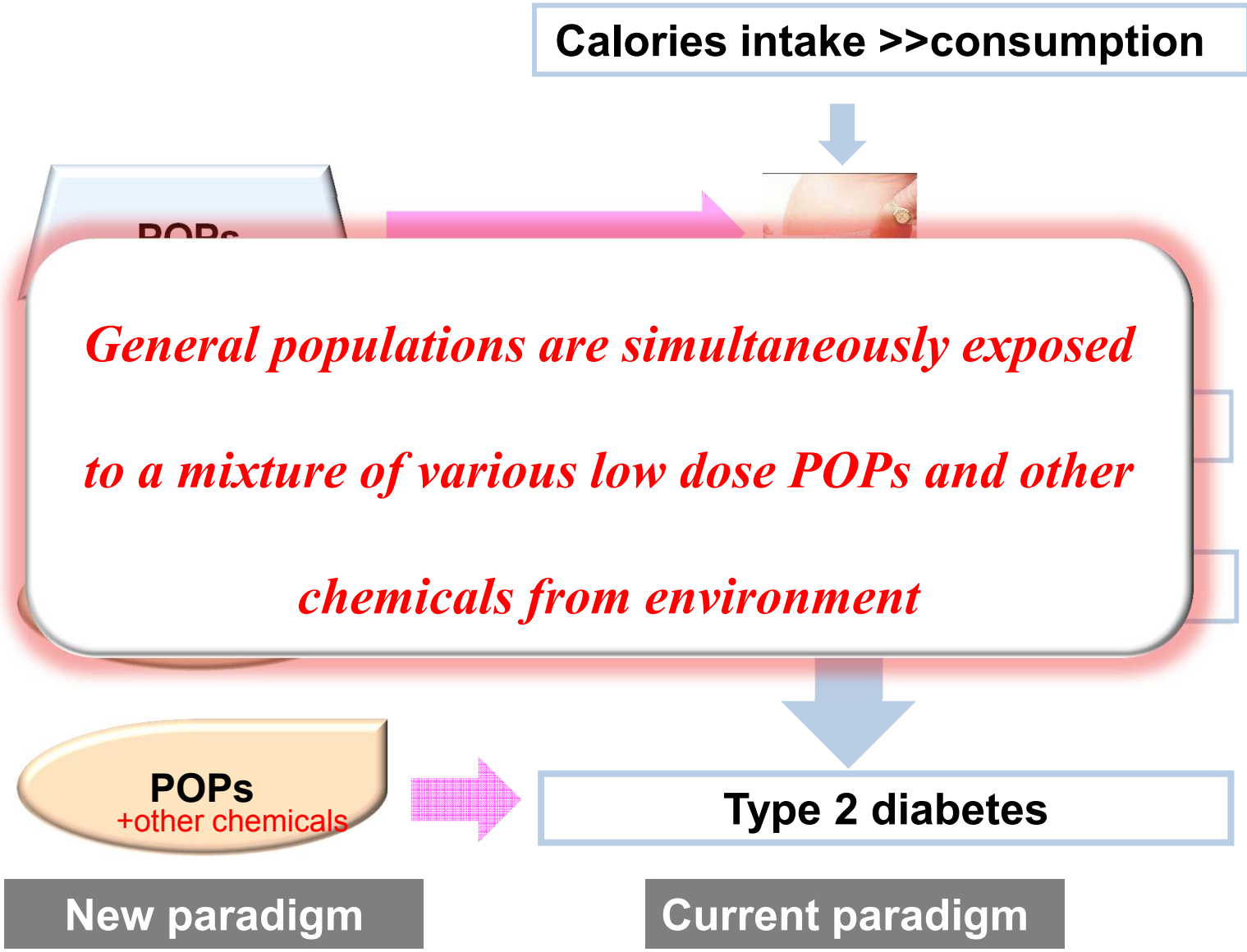
Figure 1 Numbers of people with diabetes (in millions) for 2000 and 2010 (top and middle values, respectively), and the percentage increase. Data adapted from ref. 2.



Areas with a more salient epidemic of diabetes
= OC pesticides using areas ?
= E-wastes dumping areas ?

Zimmet P, et al. Nature 2003;290:1884-90

Low dose POPs may play a role in the current epidemic of type 2 diabetes

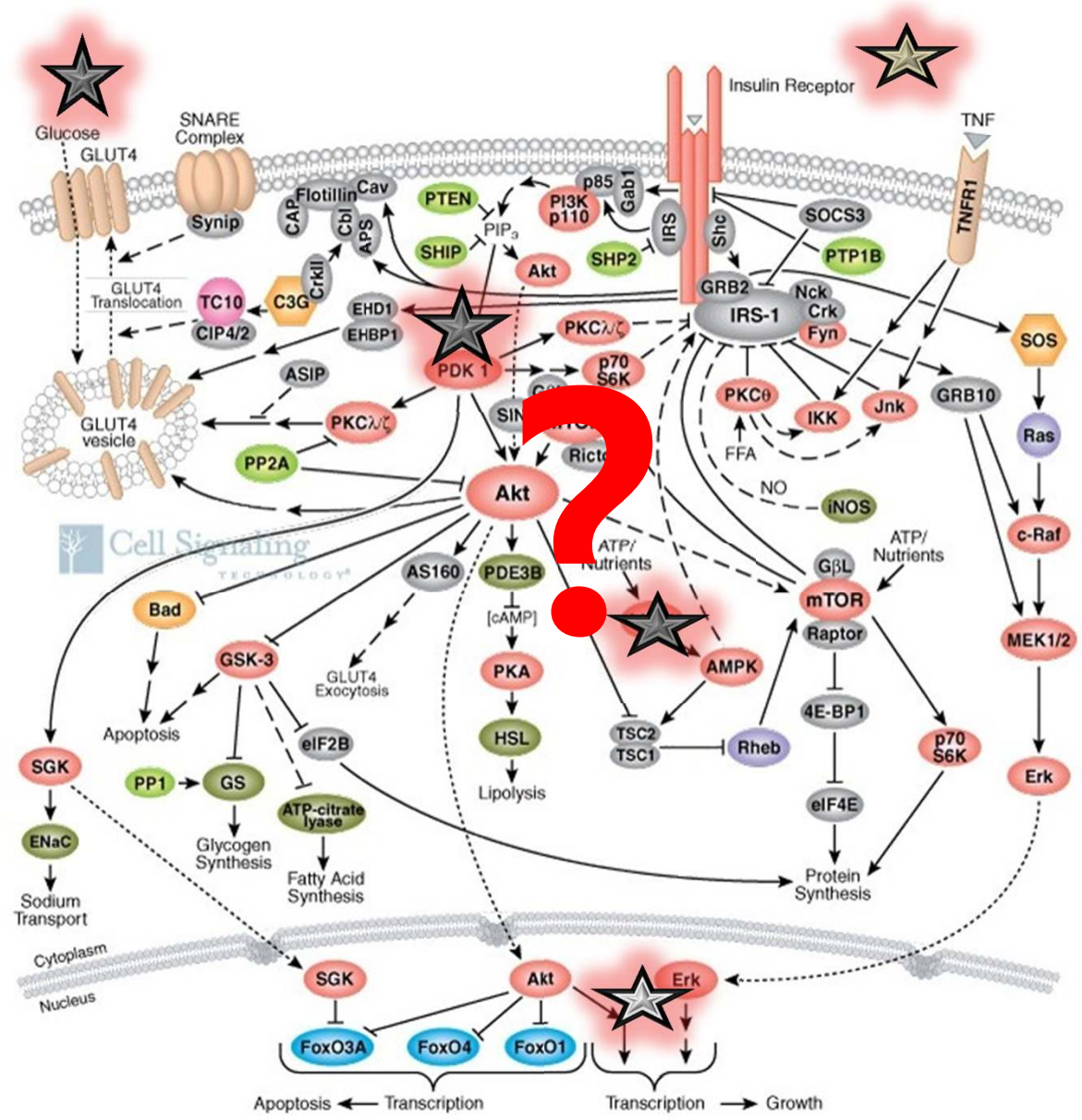


Under the current paradigm, obesity-related diseases

Greatly increased (relative risk >>3)	Moderately increased (relative risk 2-3)	Slightly increased (relative risk 1-2)
▸ Diabetes ▸ Ga ▸ Hy ▸ Dy ▸ Ins ▸ Bre ▸ Sleep apnea	▸ Coronary heart disease	▸ Cancer (breast cancer in postmenopausal women, lon ▸ Impaired fertility ▸ Low back pain ▸ Increased anesthetic risk ▸ Fetal defects arising from maternal obesity

Obesity-related diseases
or
POPs-related diseases???

Is current medical approach really reasonable?



Insulin signaling pathway

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- **CDC, U.S.: provides NHANES datasets to foreigners without any restriction**

THANKS FOR YOUR ATTENTION!!