Booze Clues:
Alcohol can be *Good* for You ?!?

Ed Cox, M.D.

Alcohol: The Good, The Bad, and The Ugly

Alcoholic beverages play are prominent part in daily life

- Relaxing, soothing, delicious ritual at the end of a day's work
- Social lubricant at meetings, parties

Used to excess or inappropriately

- Interfere with physical, intellectual and emotional performance
- Contribute to accidents, disease and death
- Take a practical and emotional toll on family and friends

Alcohol in History - Prehistoric

Alcoholic beverages at the dawn of human history

- Stone age jugs from the Neolithic period suggest intentional beverage fermentation
- Analysis of chemical residues show alcoholic beverages made ca. 7000 BCE in China
- Wine production ca. 6000 BCE in Georgia
- Medicinal use of alcohol mentioned in Egyptian and Sumerian texts ca. 2100 BCE
- "Good/bad" dichotomy evident from early descriptions

Alcohol in History - Ancient

Ancient Greece and Rome

- Wine was prominent part of daily life, celebrations, religious rituals
- Gods: Bacchus (Romans), Dionysus (Greeks)
- Tolerance ranged from "moderation in all things" to "sign of masculinity"

Alcohol in History - Medieval

Wine-making and beer-making were prominent aspects of monastic life

- Techniques were improved through methodical experiment and observation in monasteries

Consumption was ritualized and approved by religious authorities

Consumption of wine and beer was safer alternative than water, which was often contaminated with disease-causing micro-organisms.

Alcohol in History - 1800-2000

Europe

- Alcoholic beverages are almost universally accepted part of daily life
- Moderation emphasized; inappropriate use proscribed

United States

- Frontier, sweat-shop lifestyles fostered excessive consumption
- Temperance movement reaction; Prohibition
- Religious disapproval (Protestant)
- One-third of Americans consider themselves teetotalers (men ~25%, women ~50%)

Alcohol in Story & Song

Three Jolly Coachmen – Kingston Trio

- Here's to the man, drinks water pure
- And goes to bed quite sober.
- Falls as the leaves do fall.
- He'll die before October.
- Here's to the man who drinks dark ale
- And goes to bed quite mellow.
- Lives as he ought to live.
- He'll die a jolly good fellow.

The Toll of Alcohol

Intoxication

- Disruptive and violent behavior
- Drunk driving

Addiction

- Poor job performance, inability to hold a job
- Impact on family

Health

- Alcoholic liver disease, cirrhosis
- Nervous system toxicity – Wernicke-Korsakoff, folate deficiency
- Heart toxicity – alcohol cardiomyopathy
- Withdrawal / detox

The Toll of Alcohol

Mortality

- 60,000 U.S. deaths / year attributed to alcohol

Detoxification / Rehab

- Lost productivity, family turmoil

My personal history with alcohol

Methodist preacher's kid and grandson of WCTU organizer

My first drink during second year college; introduced to wine at New Year's Eve dinner with older brother

Nightly beer in dorm room

Liquor – drunk twice – enough of that!

Immersed in consequences of alcoholism during medical training

Daily beer, occasional wine, occasional twinges of doubt and concern about health impact, friction with parents

The New England
Journal of Medicine

VOLUME 337 DECEMBER 11, 1997 NUMBER 24

ALCOHOL CONSUMPTION AND MORTALITY AMONG MIDDLE-AGED AND ELDERLY U.S. ADULTS

MICHAEL J. THUN, M.D., RICHARD PETO, F.R.S., ALAN D. LOPEZ, PH.D., JANE H. MONACO, M.S., S. JANE HENLEY, B.A., CLARK W. HEATH, JR., M.D., AND RICHARD DOLL, F.R.S.

Alcohol and Mortality

Cancer Prevention Study II

- Conducted by American Cancer Society
- 490,000 subjects recruited by ACS volunteers
- Age 30 and older; 49% men, 51% women
- Questionnaires administered by mail - 1982
- Follow-up through 1991
- 12% died; cause verified by death certificates

ACS CPS II - Results

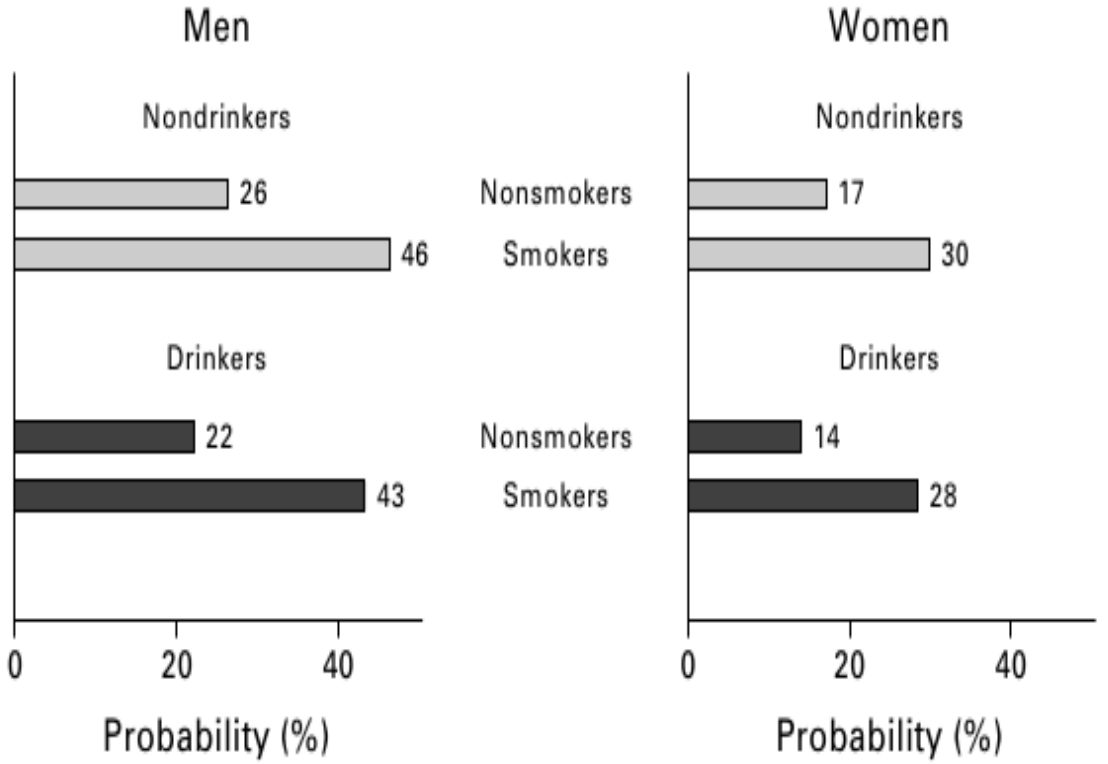


Figure 2. Estimated Probability of Death from Any Cause in the General U.S. Population from 35 to 69 Years of Age for Four Combinations of Alcohol Consumption and Smoking.

Smoking doubles the death rate

Alcohol reduces death rate nearly 20% in non-smokers

Alcohol & Health: Italian Consensus Statement

REVIEW

Moderate alcohol use and health: A consensus document

A. Poli [a,*], F. Marangoni [a], A. Avogaro [b], G. Barba [c], S. Bellentani [d], M. Bucci [e], R. Cambieri [f], A.L. Catapano [g], S. Costanzo [h], C. Cricelli [i], G. de Gaetano [j], A. Di Castelnuovo [k], P. Faggiano [l], F. Fattirolli [m], L. Fontana [n], G. Forlani [o], S. Frattini [p], R. Giacco [q], C. La Vecchia [r], L. Lazzaretto [s], L. Loffredo [t], L. Lucchin [u], G. Marelli [v], W. Marrocco [s], S. Minisola [w], M. Musicco [x], S. Novo [y], C. Nozzoli [z], C. Pelucchi [r], L. Perri [t], F. Pieralli [z], D. Rizzoni [aa], R. Sterzi [ab], R. Vettor [ac], F. Violi [t], F. Visioli [ad]

Poli et al Nutr. Metab. Cardiovasc. Dis. 2013

J-shaped curve of mortality

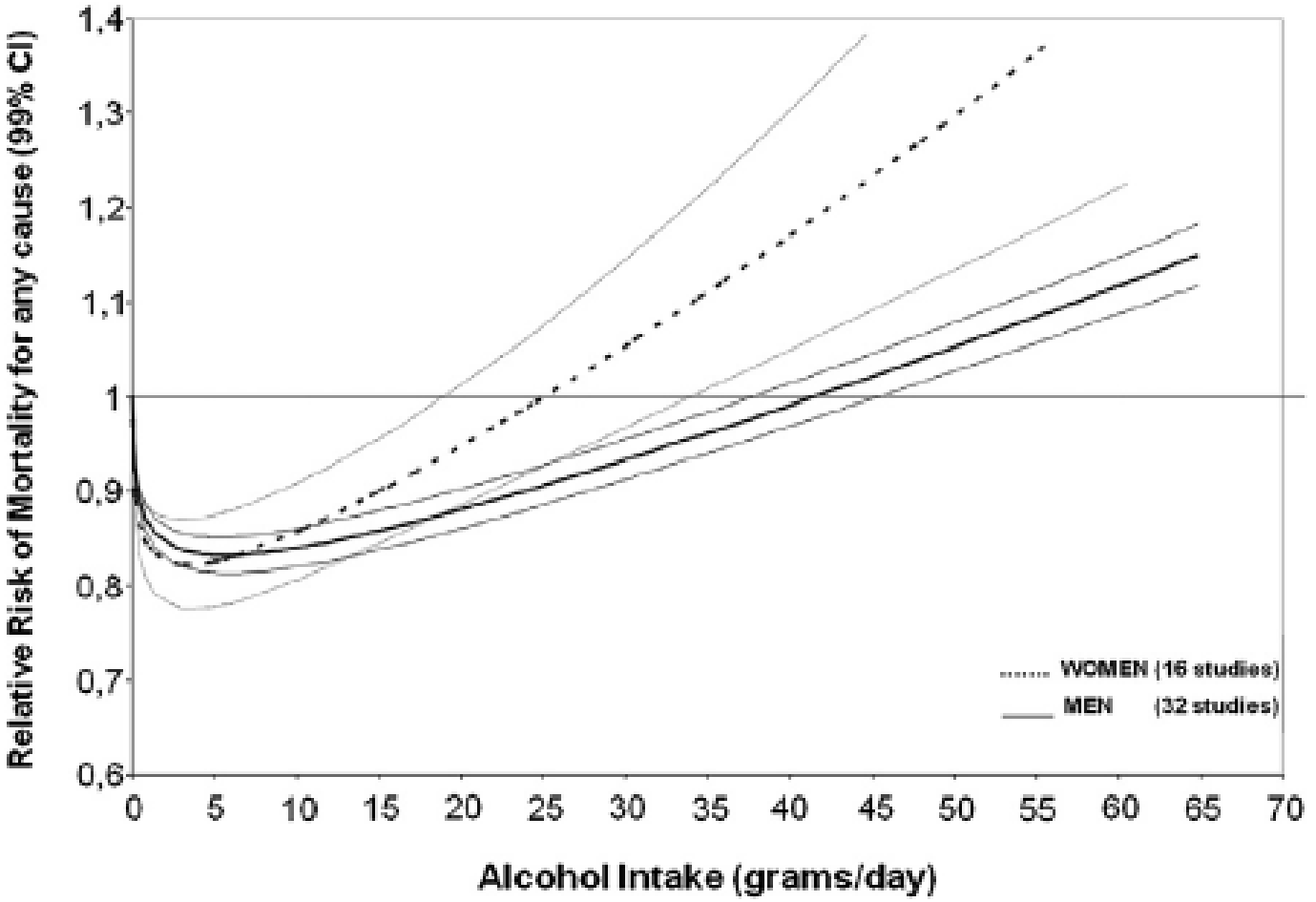


Figure 2 Relative risk of all-cause mortality and alcohol consumption in men and women. Data are from Di Castelnuovo et al. 2006 [3].

Alcohol and cancer risk

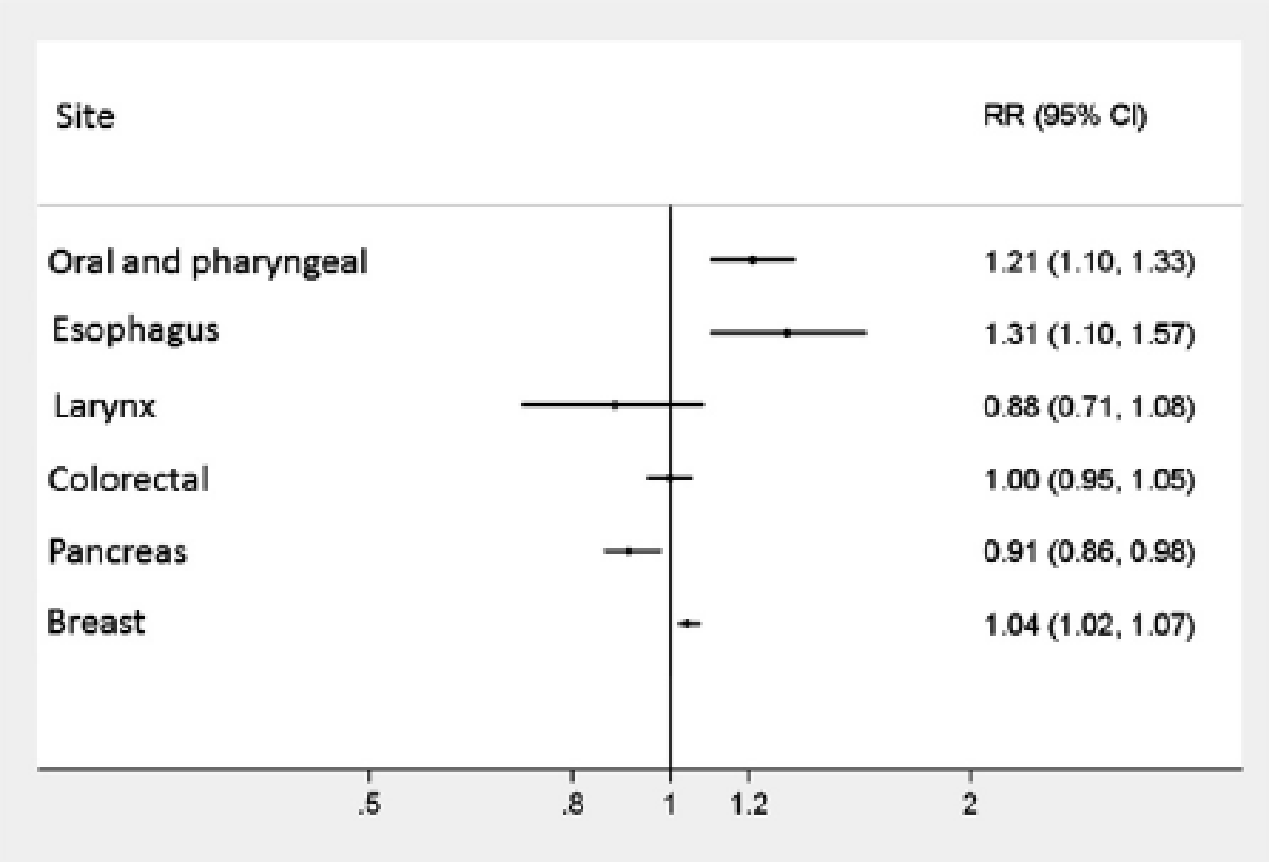


Figure 1 Moderate alcohol use and cancer risk in selected sites. RR, relative risk for alcohol intakes of ≤1 drink/d, as compared with abstainers and occasional drinkers.

Effects on cognitive decline

Table 3 Original studies and meta-analyses of the associations between alcohol intake and dementia and/or cognitive decline.

Title	Characteristics and No. participants	Outcome (cases)	Alcohol consumption	Relative risk estimate (95% CI)
Alcohol consumption and risk of dementia: the Rotterdam Study [111].	Cohort population study on 7893 non-demented subjects	Dementia (197) AD (146)	1–3 drinks/d vs. nondrinkers	0·58 (0·38–0·90)
Alcohol consumption and cognitive function in late life: a longitudinal community study [113].	Cohort study on 1098 non-demented elderlies	Reduction cognitive test or neurocognitive tests	Minimal and moderate drinker vs. nondrinker	For any increase of one SD in the reduction of MMSE the risk of being minimal drinker vs. that of an abstainer was 0.3 (0.14–0.65) and 0.08 (0.02–0.28) that of moderate drinkers
Alcohol intake and risk of dementia [112]	Cohort study on 980 non-demented elderlies	Dementia (260) AD (199)	Three vs. zero servings of wine	0.55 (0.84–0.39)
Current alcohol consumption and its relationship to incident dementia [115]	Cohort study on 3202 non-demented elderlies (≥75 years)	Dementia (217) AD (111)	Any kind of alcohol intake vs. no intake	0.71 (0.53–0.96) dementia 0.58 (0.38–0.89) AD
Alcohol consumption, mild cognitive impairment, and progression to dementia [114]	Cohort study on 121 MCI subjects	Dementia (14)	<1 drink/d vs. no intake	0.15 (0.03–0.78)
Alcohol, dementia and cognitive decline in the elderly: a systematic review [116]	Meta-analysis of 26 cohort and case–control studies	Dementia and cognitive decline	Small amounts of alcohol intake	0.63 (0.53–0.75) dementia 0.57 (0.44–0.74) AD
Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies [117]	Meta-analysis of 15 cohort studies	Dementia, VAD, AD	Light to moderate intake vs. no intake	0.74 (0.61–0.91) dementia 0.75 (0.57–0.98) VAD 0.72 (0.61–0.86) AD

AD, Alzheimer's disease; VAD, Vascular dementia; MCI, Mild cognitive impairment; MMSE, Mini Mental Status Examination; CI, Confidence Interval.

Alcohol & cognitive decline

"All studies revealed a reduction of dementias and Alzheimer's risk associated with moderate alcohol use, compared with abstainers."

"One should not forget however that alcohol in excess causes at least two well-known neurological diseases characterized by cognitive decline and dementia..."

Beneficial effects of alcohol

The "silent majority" of drinkers consume small to moderate amounts of alcohol regularly without adverse consequences to themselves or others

In fact, those who average about 1 drink a day have an 18% lower all-cause mortality compared to non-drinkers

Alcohol and CHD

If moderate drinkers have a lower death rate, what diseases are they not dying from?

- Coronary heart disease and atherosclerotic vascular disease, including stroke

Atherosclerotic vascular disease: ASVD

Atherosclerotic vascular disease is a destructive process in the walls of arteries

Earliest findings – streaks of fat in the innermost layer of artery (intima)

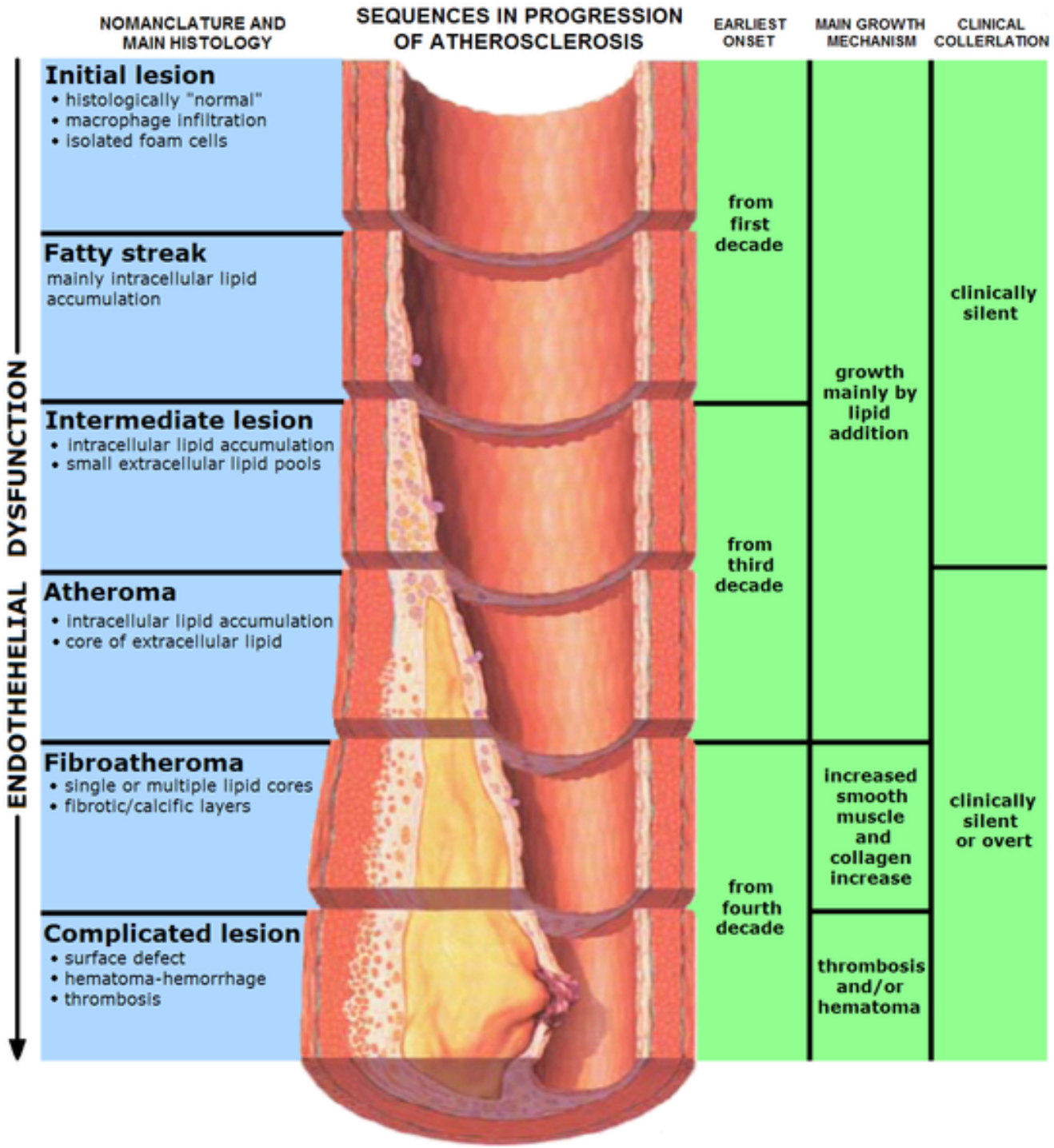
- Low-density lipoproteins diffuse between endothelial cell junctions
- White bloods cells congregate, damage wall

Progression

- Fibrosis (scar tissue), calcium deposit
- Rupture, exposure of collagen, platelet aggregation, thrombus formation, repeat
- Appearance - "lumps of gruel" (Cream of Wheat); Greek for gruel is athera

Vessel occlusion

- Thrombus blocks artery, restricting blood flow to organ
- Death of tissue (infarction)


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

ASCVD Markers

Elevated LDL

Low HDL

Platelet aggregation

Blood clotting

Endothelial dysfunction

Oxidation

Inflammation

Can we account for the effects of alcohol on cardiovascular disease and mortality by its effects on these biological factors (plausibility)?

Alcohol feeding studies

Experiments in which alcohol is given in the treatment arm and placebo to the controls

Comparisons between treatment and control in response variable

Experimental design

- Treatment / placebo assigned randomly
- Crossover – each subject given treatment and control; order randomized

Overview analysis of feeding trials

Brien *et al*, BMJ, 2011

63 studies, 1686 subjects

36 crossover, 24 before & after; 3 parallel

Control: Water, fruit juice; non-alcohol drink

Varying number of factors in each study

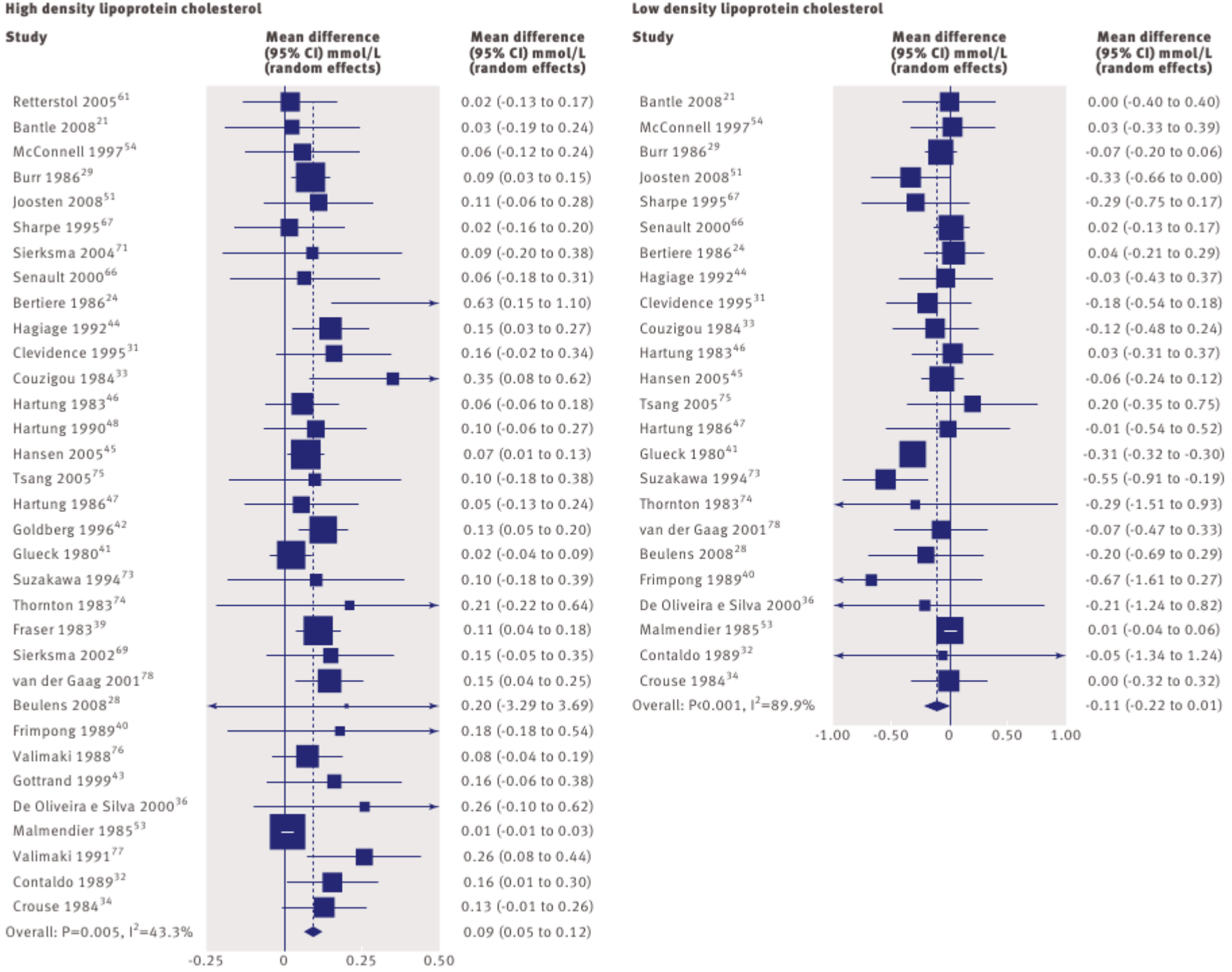


Fig 2 | **Forest plot of meta-analysis (random effects) of effect of alcohol consumption on levels of high and low density lipoprotein cholesterol**

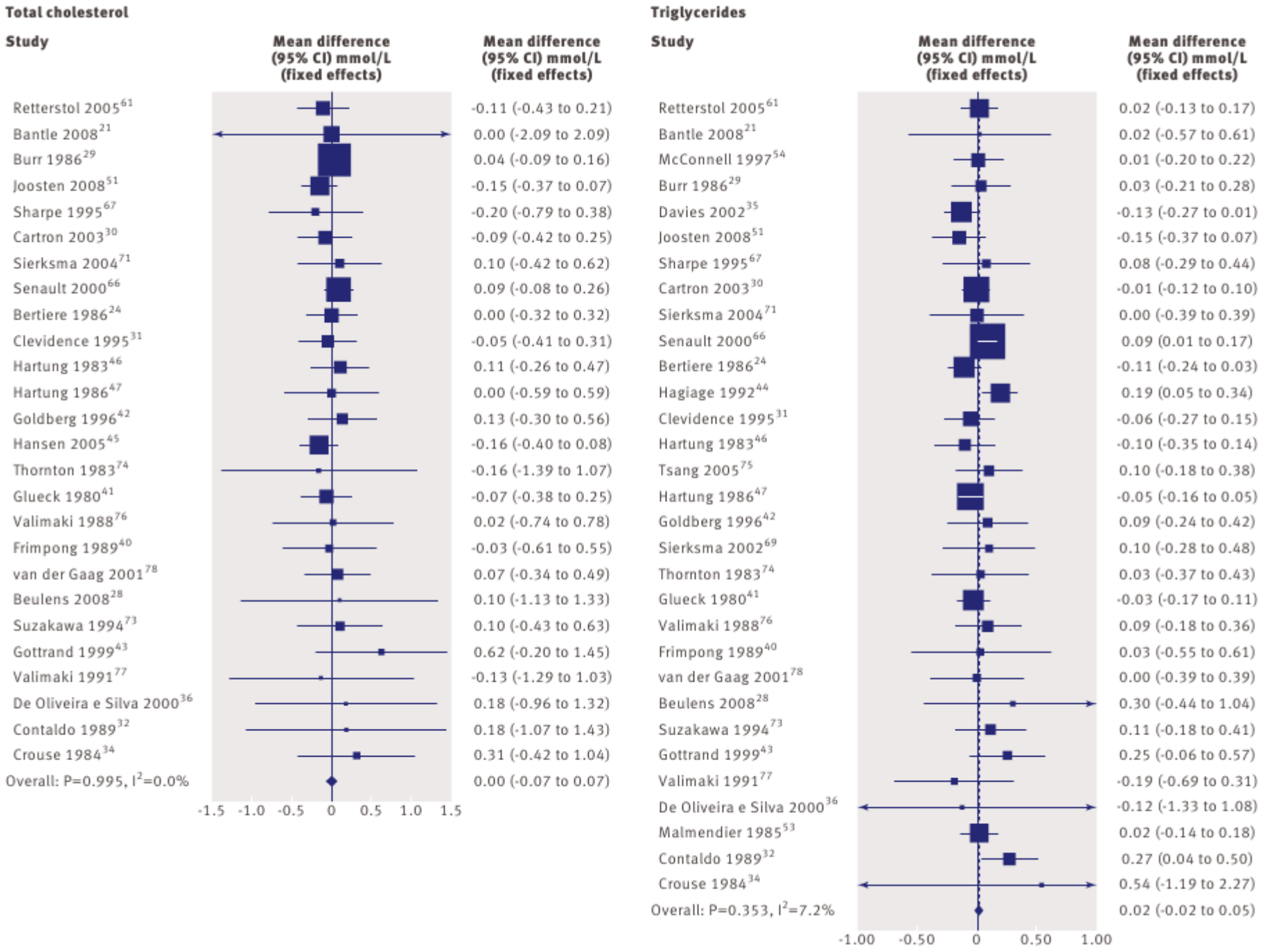


Fig 3 | Forest plot of meta-analysis (fixed effects) of effect of alcohol consumption on levels of total cholesterol and triglycerides

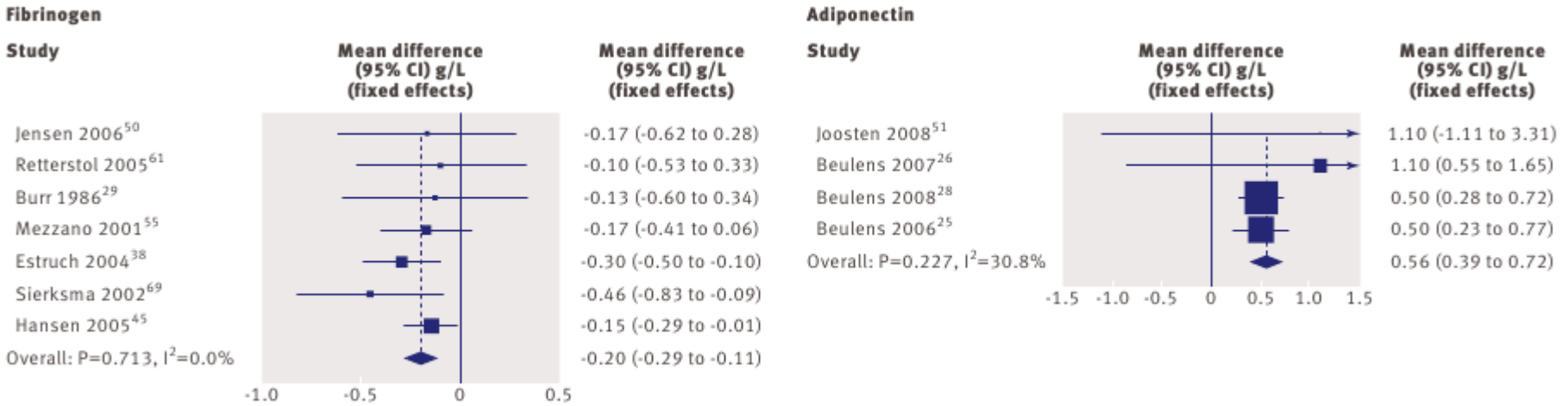


Fig 4 | Forest plot of meta-analysis of effect of alcohol consumption on levels of fibrinogen and adiponectin

Table 2 | Summary of pooled mean difference in biomarker level after alcohol use

Biomarker	No of pooled studies	No of pooled participants	Type of model	Pooled mean difference in biomarker level (95% CI)
High density lipoprotein cholesterol (mmol/L)	33	796	Random	0.094 (0.064 to 0.123)*†
Low density lipoprotein cholesterol (mmol/L)	24	513	Random	−0.11 (−0.22 to 0.006)†
Total cholesterol (mmol/L)	26	596	Fixed	0.00 (−0.066 to 0.067)
Triglycerides (mmol/L)	31	752	Fixed	0.016 (−0.018 to 0.051)
Apolipoprotein A1 (g/L)	16	374	Random	0.101 (0.073 to 0.129)*†
Lp(a) lipoprotein (mg/dL)	3	114	Fixed	0.80 (−4.17 to 5.76)
C reactive protein (mg/L)	5	186	Fixed	−0.11 (−0.31 to 0.10)
Interleukin 6 (pg/mL)	2	144	Fixed	0.502 (−3.482 to 4.486)
Tumour necrosis factor α (pg/mL)	3	121	Fixed	−0.469 (−32.02 to 31.08)
Plasminogen activator inhibitor 1 (ng/mL)	3	67	Fixed	3.285 (−0.898 to 7.469)
Tissue plasminogen activator (ng/mL)	3	67	Fixed	0.754 (−0.132 to 1.641)
Fibrinogen (g/L)	7	387	Fixed	−0.20 (−0.29 to −0.11)*
Adiponectin (mg/L)	4	108	Fixed	0.56 (0.39 to 0.72)*

*Indicates significant ($P<0.01$) change in biomarker level after alcohol use compared with a period of no alcohol use.
†Heterogeneity detected across pooled studies, where Q statistic $P<0.10$.

CHD risk factors: alcohol effects

HDL

- Higher levels are better
- Alcohol increases 3.5-4.0 mg/dL
- Fibrate increases 2.6 mg/dL

Fibrinogen

- Lower levels are better
- Alcohol decreases 0.2 g/L
- Increase of 1.0 g/L increases CHD risk 3x

Adiponectin

- Higher levels are better
- Alcohol increases 0.6 mg/L (~1 SD)
- Similar to effects of thiazolidinedione diabetic drugs (Avandia, Actos)

CHD risk factors: alcohol effect

No effect

- Total cholesterol
- LDL cholesterol
- Triglycerides
- Lp(a)
- C reactive protein
- Interleukin 6
- TNF α
- PAI 1
- TPA

Alcohol consumption and health

Moderate regular consumption of alcoholic beverages of any type is associated with beneficial effects

- Reduction of overall mortality
- Reduction of CHD incidence and mortality
- Reduction of CVD incidence and mortality
- Reduction of cognitive decline, dementia

Alcohol consumption and health

Excessive consumption of alcoholic beverages, ongoing or as binge drinking, as associated with adverse effects

- Alcoholic liver disease
- Drunk driving accidents and fatalities
- Disruption of personal, family and community life

There was a little girl,

Who had a little curl,

Right in the middle of her forehead.

When she was good,

She was very, very good,

And when she was bad, she was horrid.

Recommendations

1) In adults and in the elderly (regardless of sex), spontaneous consumption of alcoholic beverages within 30 g ethanol/d, that is ~two drinks/d for men and 15 g/d, that is ~one drink/d for women are to be considered acceptable and do not deserve intervention by the primary care physician or the health professional in charge. In fact, there is no evidence to suggest complete abstention from alcohol drinking by moderate users.
2) Patients with increased risk for specific diseases, for example women with familiar history of breast cancer, or subjects with familiar history of early CVD or cardiovascular patients should discuss their drinking habits with their physician.
3) No abstainer should be advised to drink for health reasons.
4) Alcohol use must be discouraged in specific physiological or personal situations or in selected age classes (children and adolescents, pregnant and lactating women and recovering alcoholics). Moreover, the possible interactions between alcohol and acute or chronic drug use must be discussed with the primary care physician.