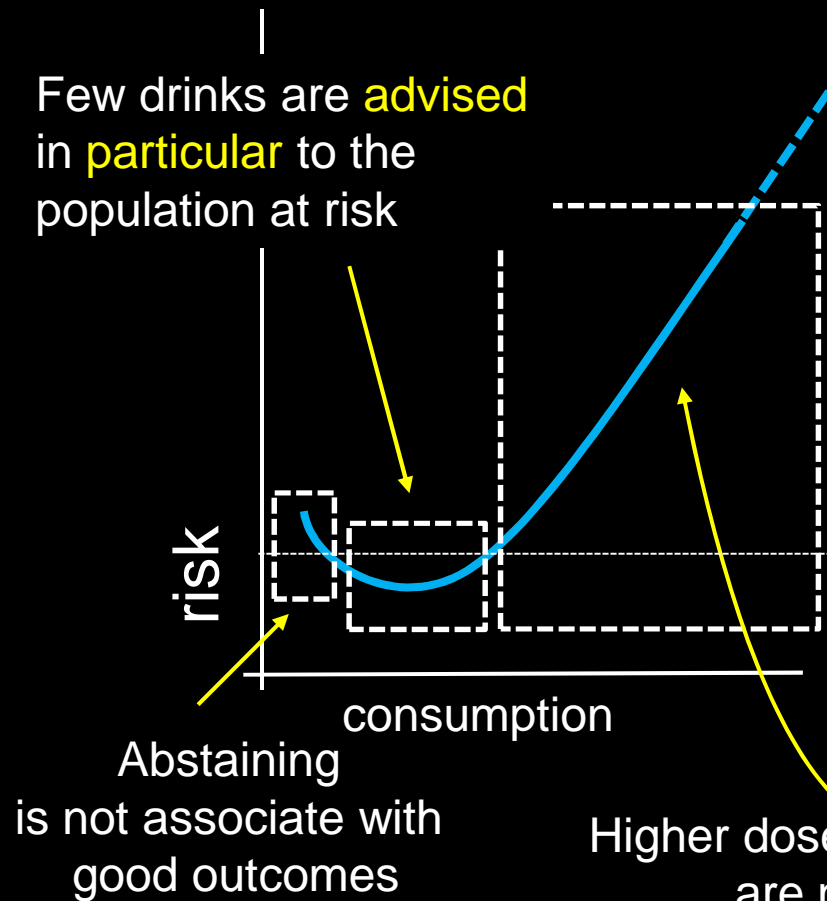


## *J-shaped vs straight line*

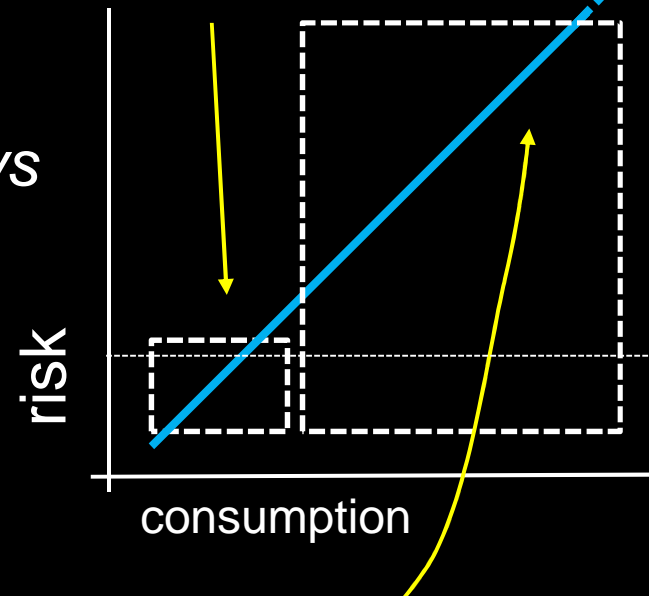
i.e.

**“advisable dose” vs “tolerated risk”:  
a paradigm shift?**



Few drinks are **allowed** but **not** to the population at risk

VS



Is the concept of  
*“bearable alcohol consumption”* scientific?

To me, it sounds like the family medical practitioner saying to the patient: “... *well my friend, if you smoke up to 5 sigarettes per day, there is no problem...*”!!!

How many studies reported a J-shaped association between alcohol consumption and disease risk?

**Actually, the majority... at least when addressing cardiovascular and “all causes”. But the specific association with cancer appears to be somehow less favorable.**

Yet, the WHO “radical” position on alcohol consumption expressed in the section 2.3 of the “World Cancer report 2014” is still controversial...

is data collection and interpretation by  
WHO, “biased”?

Even though it is clear that heavy alcohol consumption and “binge” drinking (no one would advise that!) are associated with many adverse effects, the WHO report seems to overlook solid scientific evidence showing that light-to-moderate consumption of alcohol reduces overall mortality and is very rarely associated with an increased risk of cancer.

Should we honestly abandon the J-shape based background?

Apparently, WHO is using “two separate standards” when evaluating available data.

In fact, ONLY the observation indicating a decreased risk by alcohol (e.g. renal, thyroid, lymphoid cancers) are said to be needed “to be interpreted with caution since the biological mechanisms are not understood ...”

A desirable principle of “maximum caution” does not mean “un-balanced/biased” filtering!

The WHO report states that:

*“Alcohol consumption is related to more than 200 diseases included within the ICD (international Classification of Disease) 10 code. . . including diabetes and cardiovascular diseases” ,*

while essentially all epidemiological studies have shown a *decrease* in the incidence of Type 2 diabetes and just about every type of vascular disease associated to low alcohol consumption....

For example, the WHO report does not consider that a recent analysis (*Annals Epidemiol* 2013) from the “Women’s Health Study/Health Professional’s Study” indicates that, in the USA, the association between alcohol consumption and colorectal cancer disappeared when in 1998 the dietary folate was increased.

No mention about a recent report on more than 50,000 cancer deaths (*Annals Oncol 2013*) showing *no* increase in the risk of cancer death for “moderate” drinkers (those reporting 1-3 drinks/day) when compared with non-drinkers.

Actually, almost all prospective studies suggest that non-drinkers, even lifetime abstainers, die at an earlier age than moderate drinkers...



Strong J-shaped curves between alcohol and mortality for both men and women have been recently reported  
(*Int J Epidemiol* 2013).

.... men consuming up to about 48 g/day of alcohol (approximately four “*typical drinks*”!), had a lower risk of death than that of the lifetime light users.

In women, the risk of total mortality for drinkers remained lower than that of the referent group at all reported levels of intake!

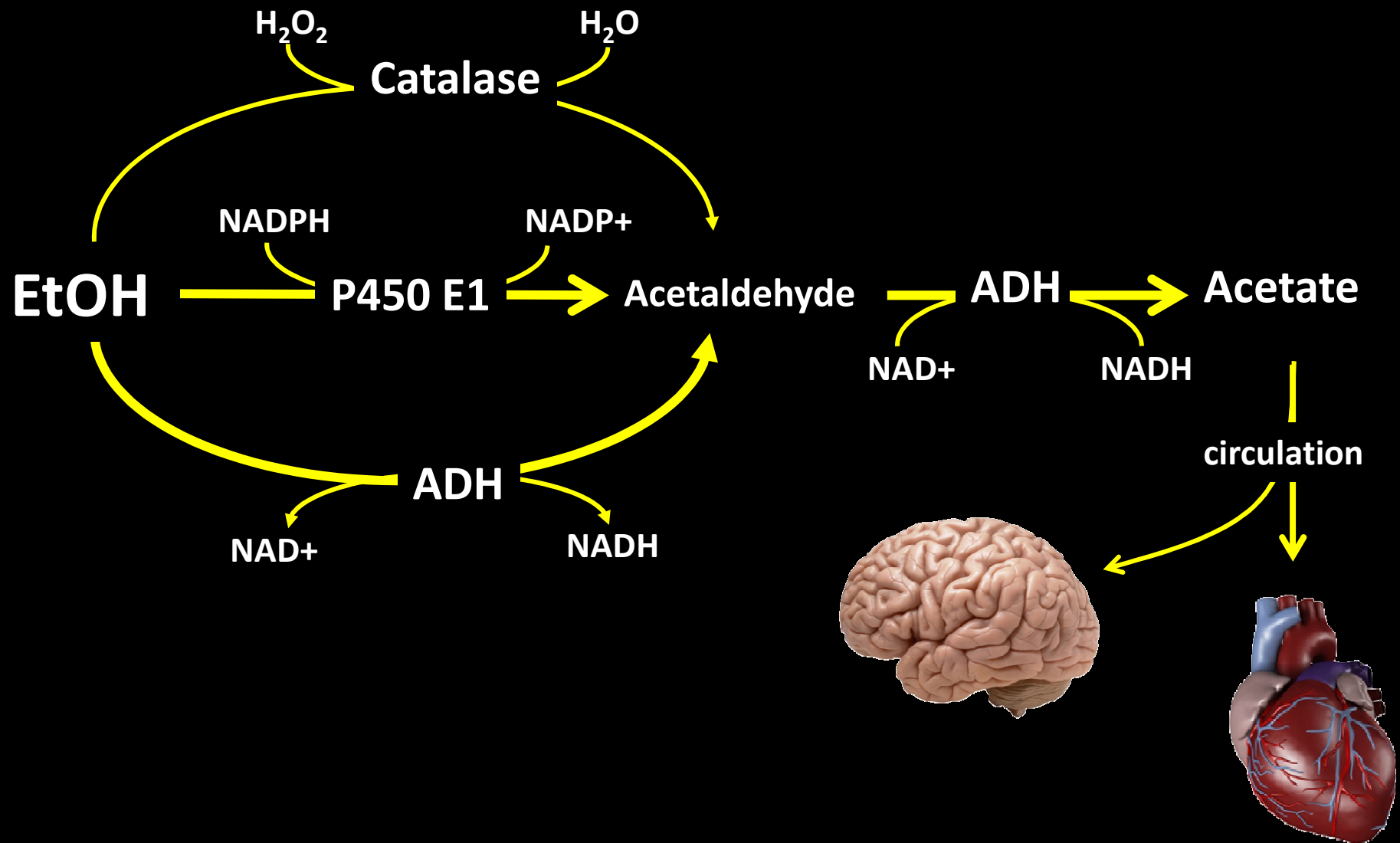
Alcohol induces a slight increase in the incidence of breast cancer from alcohol (with modification of risk by folate intake, hormonal use, and pattern of drinking).

*BUT* no mention about *the reduction in the risk of total mortality that was observed* in women who consumed alcohol *after* the diagnosis of cancer than among women abstaining after developing cancer (J Clin Oncol 2013).

No mention about many earlier major reports (e.g., see NEJM 1997) indicating **that smokers who do not drink have the highest all-cause mortality**, while those who drink light to moderate amounts of alcohol but do not smoke have the lowest mortality.

- reading the WHO report one has the impression that the task was to “educate” people to avoid “wrong behaviour” such as over-drinking and binge-drinking...
- this is not our job! We must stay on a solid scientific ground!

## A rapid “overview” about EtOH metabolism



# Why Heavy alcohol consumption promotes tumorigenesis?

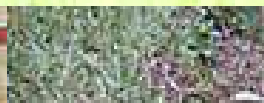
- 1) Free radicals generation and GSH depletion due to trans-sulfuration reactions. The resulting oxidative stress induces, in turn, DNA damage
- 2) Affecting gene expression a dysregulation by epigenetic control:
  - a) gene expression is dysregulated by the increase of acetate (final metabolite of ethanol) that affects the level of histone acetylation and therefore the proportion of open conformation “readable” chromatin
  - b) The decrease of folate levels and the inhibition of methionine synthase, lead to the decrease of methionine and S-adenosyl-methionine and therefore to decrease in DNA methylation. The parallel increase of homocysteine and S-adenosyl-homocysteine further inhibit DNA methyltransferases activity, ultimately resulting in global hypomethylation of DNA.

Both a) and b) results in a deregulated increase of gene expression, possibly including those related to cell cycle, proliferation and apoptosis.  
**All enzymes involved present polymorphisms, with variable prevalence within the population, but all associated with impaired activity!**

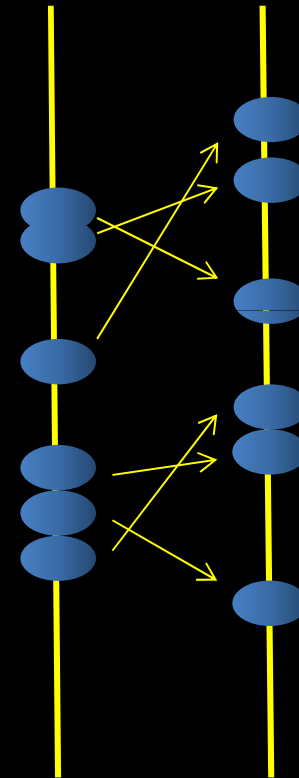
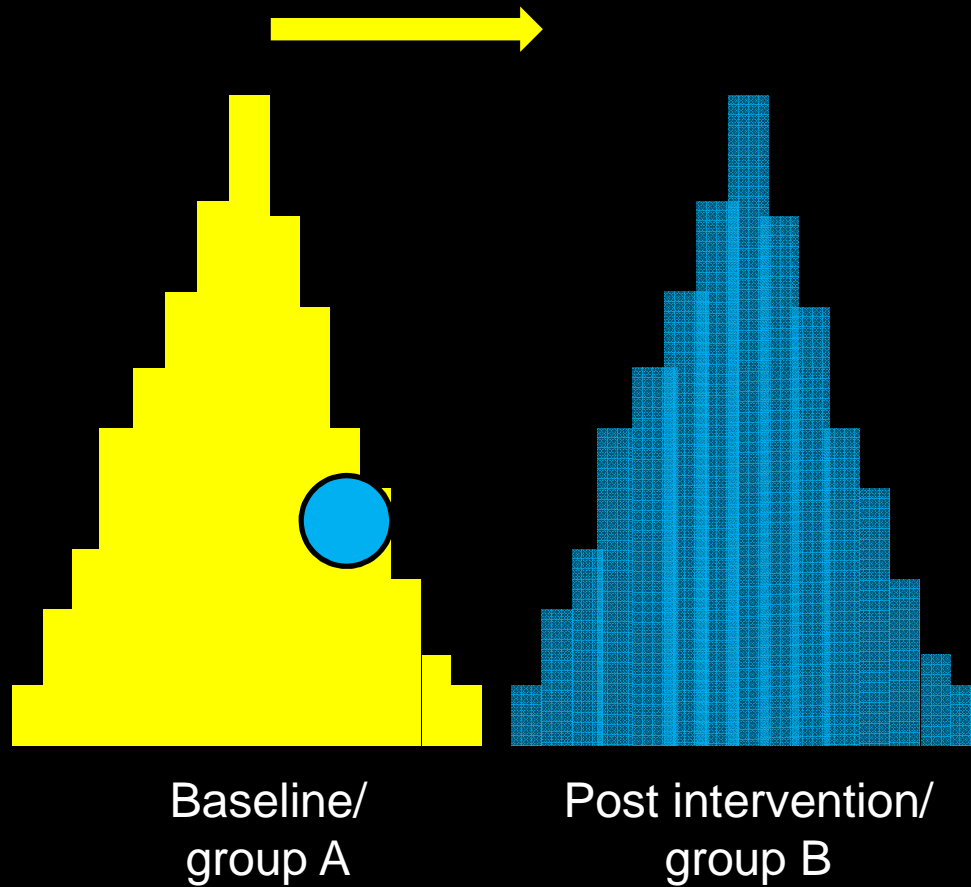
H



/...



**Variability? Who cares about that...  
we address the “population”! Not individuals!**





Original Communication

# Discovery-Based Nutritional Systems Biology: Developing N-of-1 Nutrigenomic Research

Jim Kaput<sup>1</sup> and Melissa Morine<sup>2</sup>



ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 471–480

**Journal of  
Clinical  
Epidemiology**

Aggregating single patient (n-of-1) trials in populations where recruitment and retention was difficult: The case of palliative care

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# “my” conclusions (to be possibly discussed):

- WHO is providing a biased selection and interpretation of available data probably due on the intention of “*educating people*” rather than based on solid scientific background
- Mission impossible: trying to find a reasonable compromise between “drinking is not allowed (period!)” vs “some little drinking is permitted” is like pretending to *run with the hare and hunt with the hounds!!!!*
- In general, population/intervention studies leave too much issues opened ... we need to go toward a new concept, that takes into account the “between individuals” differences allowing us to provide reasonable and balanced recommendations....