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Noise, pollution, food, or medication: what really matters in primary prevention?

Thomas F. Lüscher[1,2,3], MD, FESC

[1]Professor of Cardiology, Imperial College and Director of Research, Education & Development, Royal Brompton and Harefield Hospitals London, UK; [2]Professor and Chairman, Center for Molecular Cardiology, University of Zurich, Switzerland; and [3]Editor-in-Chief, EHJ Editorial Office, Zurich Heart House, Hottingerstreet 14, 8032 Zurich, Switzerland

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Primary prevention is of the utmost importance as it aims to avoid major cardiovascular events rather than to treat them.[1] Of note, many disease states can be primarily prevented more effectively rather than managed once they occur. However, not all preventive measures are effective, as outlined in this issue. The first step in primary prevention is lifestyle changes. What we eat is one of the most important components of our lifestyle[2] responsible for the obesity epidemic and its consequences.[2] Functional food is a new concept in primary prevention, as discussed in the review '**Importance of functional food compounds in cardioprotection through action on the epigenome**' by Vincenzo Lionetti from the Scuola Superiore Sant'Anna in Pisa, Italy, and colleagues.[3] Food constituents can promote health or contribute to its demise. Recently, attention has focused on protective effects of dietary components and their metabolites as regulators of the human epigenome,[4] which is being linked to cardiovascular diseases. Indeed, there is increasing evidence suggesting that bioactive food compounds may provide cardioprotection. As such, the epigenome may become a nutrient sensor target in cardiovascular patients. While clinical data strongly support a role for effective diet intervention in cardiovascular protection, studies linking changes to the human epigenome are now warranted for mechanistic insight and development of personalized care.

The gut microbiome has recently been implicated in cardiovascular health,[5] risk assessment,[6] and outcomes.[7] Bacteria in the gut can metabolize diverse components of ingested food and thereby produce compounds such as trimethylamine (TMA) that impairs cardiovascular function.[8] Of note, carnitine and choline are major nutrient precursors for gut microbiota-dependent generation of the atherogenic metabolite trimethylamine *N*-oxide (TMAO). In their manuscript entitled '**Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine *N*-oxide metabolism and renal excretion in healthy men and women**', Stanley L. Hazen and colleagues from the Cleveland Clinic in Cleveland, Ohio, USA performed randomized controlled three 4-week isocaloric dietary intervention studies in 113 volunteers to explore the impact of chronic dietary patterns on TMAO levels.[9] Chronic red, but not white meat or non-meat ingestion, increased plasma and urine TMAO more than two-fold. Red meat reduced fractional renal excretion of TMAO, but increased fractional renal excretion of carnitine, and two alternative gut microbiota-generated compounds, γ-butyrobetaine and crotonobetaine. Compared with non-meat, red or white meat increased TMA and TMAO production from carnitine, but not from choline. Dietary saturated fat failed to impact on TMAO or its metabolites. Thus, chronic dietary red meat increases systemic TMAO through: (i) enhanced dietary precursors; (ii) increased microbial TMAO production from carnitine, but not from choline; and (iii) reduced renal TMAO excretion. The implications for prevention are further discussed in an **Editorial** by Allan Davies and myself from the Royal Brompton Hospital in London, UK.[10]

Environmental factors such as noise and pollution are increasingly recognized novel risk factors for many diseases, including coronary artery disease.[11–13] Indeed, in experimental animals, nocturnal noise affects vascular and brain function.[14] In their article '**A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: a nationwide cohort study in Switzerland**' Martin Röösli *et al.* from the Swiss Tropical and Public Health Institute in Basel, Switzerland aimed to disentangle the risk of the three transportation noise sources, i.e. road, railway, and aircraft traffic, and their air pollutants NO_2 and $PM_{2.5}$ on myocardial infarction mortality in Switzerland.[15] They modelled long-term exposure to outdoor road traffic, railway, and aircraft noise levels, as well as NO_2 and $PM_{2.5}$ concentrations to 4.4 million adults in the Swiss National Cohort. Adjusting noise risk estimates of myocardial infarction for NO_2 and $PM_{2.5}$ did not change the hazard ratios per 10 dB increase in road traffic. Conversely, noise-adjusted hazard ratios for air pollutants were lower than corresponding estimates without noise adjustment.

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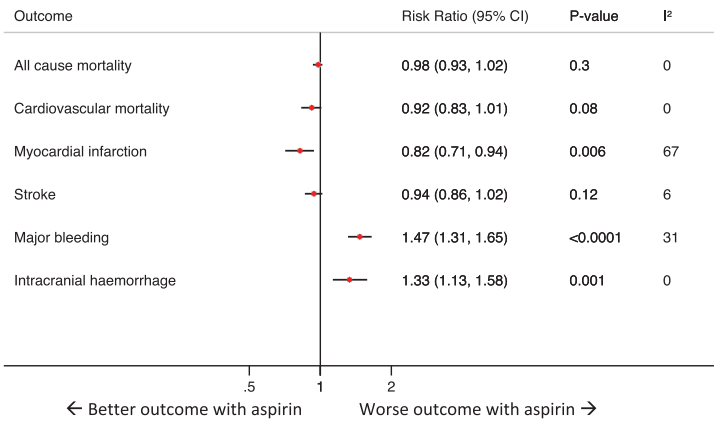

Figure 1 A forest plot illustrating the risk ratios and 95% confidence interval for all outcomes of interest. (from Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. See pages 607–617)

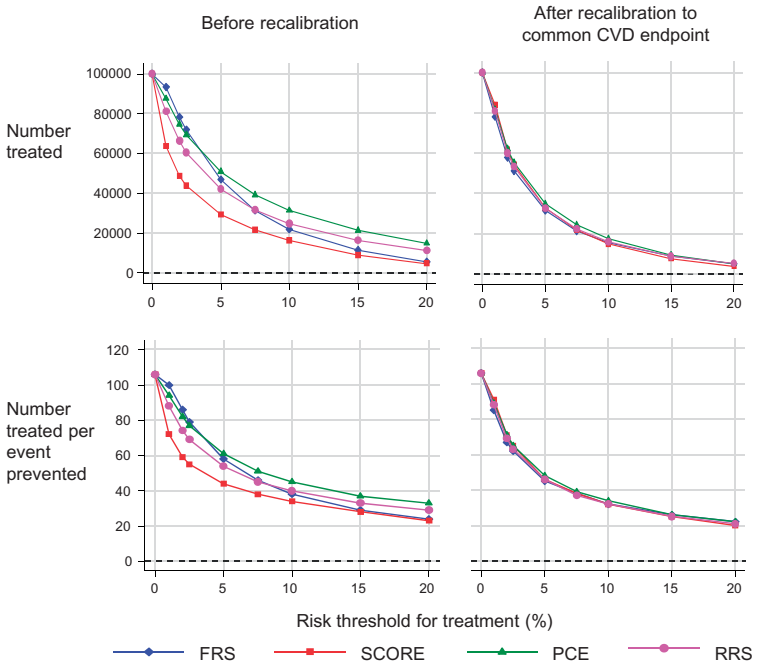

Figure 2 Recalibration equalizes the potential public health impact of different guideline recommended cardiovascular disease risk algorithms and should be regularly applied to improve targeting of intervention. Cardiovascular disease includes fatal coronary heart disease, fatal, and non-fatal myocardial infarction and any stroke. FRS, Framingham risk score; PCE, Pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation; RRS, Reynolds Risk Score. CVD includes fatal CHD, fatal and non-fatal MI, and any stroke (from Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, van der Schouw YT, Selmer R, Khaw K-T, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Völzke H, Cooper C, Ibañez AM, Casiglia E, Kauhanen J, Cooper JA, Rodriguez B, Sundström J, Barrett-Connor E, Dankner R, Nietert PJ, Davidson KW, Wallace RB, Blazer DG, Björkelund C, Donfrancesco C, Krumholz HM, Nissinen A, Davis BR, Coady S, Whincup PH, Jørgensen T, Ducimetiere P, Trevisan M, Engström G, Crespo CJ, Meade TW, Visser M, Kromhout D, Kiechl S, Daimon M, Price JF, Gómez de la Cámara A, Jukema JW, Lamarche B, Onat A, Simons LA, Kavousi M, Ben-Shlomo Y, Gallacher J, Dekker JM, Arima H, Shara N, Tipping RW, Roussel R, Brunner EJ, Koenig W, Sakurai M, Pavlovic J, Gansevoort RT, Nagel D, Goldbourt U, Barr ELM, Palmieri L, Njølstad I, Sato S, Verschuren WMM, Varghese CV, Graham I, Onuma O, Greenland P, Woodward M, Ezzati M, Psaty BM, Sattar N, Jackson R, Ridker PM, Cook NR, D'Agostino RB, Thompson SG, Danesh J, Di Angelantonio E, on behalf of The Emerging Risk Factors Collaboration. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. See pages 621–631).

Thus, transportation noise is associated with myocardial infarction mortality independent of air pollution. However, air pollution studies not adequately adjusting for transportation noise exposure may overestimate the cardiovascular disease burden of air pollution. These relevant observations are further discussed in an **Editorial** by Mette Sørensen from the Danish Cancer Society in Copenhagen, Denmark.[16]

Aspirin is an established therapy for secondary prevention of major adverse cardiovascular events[17] and recommended by current ESC Guidelines.[18,19] However, its role in primary prevention is very controversial since the publication of three major trials.[20–22] In their FAST TRACK clinical research manuscript entitled '**Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials**', Anthony A. Bavry and colleagues from the University of Florida in Gainesville, USA[23] searched electronic databases from inception through to September 2018 for randomized trials that compared aspirin vs. placebo or control in subjects without established atherosclerotic disease. A total of 11 trials with 157 248 subjects were included. After 6.6 years of follow-up, aspirin was not associated with a reduction in all-cause mortality; however, aspirin was associated with an increased risk of major bleeding with a hazard ratio of 1.47 and of intracranial haemorrhage with a hazard ratio of 1.33 (*Figure 1*). The same effect on both all-cause mortality and major bleeding was demonstrated in diabetics and high cardiovascular risk patients. Thus, among middle-aged and elderly so far healthy adults, aspirin does not reduce all-cause mortality, but rather increases the risk of major bleeding. As outlined in a thought-provoking **Editorial** by Marco Valgimigli from the University of Bern in Switzerland,[24] the routine use of aspirin for primary prevention needs to be reconsidered.

In both primary and secondary prevention, proper risk assessment is essential for therapeutic decision making. Unfortunately, the optimum algorithm for cardiovascular disease risk estimation has yet to be found as we move towards individualized prevention. In their article '**Equalization of four cardiovascular risk algorithms after systematic re-calibration: individual-participant meta-analysis of 86 prospective studies**', Emanuele Di Angelantonio and colleagues of the Emerging Risk Factors Collaboration conducted head-to-head comparisons of four algorithms recommended by primary prevention guidelines in 360 737 healthy participants of 86 prospective studies from 22 countries, before and after 're-calibration', a method that adapts risk algorithms to take account of differences in the risk characteristics of the populations being studied.[25] The four algorithms had similar risk discrimination. Before re-calibration, Framingham Risk Score, Systematic Coronary Risk Evaluation, and Pooled Cohort Equations overpredicted cardiovascular disease risk by 10, 52, and 41%, respectively, while Reynolds Risk Score underpredicted it by 10% (*Figure 2*). Original versions of algorithms classified 29–39% of individuals aged ≥40 years as high risk. In contrast, re-calibration reduced this proportion to 22–24% for every algorithm. Thus, before re-calibration, the clinical performance of four widely used cardiovascular disease risk algorithms varied substantially. In contrast, simple re-calibration nearly equalized their performance and improved modelled targeting of preventive action to clinical need. These important findings are put into context in an interesting **Editorial** authored by Jari Antero Laukkanen from the University of Jyväskylä in Finland.[26]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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