Triangulation and Mendelian randomization

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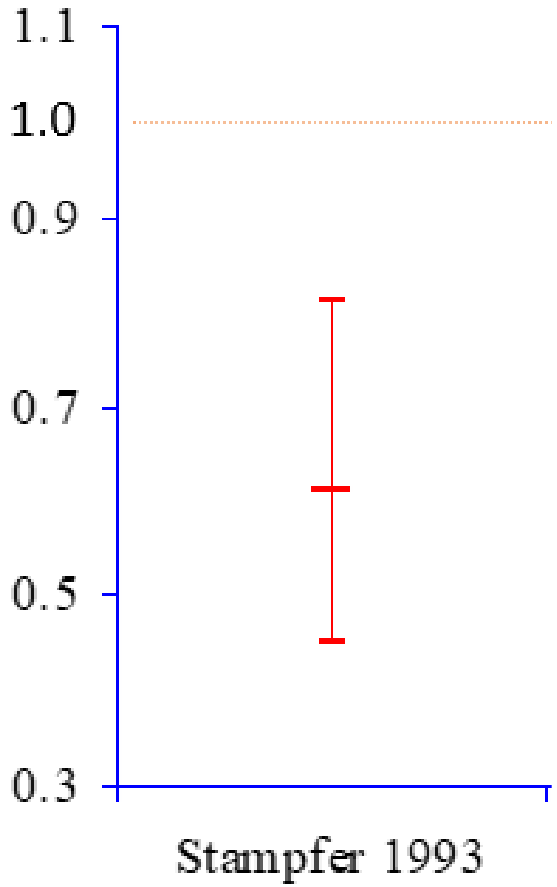
Outline

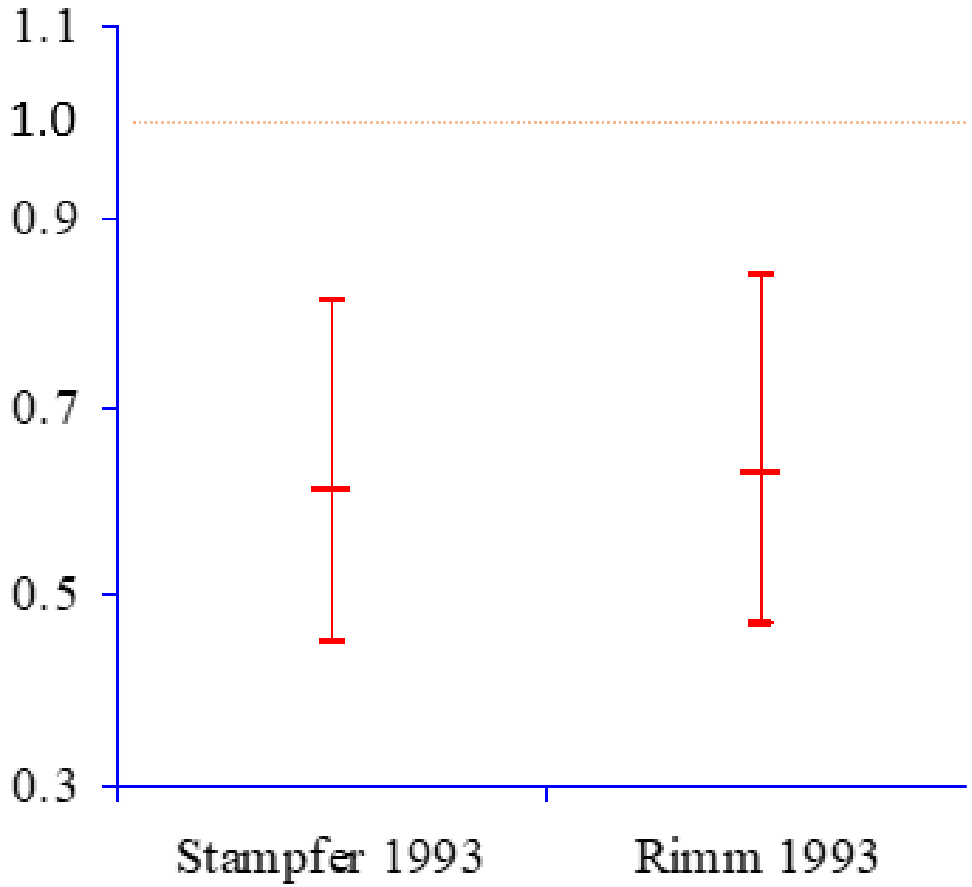
- Nutritional epidemiology as faux-science
- Triangulation
- Mendelian randomization

Vitamin E supplement use and risk of Coronary Heart Disease



Stampfer et al NEJM 1993; 328: 144-9

Vitamin E supplement use and risk of Coronary Heart Disease



Stampfer et al NEJM 1993; 328: 144-9; Rimm et al NEJM 1993; 328: 1450-6

The New York Times
nytimes.com

May 20, 1993

Vitamin E Greatly Reduces Risk Of Heart Disease, Studies Suggest

By JANE E. BRODY

Two new studies of more than 120,000 men and women strongly suggest that supplements of vitamin E can significantly reduce the risk of disease and death from fat-clogged coronary arteries. But the researchers and other experts cautioned against rushing out to buy the vitamin supplements before further clinical trials confirm that they are beneficial and safe.

The studies, by researchers at the Harvard School of Public Health and Brigham and Women's Hospital in Boston, showed that initially healthy people with the highest daily intakes of vitamin E developed coronary disease at a rate about 40 percent lower than comparable men and women whose intake of this vitamin was lowest. The preventive effects of vitamin E occurred independently of any change in blood levels of cholesterol.

The greatest protection was found at levels of about 100 international units of vitamin E a day for more than two years. The Federal recommended daily allowance for vitamin E is 15 units, and most people consume fewer than 25 units from foods like vegetable oils, wheat germ, seeds, whole grains and nuts.

The researchers said vitamin E, as an antioxidant, might reduce heart disease by having an effect on low-density lipoprotein cholesterol, or LDL, the so-called bad cholesterol. Studies have shown that this type of cholesterol damages arteries primarily after it has been oxidized.

The new findings, which appear today in The New England Journal of Medicine, are some of the first to find health benefits from taking large-dose vitamin supplements. Most medical experts have viewed "megadoses" of vitamins as a popular remedy whose value is unproven. Expert Urge Caution

While a person might conclude from the findings that it would be wise to take large doses of vitamin E supplements daily, their long-term safety has not been established. Experts say, however, many people take upward of 400 units of vitamin E supplements a day with no apparent harm.

Although experts expressed enthusiasm for the results, the researchers who conducted the studies and independent scientists cautioned against "leaping on the supplement bandwagon," as Dr. Claude L'Enfant, director of the National Heart, Lung and Blood Institute in Bethesda, Md., put it.

Dr. L'Enfant said in an interview that recommendations about taking vitamin E supplements must await the completion of more stringently designed clinical trials that clearly establish a benefit of vitamin E supplements and define any possible risks. Until such trials are completed, he said, researchers cannot be sure that vitamin E itself and not some other factor they neglected to account for was responsible for the reduction in coronary disease. Overreliance on Vitamin

Experts also warned against relying on vitamin E for protection instead of making the more difficult changes in diet, exercise, smoking and other habits that are known to affect coronary risk.

Dr. Michael Brown of the University of Texas Southwestern Medical Center in Dallas said, "Vitamin E may help to minimize the toxicity of LDL cholesterol, but the real problem is that the LDL levels we accept as normal are really unnaturally high." Dr. Brown and his colleague, Dr. Joseph Goldstein, shared a Nobel Prize for elucidating how the body processes cholesterol.

Dr. Brown said that while people may view vitamin E as an innocuous substance, "the doses that seem protective are no longer in the category of vitamin, they are really drugs, and all drugs must be studied to determine their relative benefits and risks." He added: "The data are very suggestive but not definitive. We have to wait and see."

Still, Dr. Brown said, "the whole area is very exciting, and suggests that there may be a way to intervene therapeutically in coronary artery disease with antioxidants."

BMJ

LONDON, SATURDAY 11 JUNE 1994

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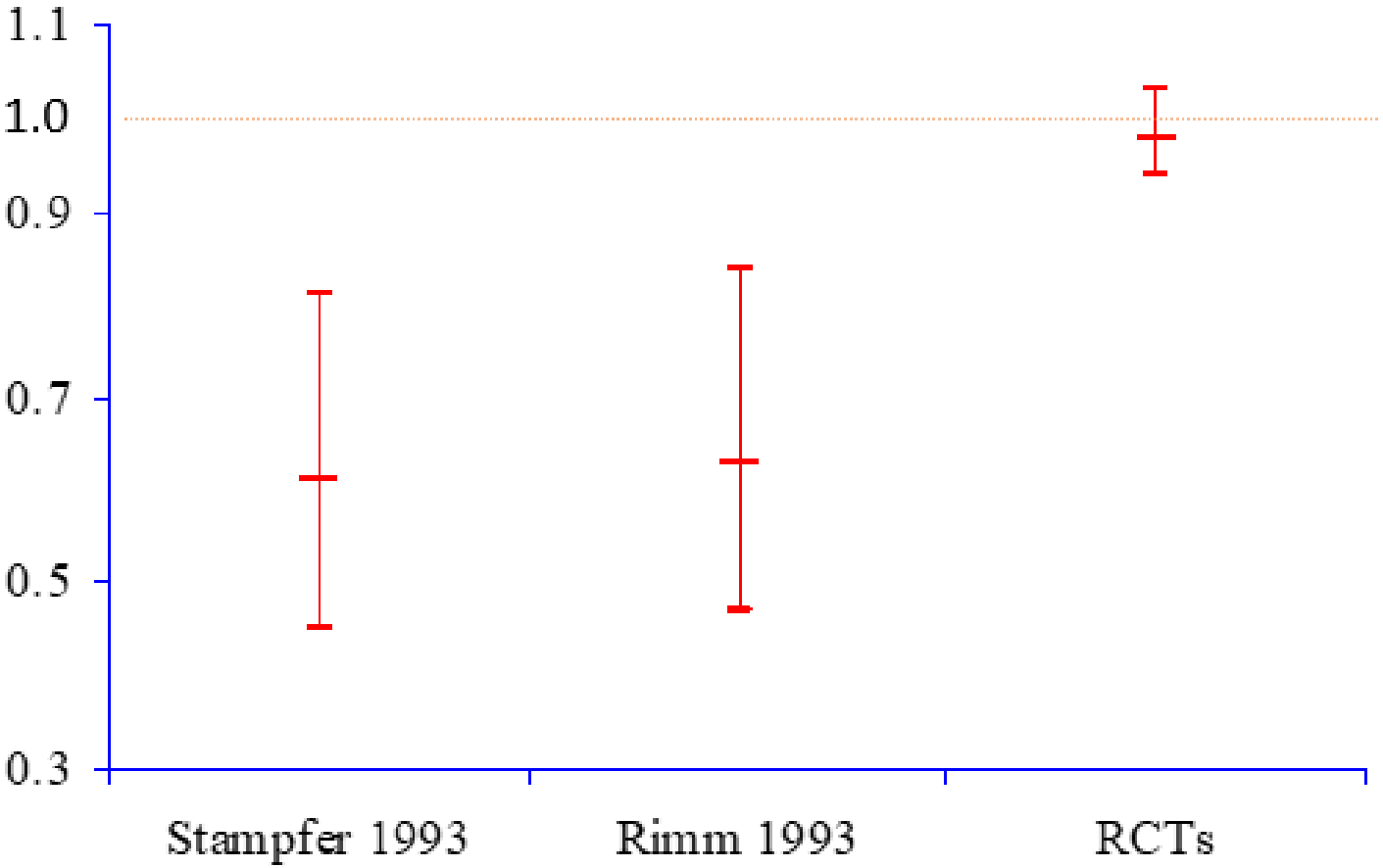
If papers submitted to journals had to be accompanied by a disk copy of the data on which they were based then statistical referees could check that the results were not the product of overenthusiastic data torture.[25] In this way sharing of data could contribute to improving the quality of published research. The fall in submissions to a journal brave enough to implement this policy would be a useful indicator of its success.

existing data to answer issues not directly addressed by the primary researchers represents an efficient use of resources. Sharing data can also reduce the burden imposed upon study

ferring the costs of preparing databases to secondary analysts, ensuring no commercial exploitation of shared data by the recipient, and constructing formal agreements on sharing

Davey Smith G. Increasing the accessibility of data (editorial). BMJ 1994;308:1519-1520.

Vitamin E supplement use and risk of Coronary Heart Disease



Stampfer et al NEJM 1993; 328: 144-9; Rimm et al NEJM 1993; 328: 1450-6; Eidelman et al Arch Intern Med 2004; 164:1552-6

Vitamin E levels and risk factors: Women's Heart Health Study

Childhood SES	↓
Manual social class	↓
No car access	↓
State pension only	↓
Smoker	↓
Daily alcohol	↑
Exercise	↑
Low fat diet	↑
Obese	↓
Height	↑
Leg length	↑

Lawlor et al, Lancet 2004

International Journal of Epidemiology, 2016, 1866–1886
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Original article

Approaches to causal inference

Triangulation in aetiological epidemiology

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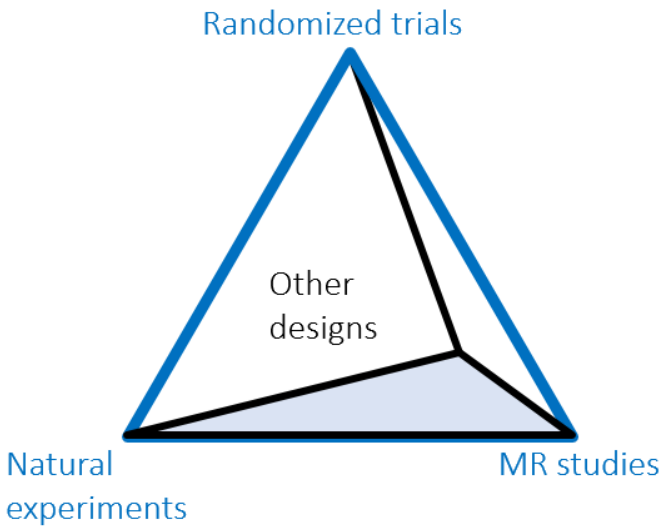

Triangulation approaches

- Positive controls

Triangulation approaches

- Positive controls
- Negative controls

BMJ

BMJ 2014;348:g1610 doi: 10.1136/bmj.g1610 (Published 19 March 2014)

RESEARCH

Fried food consumption, genetic risk, and body mass index: gene-diet inte studies

OPEN ACCESS

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Jinyan Huang *research fellow*[5], Lyr
Liming Liang *assistant professor*[5],
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Andrew T Chan *associate professc*
professor[4 5], Paul M Ridker *professor*[3 9 10], David J Hunter *professor*[1 4 5], Walter C Willett *professor*[1 4 5], Eric B Rimm *associate professor*[1 4 5], Daniel I Chasman *associate professor*[3 10], Frank B Hu *professor*[1 4 5], Lu Qi *assistant professor*[1 4]

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"Our findings further emphasize the importance of reducing consumption of fried food in the prevention of obesity".

Abstract

Objective To examine the interactions between genetic predisposition and consumption of fried food in relation to body mass index (BMI) and obesity.

consumed fried foods less than once a week amounted to 1.0 (SE 0.2) in women and 0.7 (SE 0.2) in men, whereas the corresponding differences were 0.5 (SE 0.2) and 0.4 (SE 0.2) in the lowest third of the genetic risk score. The gene-diet interaction was replicated in the

The NEW ENGLAND JOURNAL of MEDICINE

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Sugar-Sweetened Beverages and Genetic Risk of Obesity

Qibin Qi, Ph.D., Audrey Y. Chu, Ph.D., Jae H. Kang, Sc.D., Majken K. Jensen, Ph.D., Gary C. Curhan, M.D., Sc.D., Louis R. Pasquale, M.D., Paul M. Ridker, M.D., M.P.H., David J. Hunter, M.B., B.S., Sc.D., Walter C. Willett, M.D., Dr.P.H., Eric B. Rimm, Sc.D., D

"Our findings further emphasize the importance of reducing consumption of sugar sweetened beverages in the prevention of obesity".

BACKGROUND

Temporal increases in the consu leled the rise in obesity prevalen acts with the genetic predisposit

METHODS

We analyzed the interaction be sugar-sweetened beverages in relation to body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and obesity risk in 6934 women from the Nurses' Health Study (NHS) and in 4423 men from the Health Professionals Follow-up Study (HPFS) and also in a replication cohort of 21,740 women from the Women's Genome Health Study (WGHS). The genetic-predisposition score was calculated on the basis of 32 BMI-associated loci. The intake of sugar-sweetened beverages was examined prospectively in relation to BMI.

RESULTS

In the NHS and HPFS cohorts, the genetic association with BMI was stronger among participants with higher intake of sugar-sweetened beverages than among those with lower intake. In the combined cohorts, the increases in BMI per increment of 10 risk alleles were 1.00 for an intake of less than one serving per month, 1.12 for one to four servings per month, 1.38 for two to six servings per week, and 1.78 for one or more servings per day ($P<0.001$ for interaction). For the same categories of intake, the relative risks of incident obesity per increment of 10 risk alleles

Network Medicine (J.H.K., G.C.C., L.R.P., D.J.H., W.C.W., E.B.R., F.B.H., L.Q.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; and the Department of Ophthalmology (L.R.P.), Massachusetts Eye and Ear Infirmary, Harvard Medical School — all in Boston. Address reprint requests to Dr. Lu Qi at the Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115, or at nhlqi@channing.harvard.edu.

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doi: 10.1093/ije/dyw337
Advance Access Publication Date: 10 January 2017
Original article

Obesogenic Risks

Gene–obesogenic environment interactions in the UK Biobank study

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[1]Genetics [illegible] Centre for [illegible] Truro, TR[illegible] Exeter, RI[illegible] the Unive[illegible] Geograph[illegible] Engineeri[illegible] of Population Epidemiology, Division of Primary Care Medicine, Department of Community Medicine, Primary Care and Emergency Medicine, Geneva University Hospitals and University of Geneva, Geneva, Switzerland, [7]Department of Ambulatory care and Community medicine, University of Lausanne, Lausanne, Switzerland, [8]Department of Epidemiology, Emory University, Atlanta, GA, USA, [9]Population Health Research Institute, St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK, [10]Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital (CHUV), Lausanne, Switzerland and [11]Swiss Institute of Bioinformatics, Lausanne, Switzerland

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Accepted 31 October 2016

Our findings further emphasise the importance of increasing sun cream use in the prevention of obesity.

Abstract

Background: Previous studies have suggested that modern obesogenic environments accentuate the genetic risk of obesity. However, these studies have proven controversial as to which, if any, measures of the environment accentuate genetic susceptibility to high body mass index (BMI).

Triangulation approaches

- Positive controls
- Negative controls
- Cross-context comparisons

Age-standardized death rates by fried food consumption per 100,000 man-years for men, aged 40-69 stratified by smoking status

Definition of subgroup	Age-standardized death rates*	
	Never smoked regularly	Cigarettes 20+ a day
Fried food		
None	1,208*	2,573*
1–2 times a wk	1,004	1,694
3–4 " " "	642	1,714
5–9 " " "	781	1,520
10–14 " " "	722	1,524
15+ " " "	702	1,399

Cuyler Hammond E. Smoking In Relation to Mortality and Morbidity. Findings in First Thirty-Four Months of Follow-Up in a Prospective Study Started in 1959. Journal of the National Cancer Institute 1964;32:1161-1188.

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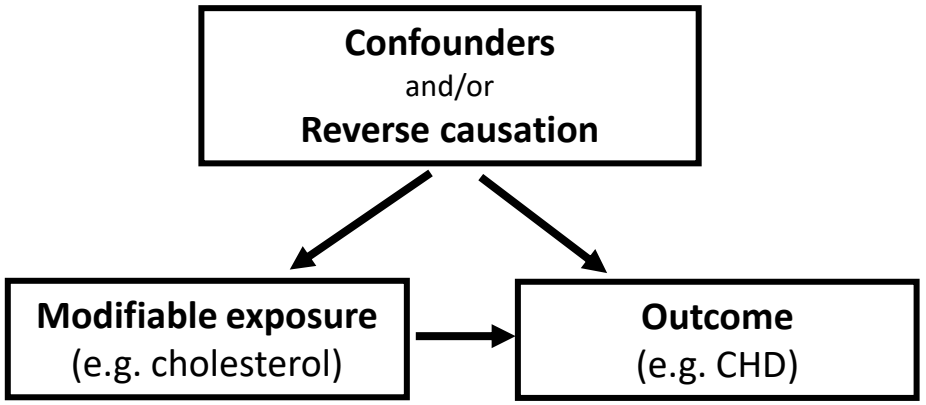
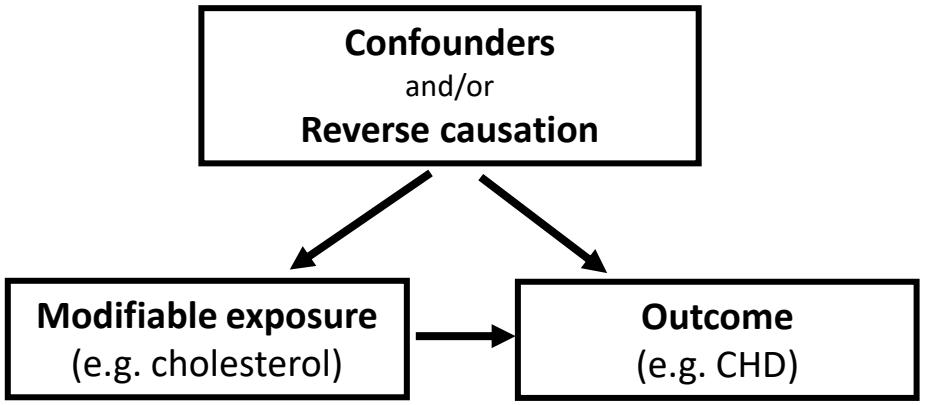
- Mendelian randomization

Conventional observational epidemiology

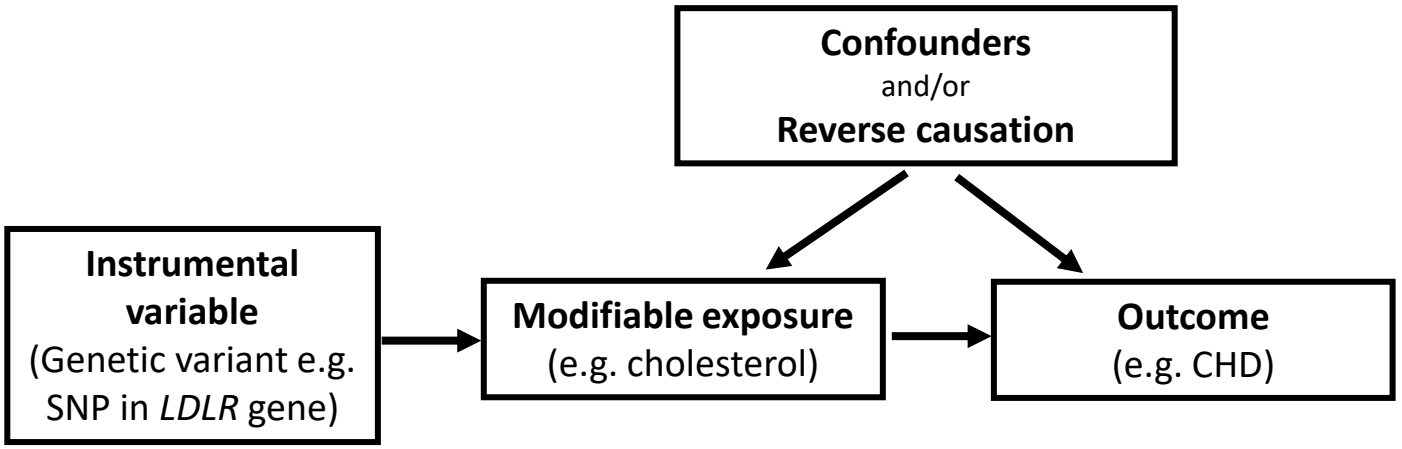


Conventional observational epidemiology



It is often impossible to exclude confounding and /or reverse causation as an explanation for observed exposure/outcome associations

Mendelian randomization approach



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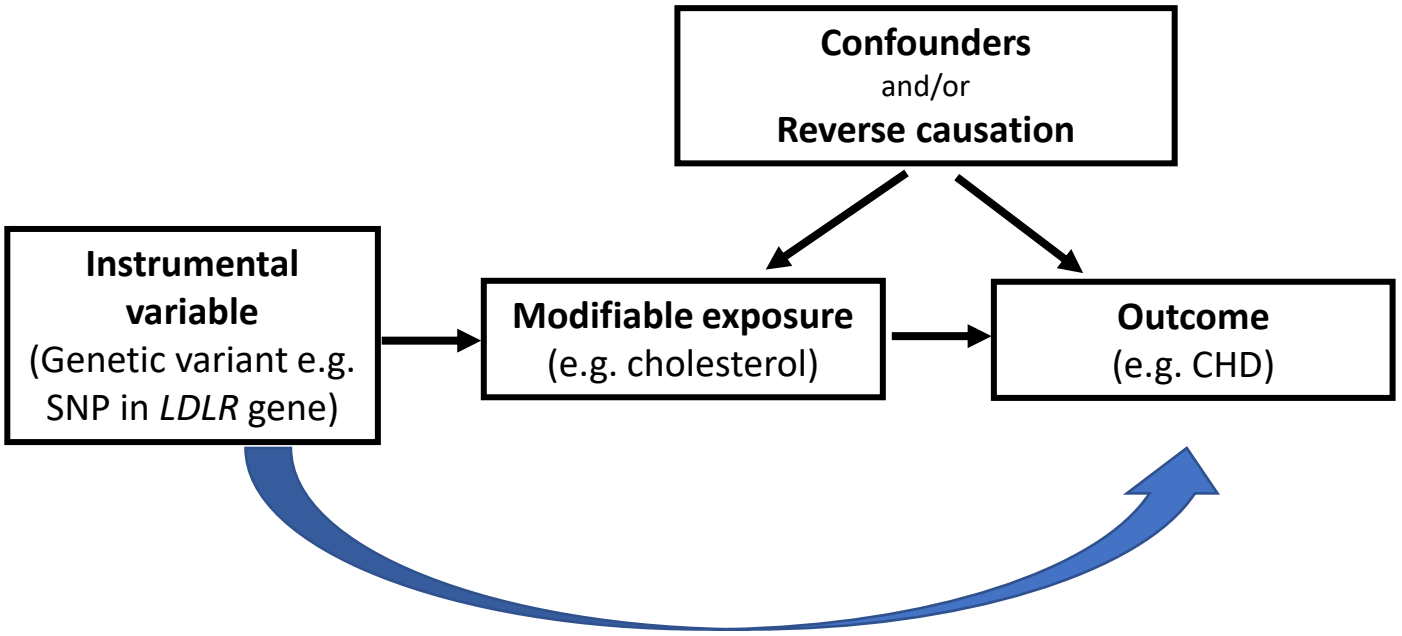

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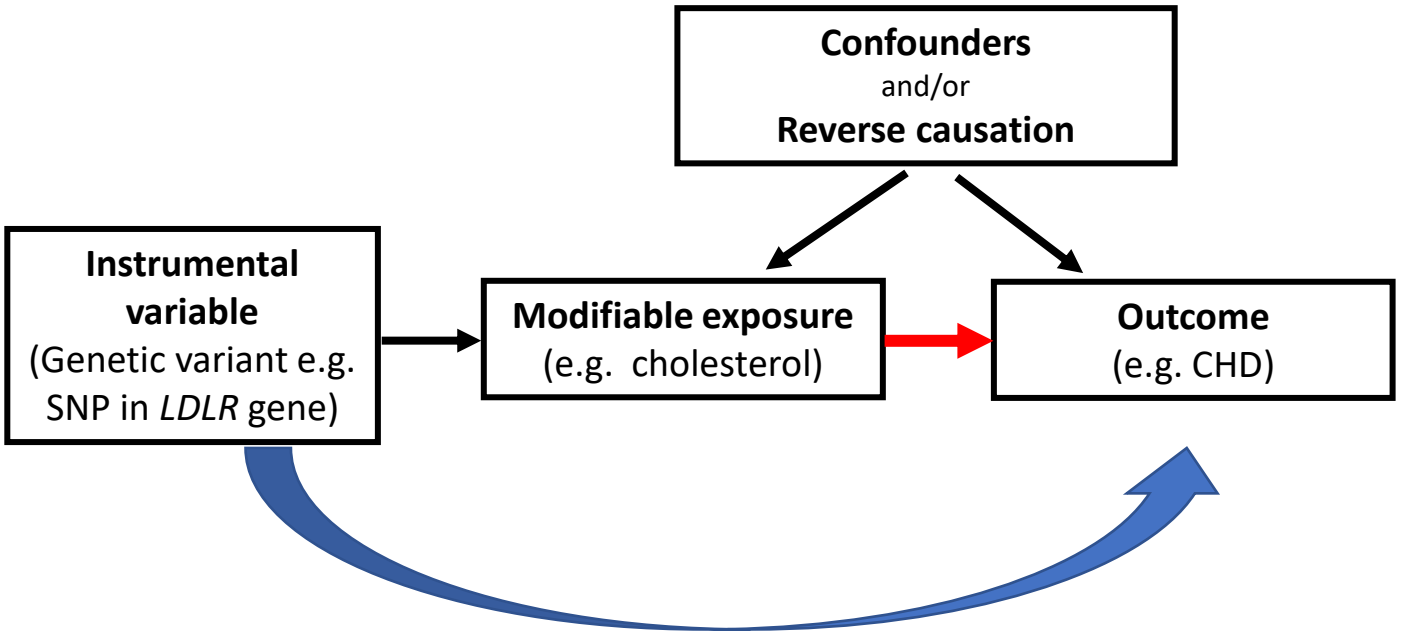

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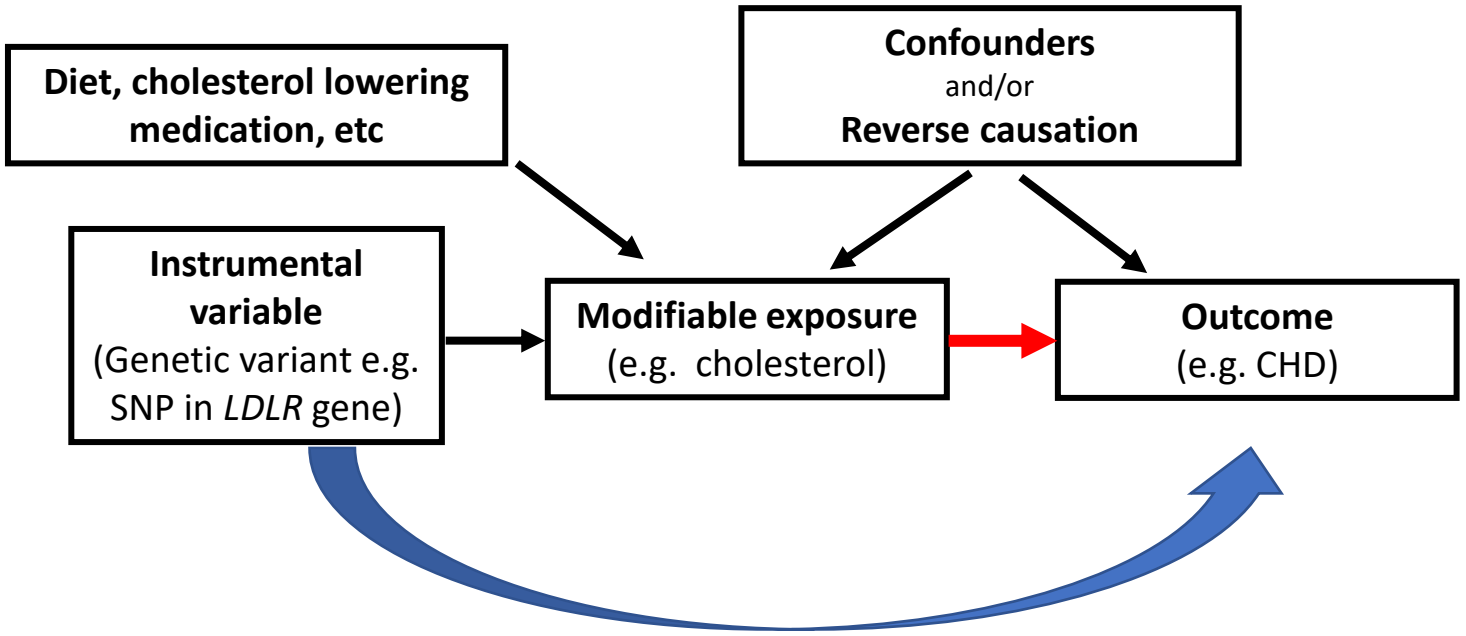
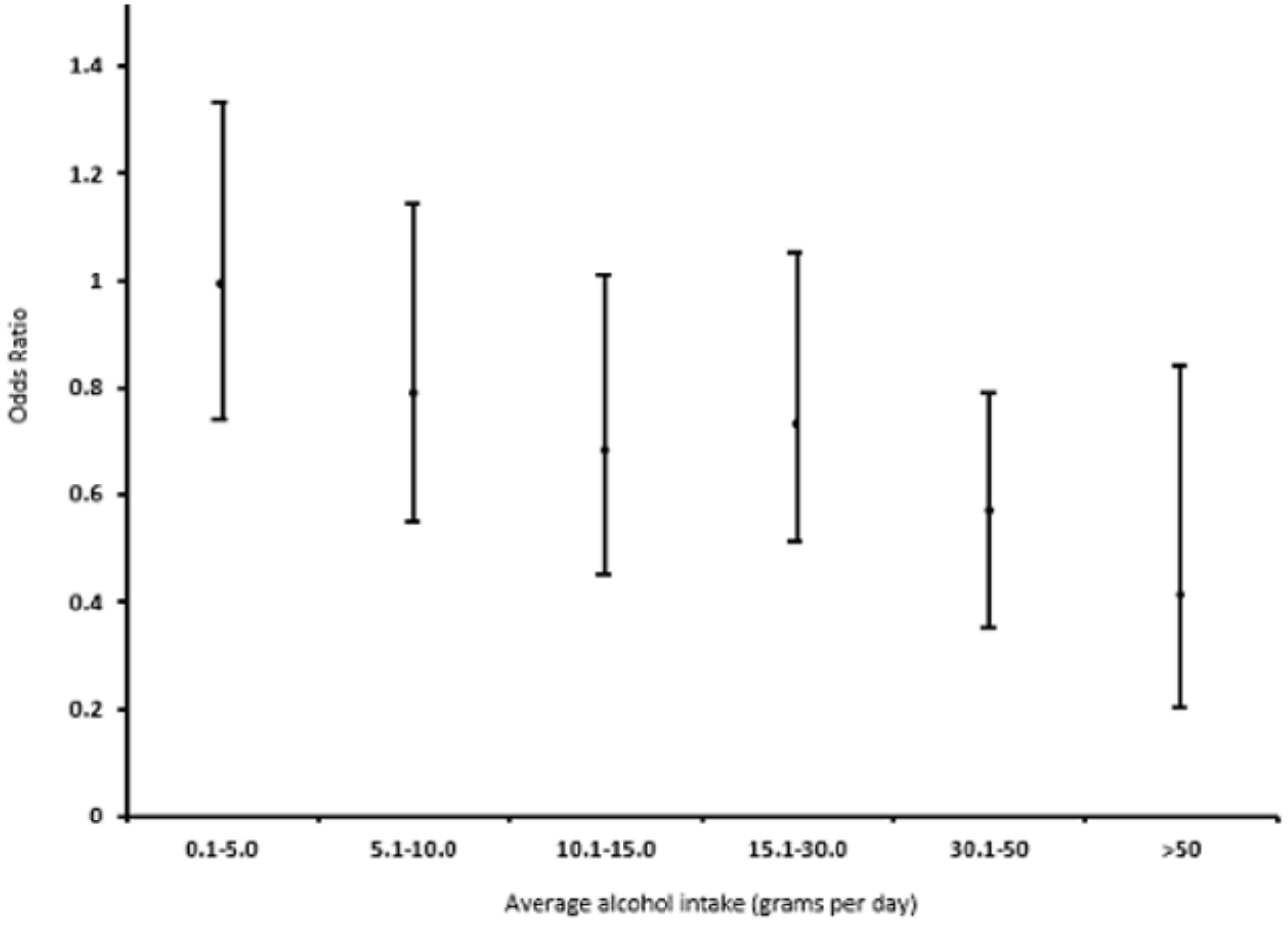
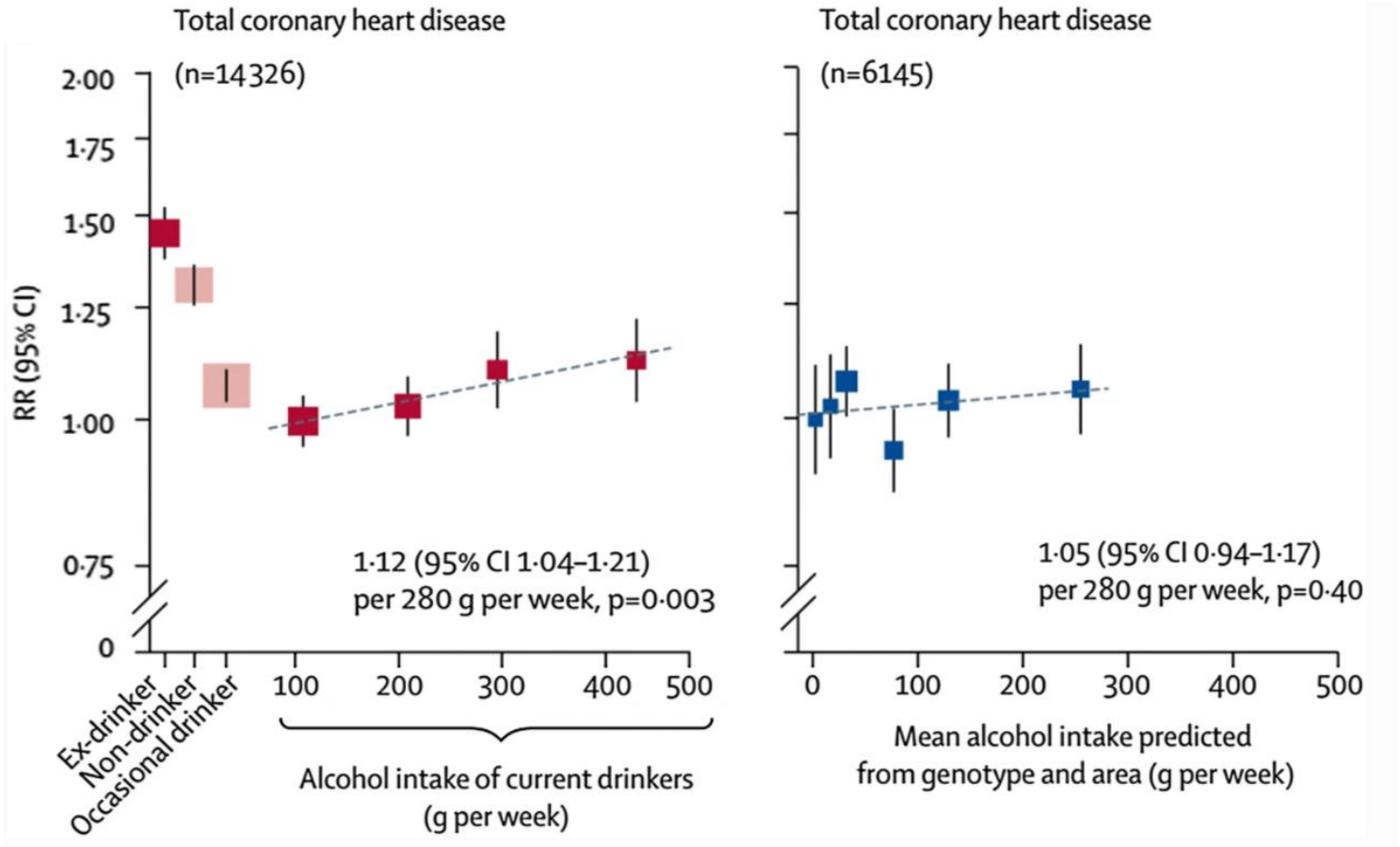


Relative risk of coronary heart disease by daily alcohol consumption, compared to non-drinkers



Rimm EB et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet. 1991;338(8765):464–8

Is alcohol good for you?



Milwood IY et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet* 2019;393:1831-1842

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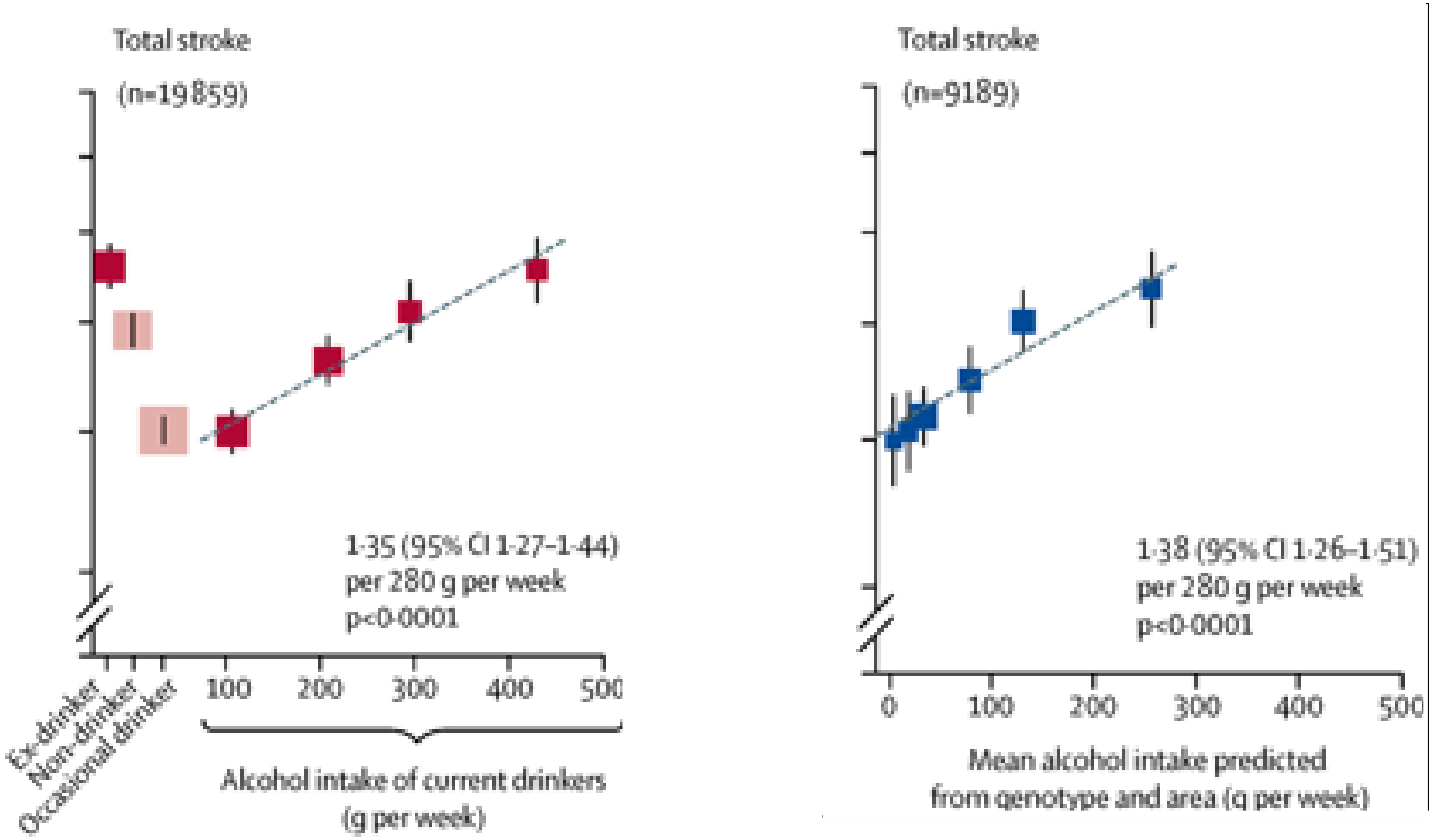
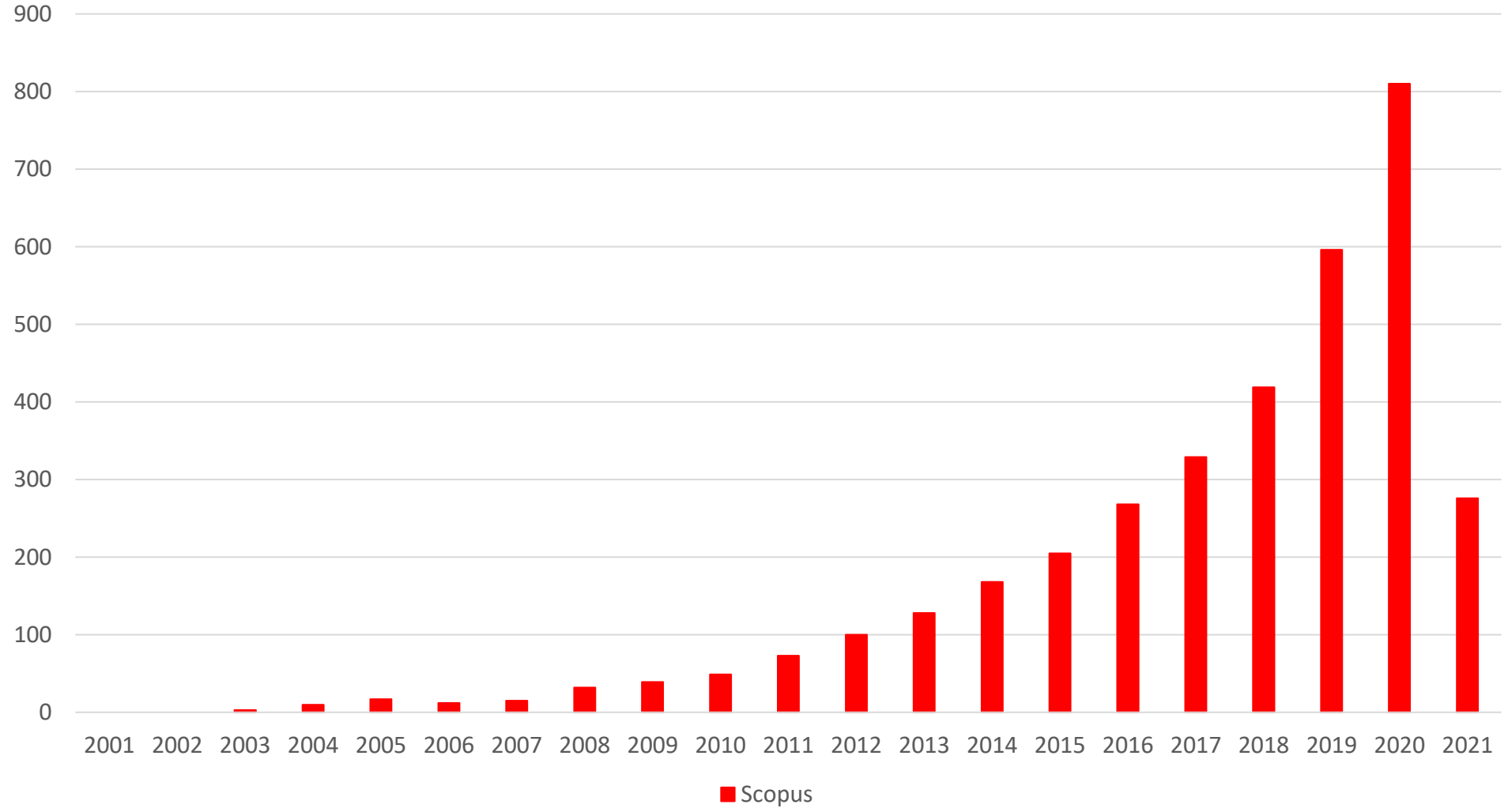


Milwood IY et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet* 2019;393:1831-1842

“Mendelian randomisation" and "Mendelian randomization"



Triangulation approaches

- Positive controls
- Negative controls
- Cross-context comparisons
- Natural experiments
- Instrumental variables
- Mendelian randomization
- Randomized controlled trials

Medical News & Perspectives

Backlash Over Meat Dietary Recomme About Corporate Ties to Nutrition Scie

Rita Rubin, MA

It's almost unheard of for medical journals to get blowback for studies before the data are published. But that's what happened to the *Annals of Internal Medicine* last fall as editors were about to post several studies showing that the evidence linking red meat consumption with cardiovascular disease and cancer is too weak to recommend that adults eat less of it.

Annals Editor-in-Chief Christine Laine, MD, MPH, saw her inbox flooded with roughly 2000 emails—most bore the same message, apparently generated by a bot—in a half hour. Laine's inbox had to be shut down, she said. Not only was the volume unprecedented in her decade at the helm of the respected journal, the tone of the emails was particularly caustic.

"We've published a lot on firearm injury prevention," Laine said. "The response from the NRA (National Rifle Association) was less vitriolic than the response from the True Health Initiative."

The True Health Initiative (THI) is a nonprofit founded and headed by David Katz, MD. The group's website describes its work as "fighting fake facts and combating false doubts to create a world free of pre-

recalled in an intervi
haps that's not surpr
researchers have bu
nutrition epidemiolog
understand it's upsett

Katz *et al. BMC Medical Research Methodology* (2019) 19:178
https://doi.org/10.1186/s12874-019-0811-z

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review

D. L. Katz[1,2,3], M. C. Karlsen[1,4*], M. Chung[5], M. M. Shams-White[6], L. W. Green[7], J. Fielding[8], A. Saito[9] and W. Willett[10,11]

Abstract

Background: Current methods for assessing strength of evidence prioritize the contributions of randomized controlled trials (RCTs). The objective of this study was to characterize strength of evidence (SOE) tools in recent use, identify their application to lifestyle interventions for improved longevity, vitality, or successful aging, and to assess implications of the findings.

Methods: The search strategy was created in PubMed and modified as needed for four additional databases: Embase, AnthropologyPlus, PsycINFO, and Ageline, supplemented by manual searching. Systematic reviews and meta-analyses of intervention trials or observational studies relevant to lifestyle intervention were included if they used a specified SOE tool. Data was collected for each SOE tool. Conditions necessary for assigning the highest SOE grading and treatment of prospective cohort studies within each SOE rating framework were summarized. The expert panel convened to discuss the implications of findings for assessing evidence in the domain of lifestyle medicine.

Results and conclusions: A total of 15 unique tools were identified. Ten were tools developed and used by governmental agencies or other equivalent professional bodies and were applicable in a variety of settings. Of these 10, four require consistent results from RCTs of high quality to award the highest rating of evidence. Most SOE tools include prospective cohort studies only to note their secondary contribution to overall SOE as compared to RCTs. We developed a new construct, *Hierarchies of Evidence Applied to Lifestyle Medicine* (HEALM), to illustrate the feasibility of a tool based on the specific contributions of diverse research methods to understanding lifetime effects of health behaviors. Assessment of evidence relevant to lifestyle medicine requires a potential adaptation of SOE approaches when outcomes and/or exposures obviate exclusive or preferential reliance on RCTs. This systematic review was registered with the International Prospective Register of Systematic Reviews, PROSPERO [CRD42018082148].

Keywords: Strength of evidence, SOE, Systematic review, Lifestyle medicine, Lifetime effects, HEALM

Archie Cochrane with the Times crossword puzzle, early 1980s

SPECIAL ARTICLE

EPIDEMIOLOGY AS A GUIDE TO CLINICAL DECISIONS

The Association between Triglyceride and Coronary Heart Disease

STEPHEN B. HULLEY, M.D., M.P.H., RAY H. ROSENMAN, M.D., RICHARD D. BAWOL, PH.D., AND RICHARD J. BRAND, PH.D.

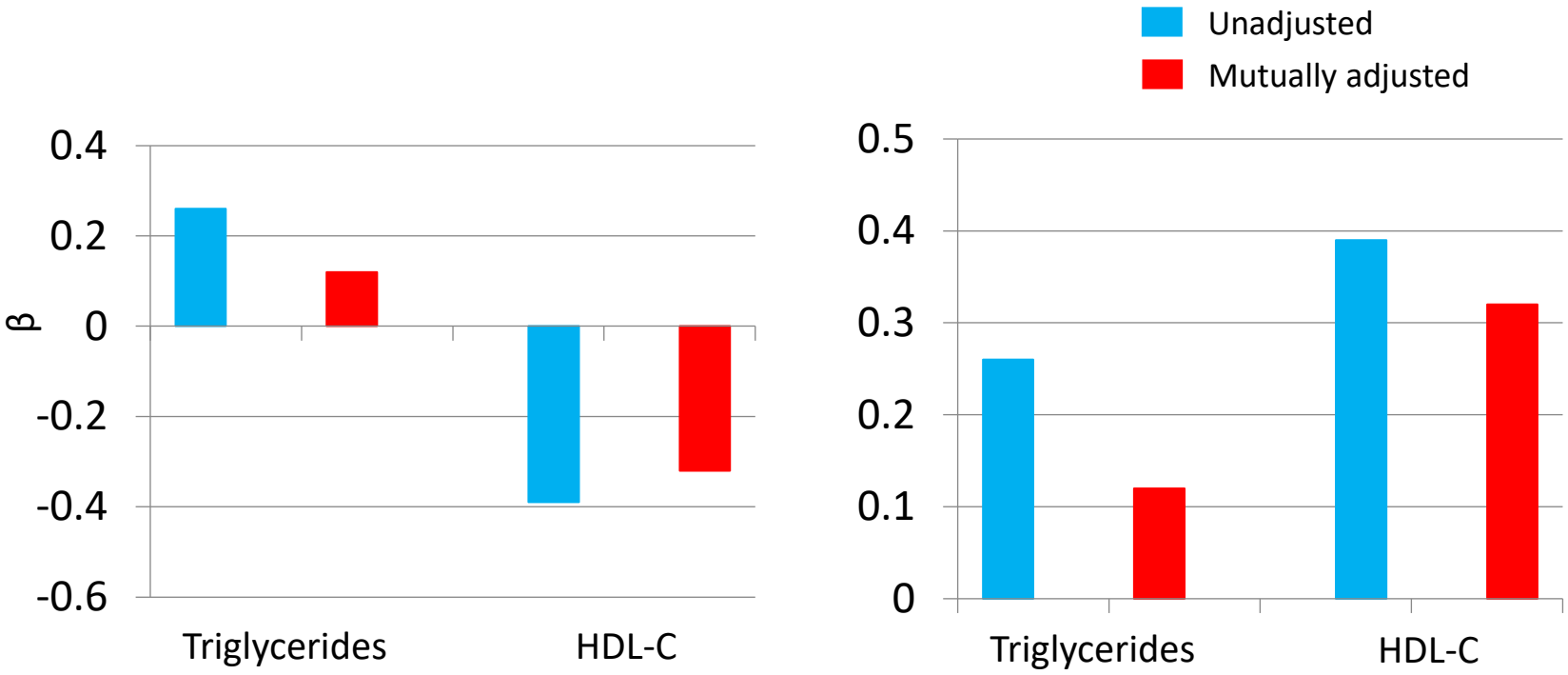
Abstract The hypothesis that triglyceride is a cause of coronary heart disease, although unconfirmed and never universally accepted, has nonetheless strongly influenced the practice of preventive medicine. We have examined the epidemiologic association between triglyceride and coronary heart disease to evaluate the validity of inferring that there is a causal relation between the two. Neither the evidence from published studies nor an analysis of data from the Western Collaborative Group Study provides strong support for the causal hypothesis. Information from other scientific disciplines is also meager, contrasting with the coherence of diverse evidence supporting the hypothesis that cholesterol is a cause of coronary heart disease.

These arguments fall short of disproving the belief that lowering triglyceride will prevent coronary heart disease, especially since triglyceride and cholesterol are inextricably associated through mutual lipoprotein carriers. But we propose that the ethics of preventive medicine place the burden of proof on the proponents of intervention. We therefore recommend that widespread screening and treatment of healthy persons for hypertriglyceridemia be abandoned until more persuasive evidence becomes available. (N Engl J Med. 1980; 302:1383-9.)

IN 1959, Albrink and Man found high serum levels of triglyceride in men with a history of myocardi-

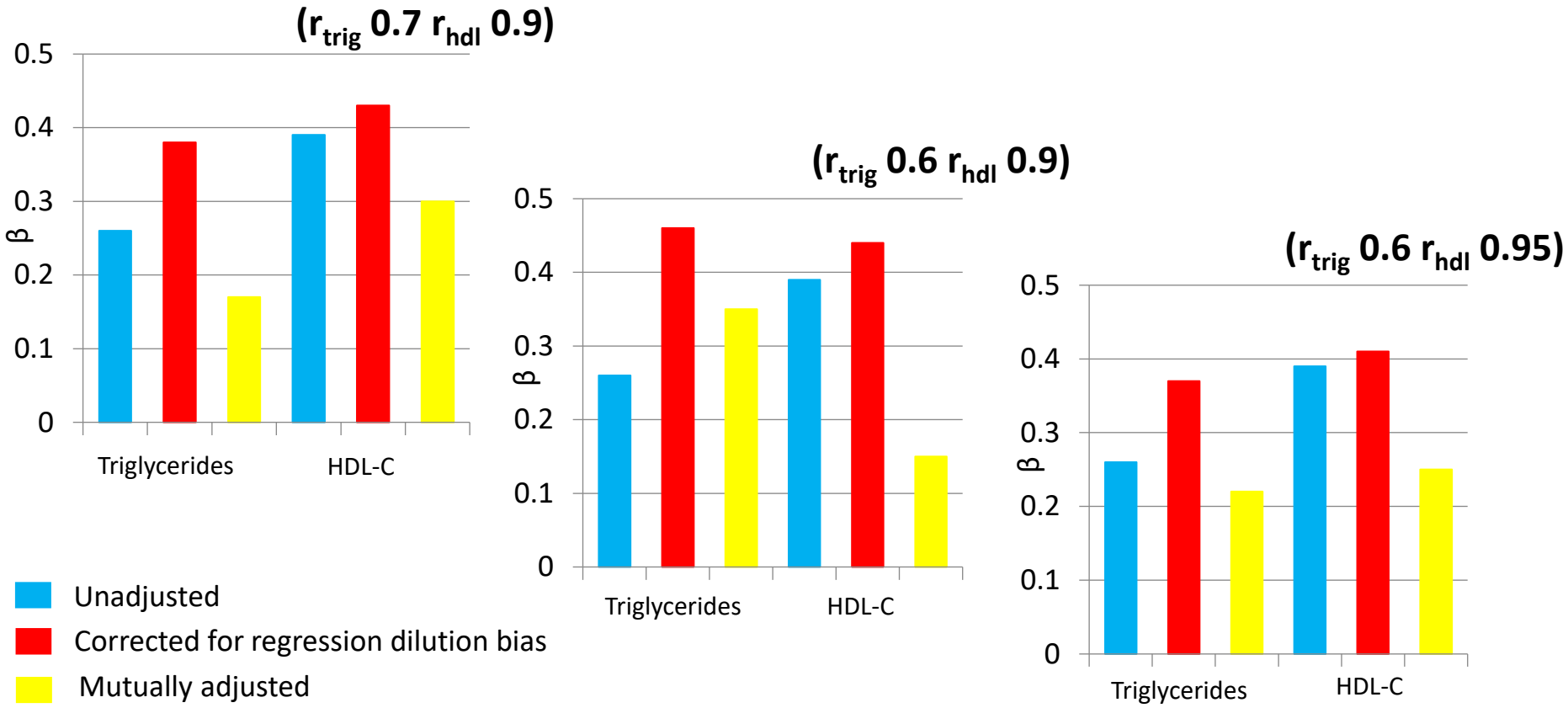
prescribing diet and drugs for otherwise healthy persons with hypertriglyceridemia[34,35] has given way to a

Triglycerides and HDL cholesterol – which has the stronger association with coronary heart disease?



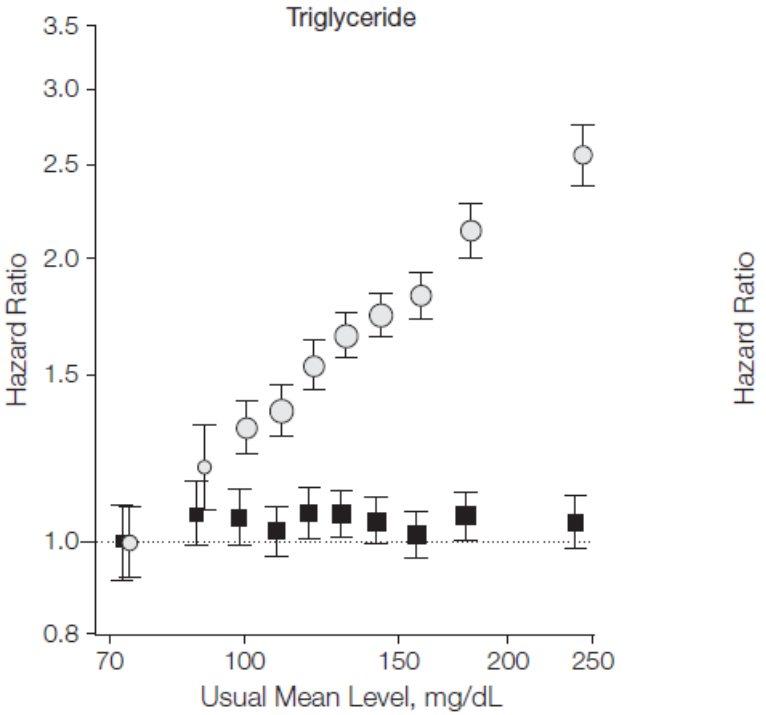
Phillips A, Davey Smith G. How independent are "independent" effects? Relative risk estimation when correlated exposures are measured imprecisely. J Clin Epidemiol 1991;44:1223-31.

Triglycerides and HDL cholesterol with measurement error. Which now has the stronger association with coronary heart disease?



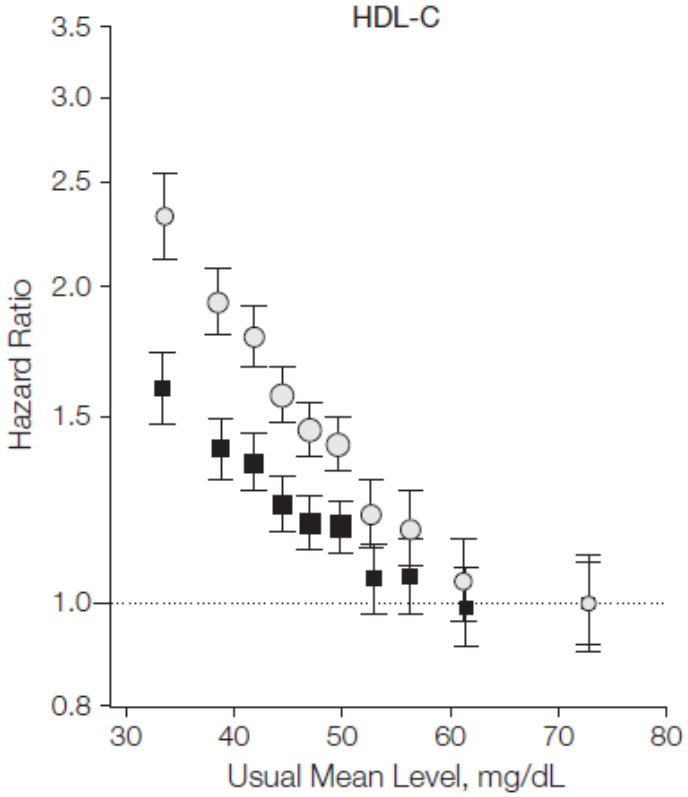
Phillips A, Davey Smith G. How independent are "independent" effects? Relative risk estimation when correlated exposures are measured imprecisely. J Clin Epidemiol 1991;44:1223-31.

Risk of coronary heart disease according to triglyceride level, with and without adjustment



The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000

Risk of coronary heart disease according to HDL-C level, with and without adjustment

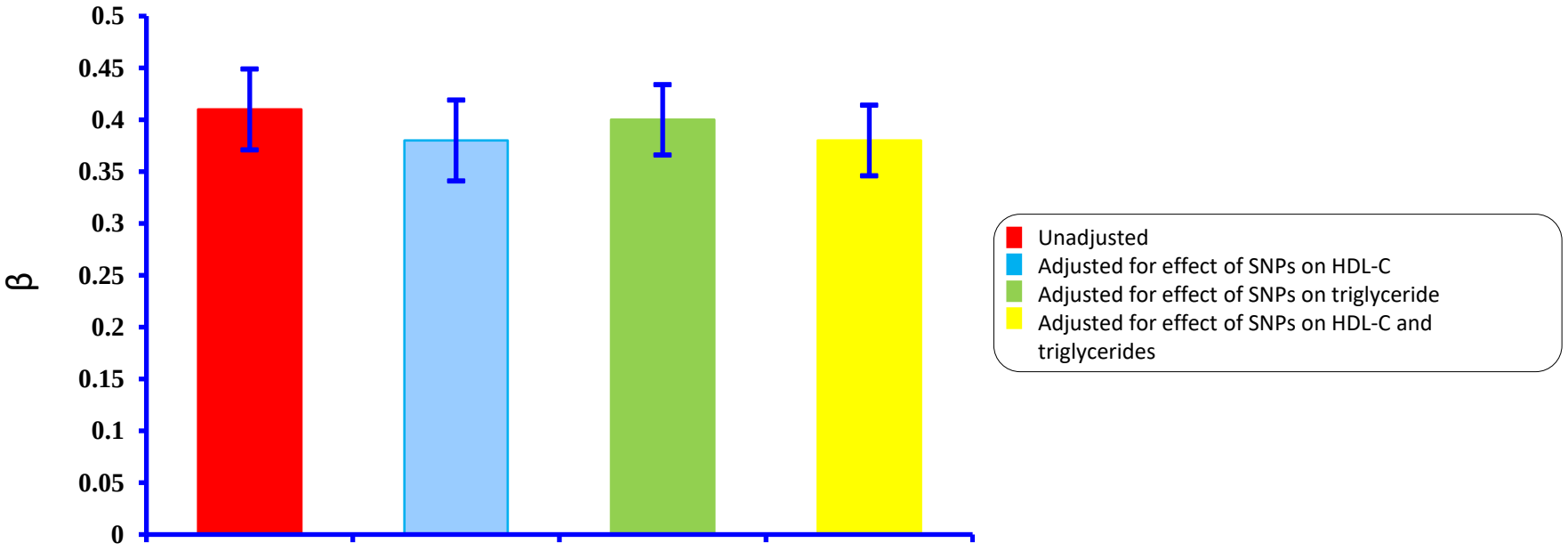


The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000

“The current findings suggest that therapy directed at HDL-C as well as non-HDL-C may generate substantial additional benefit”

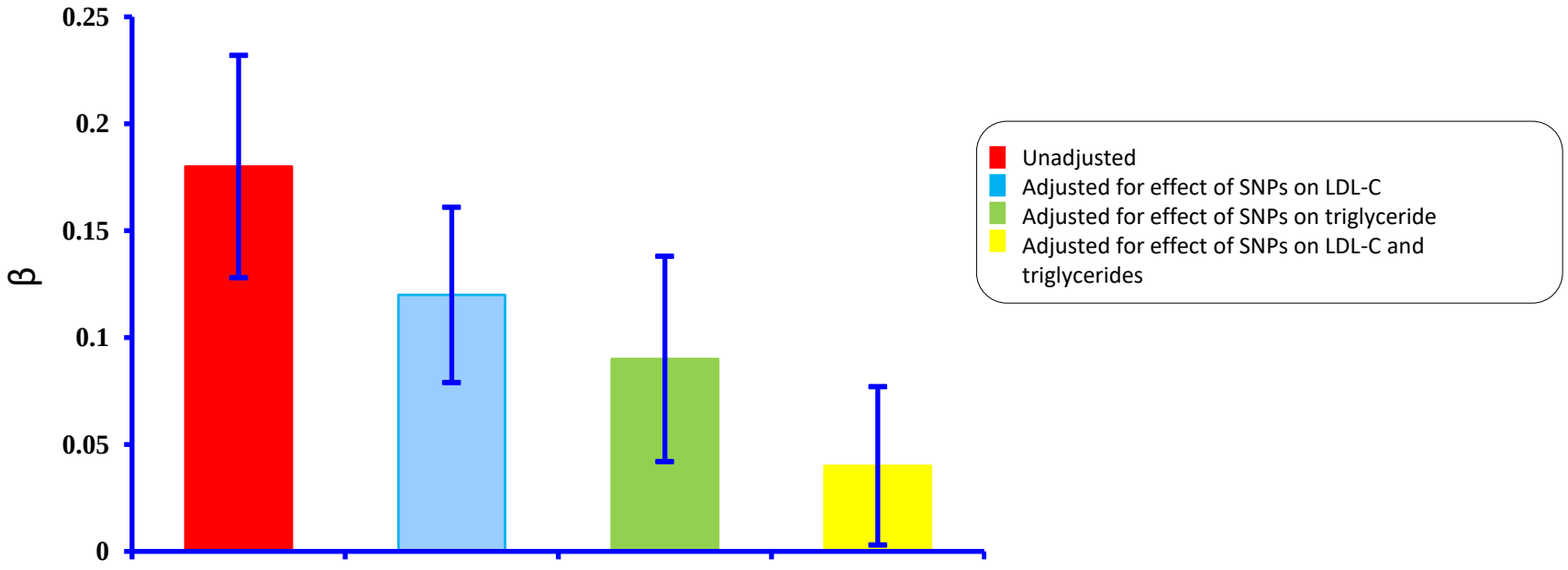
The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000

Association of strength of a SNP's effect on LDL-C with its strength of effect on CHD risk, with adjustment



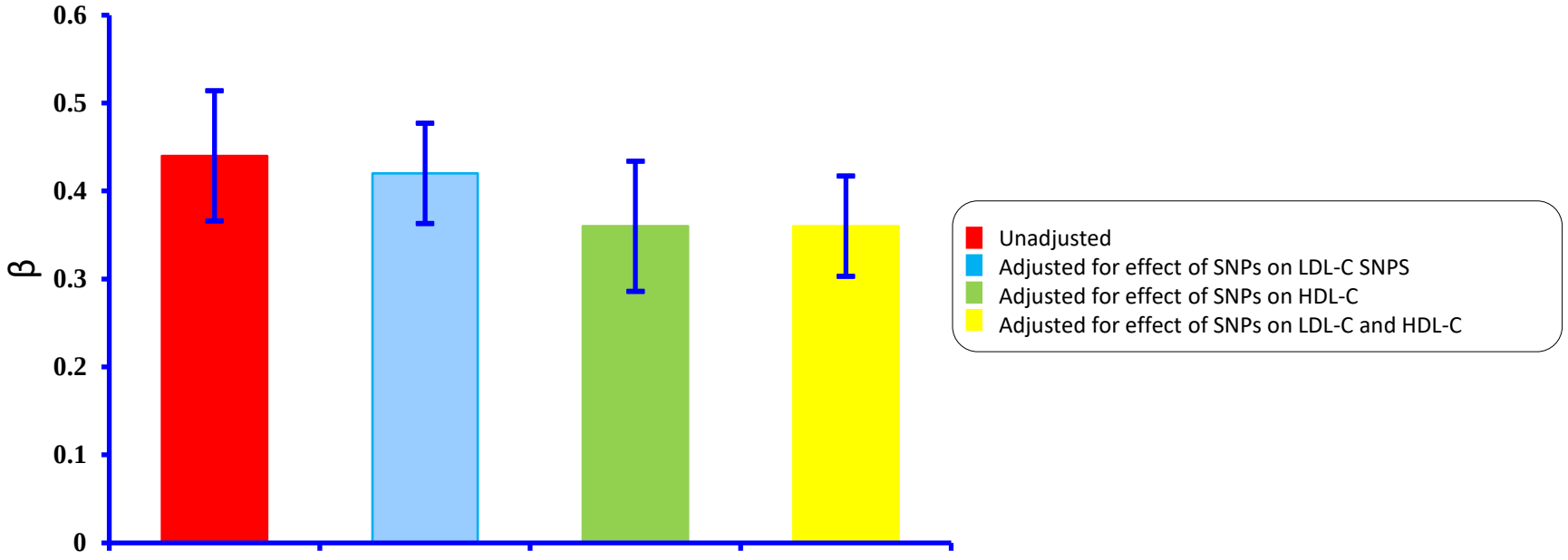
Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013;45:1345–1352

Association of strength of a SNP's effect on HDL-C with its strength of effect on CHD risk, with adjustment



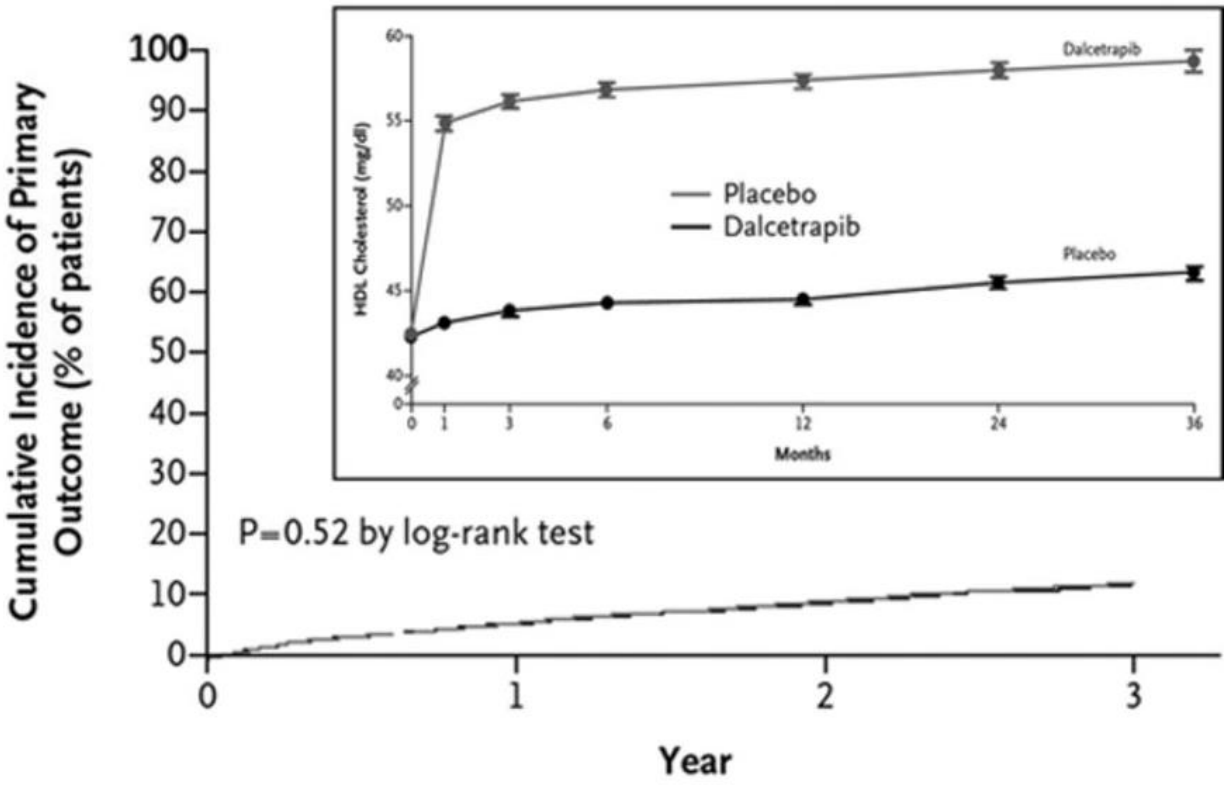
Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013;45:1345–1352

Association of strength of a SNP's effect on triglycerides with its strength of effect on CHD risk, with adjustment



Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013;45:1345–1352

Effect of CETP inhibitor dalcetrapib on HDL-C levels and on cardiovascular outcomes in the dal-OUTCOMES trial



Schwartz GG. dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;367:2089–2099.

Conclusions

- The causal effect of many exposures, including biomarkers, simply cannot be assessed through conventional epidemiological study
- Triangulation of evidence can help strengthen causal inference
- Combined study designs (eg RCT of diet onto biomarkers and MR to assess causal influence of such) can be part of this process