INSTITUT DE CARDIOLOGIE DE MONTRÉAL

Université de Montréal

EXERCICE, ALIMENTATION ET PRÉVENTION CARDIOVASCULAIRE

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INSTITUT DE CARDIOLOGIE DE MONTRÉAL
CENTRE ÉPIC

Montréal 20 OCTOBRE 2017

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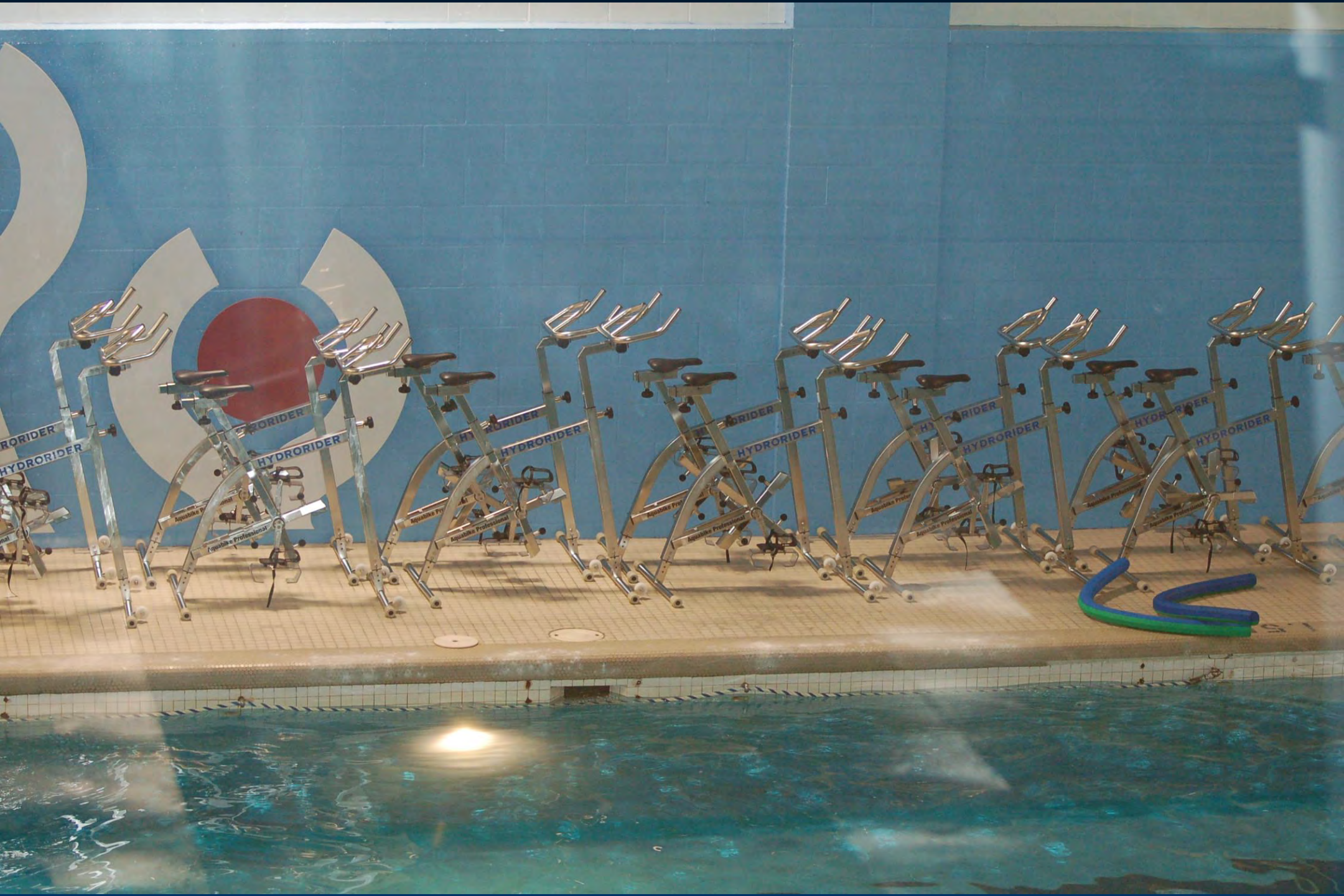
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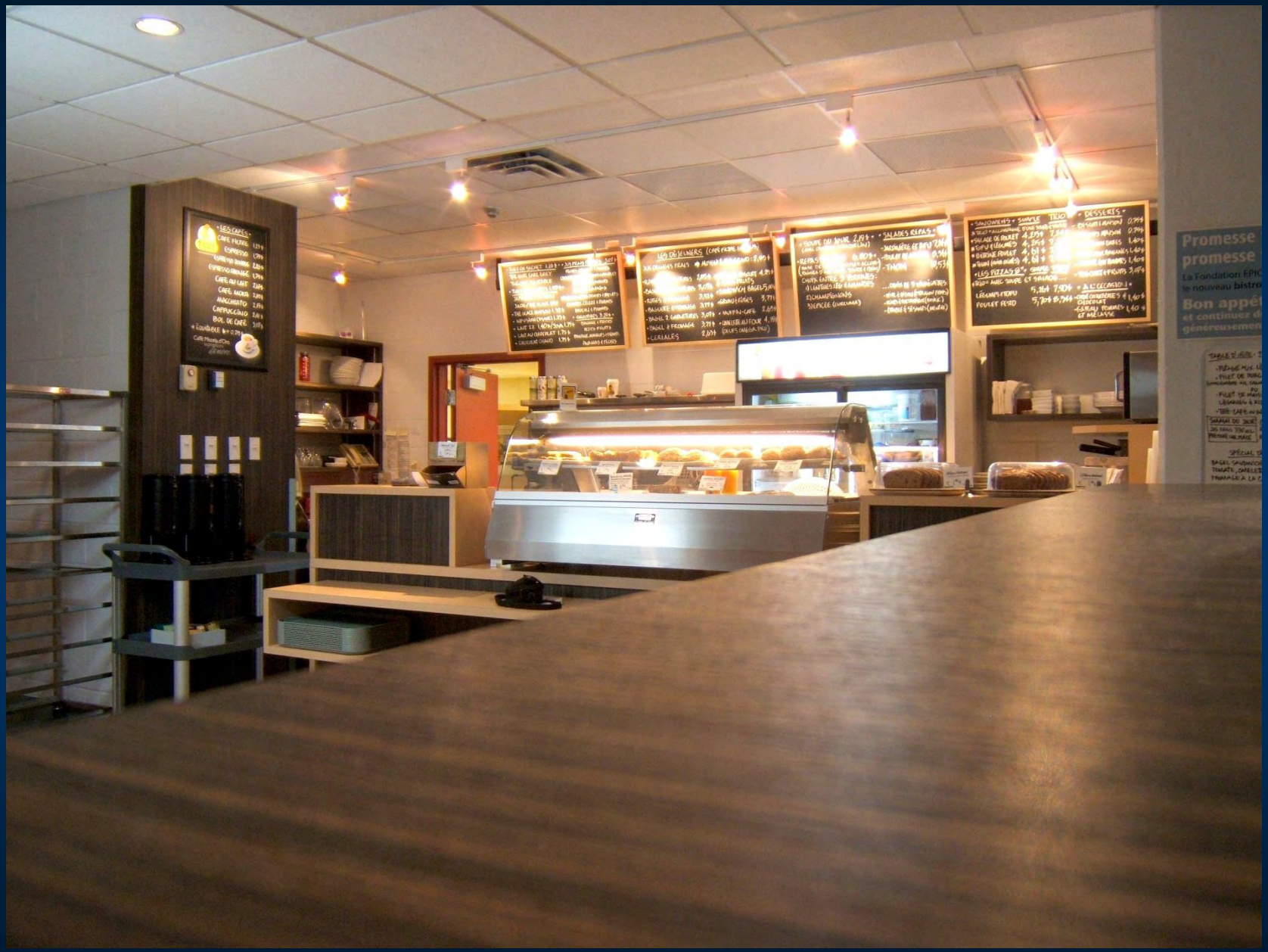
Easier to sweat while wet, study finds

During spinning class, I often find myself wishing I was in a pool. For one, water would make the sweat dripping down my back less noticeable. Two, it has to be easier to sneak a break when the instructor can't see your legs below the surface.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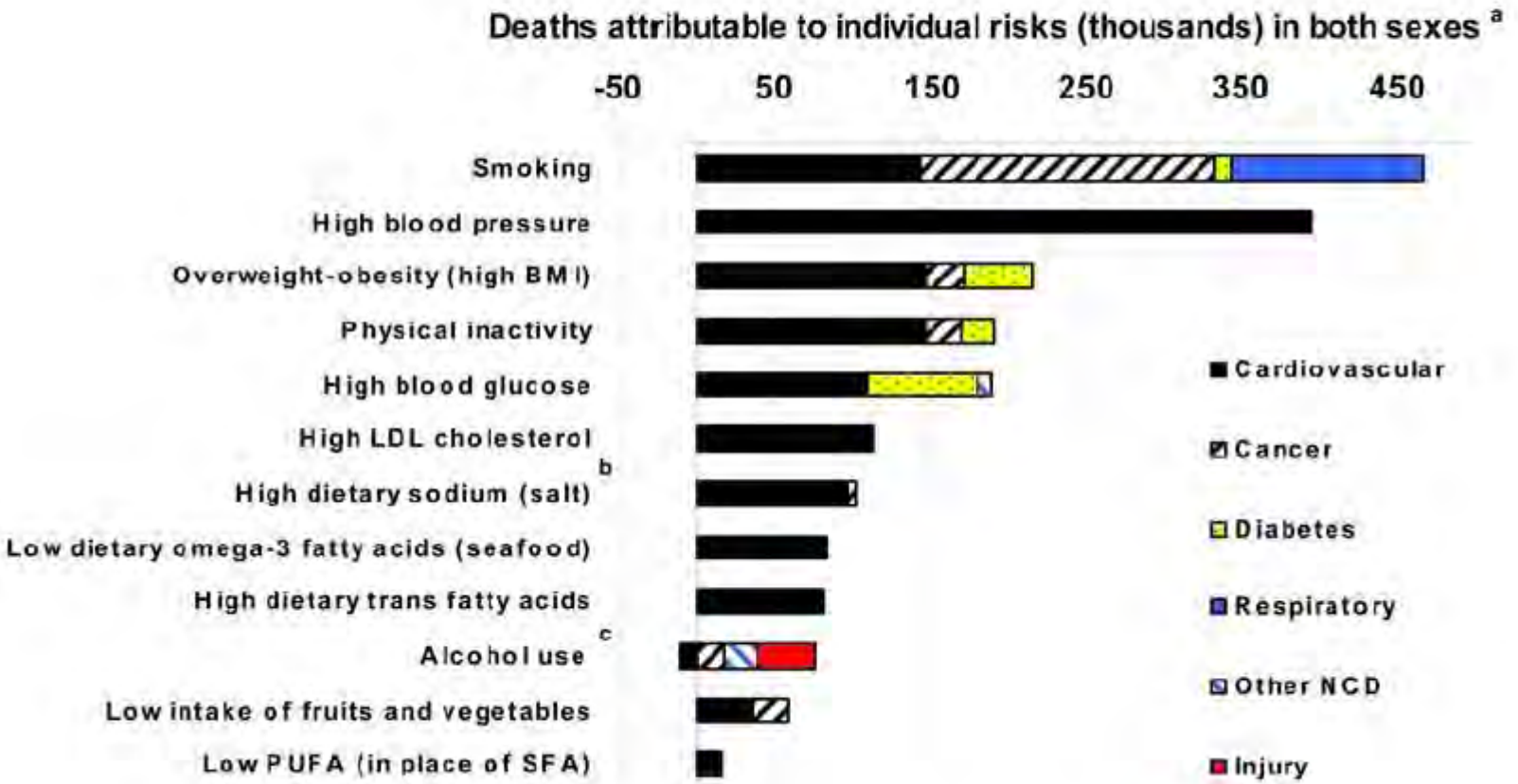
Mortality Effects of Risk Facto



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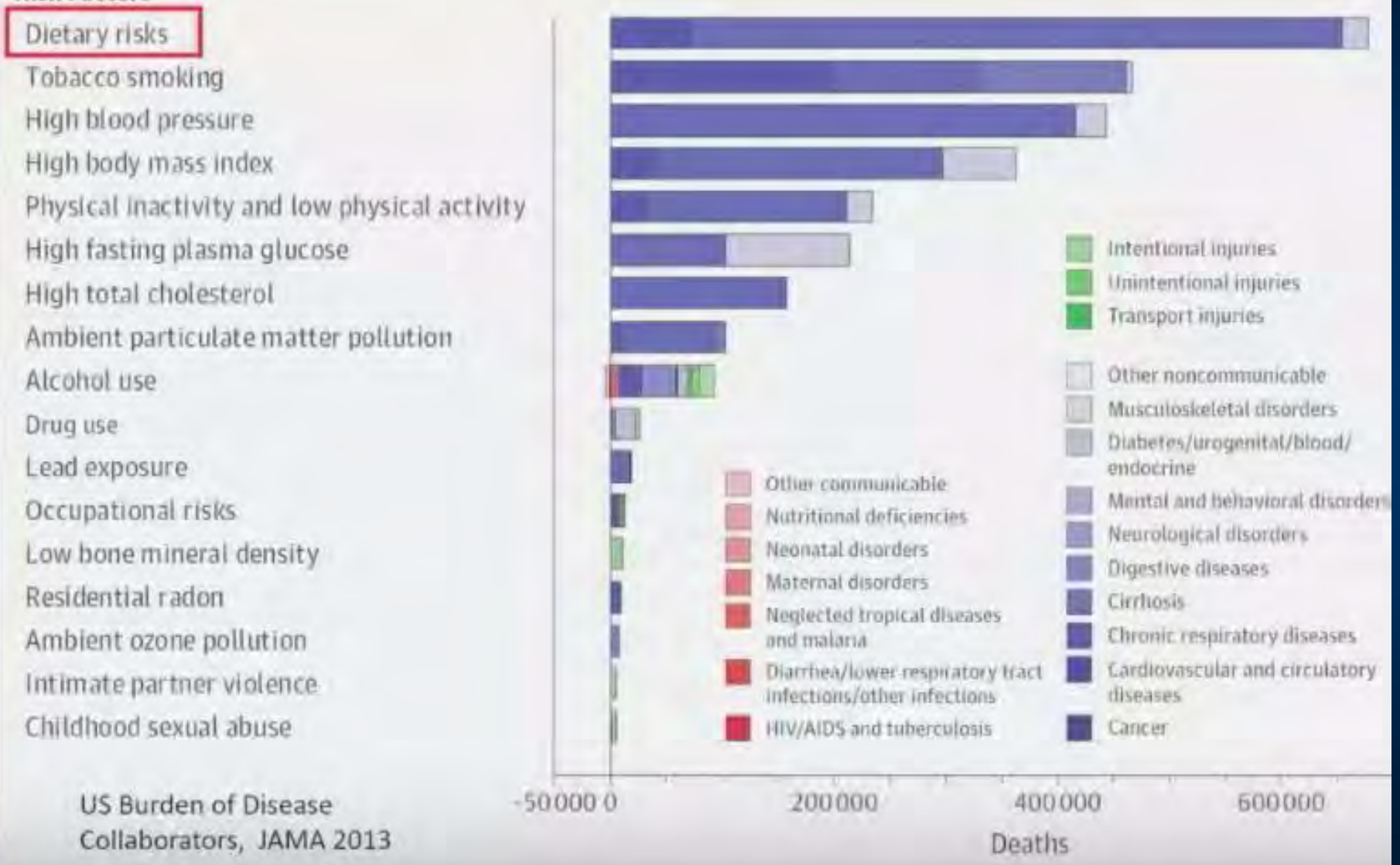
Causes of US Deaths in 2010



US Burden of Disease Collaborators, JAMA 2013

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Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition

*GBD 2013 DALYs and HALE Collaborators**

Summary

Background The Global Burden of Disease Study 2013 (GBD 2013) aims to bring together all available epidemiological data using a coherent measurement framework, standardised estimation methods, and transparent data sources to enable comparisons of health loss over time and across causes, age–sex groups, and countries. The GBD can be used to generate summary measures such as disability-adjusted life-years (DALYs) and healthy life expectancy (HALE) that make possible comparative assessments of broad epidemiological patterns across countries and time. These summary measures can also be used to quantify the component of variation in epidemiology that is related to sociodemographic development.

Methods We used the published GBD 2013 data for age-specific mortality, years of life lost due to premature mortality (YLLs), and years lived with disability (YLDs) to calculate DALYs and HALE for 1990, 1995, 2000, 2005, 2010, and 2013 for 188 countries. We calculated HALE using the Sullivan method; 95% uncertainty intervals (UIs) represent uncertainty in age-specific death rates and YLDs per person for each country, age, sex, and year. We estimated DALYs for 306 causes for each country as the sum of YLLs and YLDs; 95% UIs represent uncertainty in YLL and YLD rates. We quantified patterns of the epidemiological transition with a composite indicator of sociodemographic status, which we constructed from income per person, average years of schooling after age 15 years, and the total fertility rate and mean age of the population. We applied hierarchical regression to DALY rates by cause across countries to decompose variance related to the sociodemographic status variable, country, and time.

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*Collaborators listed at the end of the Article

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cjlm@uw.edu

	1990				2005				2013			
	Male population		Female population		Male population		Female population		Male population		Female population	
	Life expectancy (years)	HALE (years)	Life expectancy (years)	HALE (years)	Life expectancy (years)	HALE (years)	Life expectancy (years)	HALE (years)	Life expectancy (years)	HALE (years)	Life expectancy (years)	HALE (years)
Global	63·01 (62·59–63·46)	55·40 (53·10–57·42)	67·68 (67·20–68·10)	58·51 (55·90–60·87)	66·23 (65·90–66·57)	58·27 (55·96–60·39)	71·31 (70·95–71·64)	61·54 (58·67–64·08)	68·80 (68·16–69·41)	60·59 (58·15–62·89)	74·29 (73·79–74·79)	64·13 (61·25–66·84)
Developed	70·64 (70·56–70·71)	62·12 (59·70–64·26)	77·97 (77·90–78·04)	67·18 (64·15–69·86)	72·55 (72·51–72·59)	63·56 (61·04–65·82)	79·85 (79·82–79·89)	68·48 (65·28–71·34)	75·50 (75·27–75·76)	66·00 (63·26–68·39)	81·82 (81·62–82·02)	70·03 (66·71–73·04)
Developing	61·40 (60·86–61·99)	54·04 (51·75–56·06)	64·89 (64·25–65·43)	56·26 (53·79–58·54)	64·96 (64·54–65·41)	57·30 (55·07–59·35)	69·14 (68·67–69·57)	59·88 (57·14–62·28)	67·30 (66·50–68·09)	59·47 (57·11–61·77)	72·28 (71·67–72·92)	62·65 (59·89–65·27)
Canada	74·20	65·13	80·59	68·74	77·87	67·84	82·64	70·31	79·44	69·11	83·43	71·04
USA	71·87	62·66	78·84	66·96	75·04	64·78	80·25	67·68	76·33	65·84	81·42	68·61

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ORIGINAL INVESTIGATIONS

Trends in Acute Myocardial Infarction in Young Patients and Differences by Sex and Race, 2001 to 2010

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ABSTRACT

BACKGROUND Various national campaigns launched in recent years have focused on young women with acute

TABLE 2 Hospitalization Rates (per 100,000 Persons) for Young Patients With AMIs Stratified by Age and Sex, 2001 to 2010

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p for Trend
Overall											
Male	174	168	173	150	153	160	153	173	181	171	0.70
Female	56	57	57	52	53	55	55	61	65	61	0.40
Age 30-34 yrs											
Male	25	25	28	23	26	25	26	26	27	26	0.80
Female	8	8	8	8	8	9	9	9	8	9	0.70
Age 35-39 yrs											
Male	62	59	61	51	54	55	57	66	65	63	0.50
Female	20	21	20	20	20	19	19	21	25	22	0.60
Age 40-44 yrs											
Male	142	136	137	114	125	128	118	138	139	132	0.80
Female	44	46	44	43	41	45	43	49	51	50	0.40
Age 45-49 yrs											
Male	258	251	259	224	220	229	217	246	259	237	0.50
Female	80	80	81	74	76	79	78	88	92	88	0.20
Age 50-54 yrs											
Male	427	406	412	357	348	361	343	379	399	370	0.06
Female	140	137	138	116	115	118	118	127	139	126	0.50

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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Metabolic Syndrome and Risk of Acute Myocardial Infarction

A Case-Control Study of 26,903 Subjects From 52 Countries

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Matthew J. McQueen, MBCHB, PHD,*‡ Supachai Tanomsup, MD,§ Churchill L. Onen, MD,‖
Sumathy Rangarajan, MS,* Hertzel C. Gerstein, MD, MS,*† Sonia S. Anand, MD, PHD,*†
for the INTERHEART Investigators

Hamilton, Ontario, Canada; Bangkok, Thailand; and Gaborone, Botswana

Objectives This study examines the risk of acute myocardial infarction (MI) conferred by the metabolic syndrome (MS) and its individual factors in multiple ethnic populations.

Background The risk of the MS on MI has not been well characterized, especially in multiple ethnic groups.

Methods Participants in the INTERHEART study (n = 26,903) involving 52 countries were classified using the World Health Organization (WHO) and International Diabetes Federation (IDF) criteria for MS, and their odds ratios (ORs) for MI were compared with the individual MS component factors.

Results The MS is associated with an increased risk of MI, both using the WHO (OR: 2.69; 95% confidence interval [CI]: 2.45 to 2.95) and IDF (OR: 2.20; 95% CI: 2.03 to 2.38) definitions, with corresponding population attributable risks of 14.5% (95% CI: 12.7% to 16.3%) and 16.8% (95% CI: 14.8% to 18.8%), respectively. The associations are directionally similar across all regions and ethnic groups. Using the WHO definition, the association with MI by the MS is similar to that of diabetes mellitus (OR: 2.72; 95% CI: 2.53 to 2.92) and hypertension (OR: 2.60; 95% CI: 2.46 to 2.76), and significantly stronger than that of the other component risk factors. The clustering of ≥3 risk factors with subthreshold values is associated with an increased risk of MI (OR: 1.50; 95% CI: 1.24 to 1.81) compared with having component factors with "normal" values. The IDF definition showed similar results.

Conclusions In this large-scale, multi-ethnic, international investigation, the risk of MS on MI is generally comparable to that conferred by some, but not all, of its component risk factors. The characterization of risk factors, especially continuous variables, as dichotomous will underestimate risk and decrease the magnitude of association between MS and MI. (J Am Coll Cardiol 2010;55:2390–8) © 2010 by the American College of Cardiology Foundation

The common clustering of metabolic abnormalities including abdominal obesity, elevated glucose, abnormal lipids, and elevated blood pressure has been extensively referred to in the medical literature as the "metabolic syndrome" (MS) (1,2). The presence of MS is associated with an increased risk of coronary heart disease (3–5), with limited evidence that this risk is greater than that conferred by its constituent components (6). The value of classifying subjects with MS has recently been called into question as the definition of MS is arbitrary (7,8), and the American Diabetes Association and the European Association for the Study of Diabetes have called for an aggressive research agenda to bring clarity to this debate (8). In this large-scale, multi-ethnic, international investigation, the objectives are to: 1) determine the risk of acute myocardial infarction (MI) among patients with MS defined using existing criteria; 2) assess if

From the *Population Health Research Institute, Hamilton Health Sciences, and the Departments of †Medicine and Clinical Epidemiology and Biostatistics, and ‡Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada; §Division of Cardiology, Ramathibodi Hospital, Bangkok, Thailand; and the ‖Center for Chronic Diseases, Gaborone Private Hospital, Gaborone, Botswana. This study was supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the International Clinical Epidemiology Network, and unrestricted grants from several pharmaceutical companies (with major contributions from AstraZeneca, Novartis, Hoechst Marion Roussel [now Aventis], Knoll Pharmaceuticals [now Abbott], Bristol-Myers Squibb, and Sanofi-Synthélabo), and various national bodies in different countries. Dr. Mente is supported by a Heart and Stroke Foundation of Canada Postdoctoral Research Fellowship. Dr. Yusuf is supported by an endowed chair of the Heart and Stroke Foundation of Ontario and a Senior Scientist Award from the Canadian Institutes of Health Research. Dr. Anand holds the Michael G. DeGroote Heart and Stroke Foundation of Ontario Chair in Population Health Research and the Eli Lilly Canada/May Cohen Chair in Women's Health.

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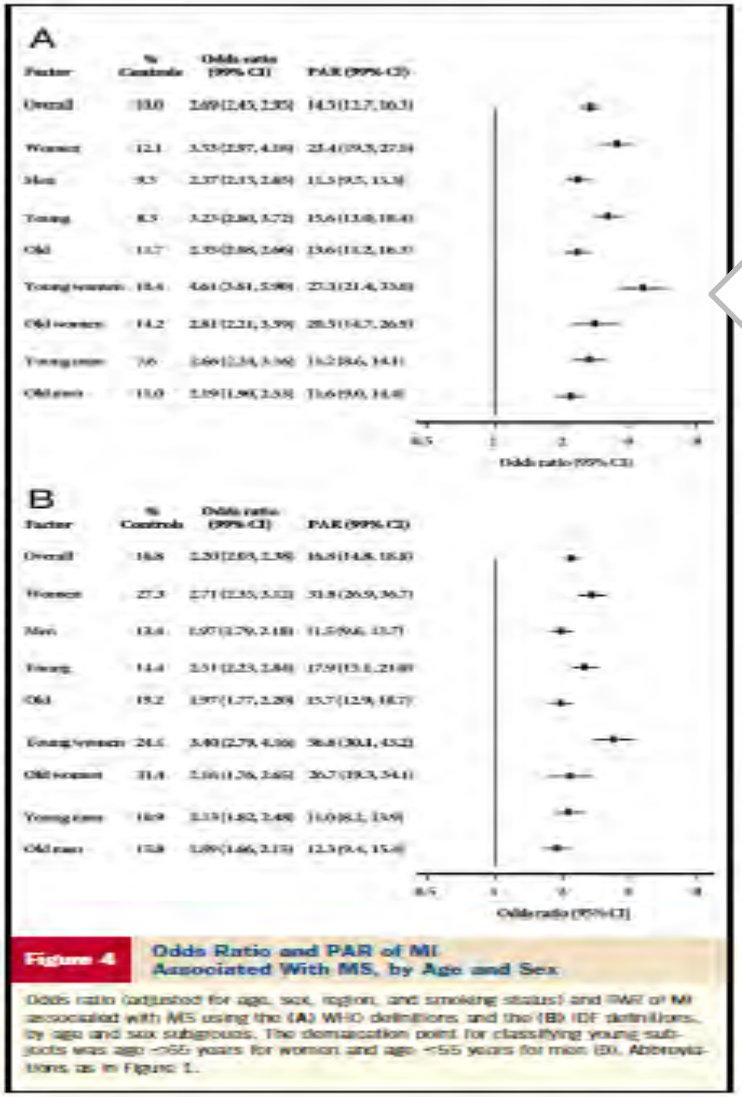

Figure 4 **Odds Ratio and PAR of MI Associated With MS, by Age and Sex**

Odds ratio (adjusted for age, sex, region, and smoking status) and PAR of MI associated with MS using the (**A**) WHO definitions and the (**B**) IDF definitions, by age and sex subgroups. The demarcation point for classifying young subjects was age <66 years for women and age <55 years for men (B). Abbreviations as in Figure 1.

suggest that the risk associated with MS is not greater than the sum of its component factors.

The MS refers to a cluster of risk factors which when present together is believed to confer an increased risk of cardiovascular disease (1,2). Subjects with MS have a higher cardiovascular disease risk than do subjects without the

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Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011

Evidence for Stagnation in Young Adults, Especially Women

Kobina A. Wilmot, MD; Martin O'Flaherty, MD, PhD, MSc; Simon Capewell, MD, DSc; Earl S. Ford, MD, MPH; Viola Vaccarino, MD PhD

Background—Coronary heart disease (CHD) mortality rates have fallen dramatically over the past 4 decades in the Western world. However, recent data from the United States and elsewhere suggest a plateauing of CHD incidence and mortality among young women. We therefore examined recent trends in CHD mortality rates in the United States according to age and sex.

Methods and Results—We analyzed mortality data between 1979 and 2011 for US adults ≥25 years of age. We calculated age-specific CHD mortality rates and compared estimated annual percentage changes during 3 approximate decades of data (1979–1989, 1990–1999, and 2000–2011). We then used Joinpoint regression modeling to assess changes in trends over time on the basis of inflection points of the mortality rates. Adults ≥65 years of age showed consistent mortality declines, which became even steeper after 2000 (women, −5.0%; men, −4.4%). In contrast, young men and women (<55 years of age) initially showed a clear decline in CHD mortality from 1979 until 1989 (estimated annual percentage change, −5.5% in men and −4.6% in women). However, the 2 subsequent decades saw stagnation with minimal improvement. Notably, young women demonstrated no improvements between 1990 and 1999 (estimated annual percentage change, 0.1%) and only −1% estimated annual percentage change since 2000. Joinpoint analyses provided consistent results.

Conclusions—The dramatic decline in CHD mortality since 1979 conceals major heterogeneities. CHD death rates in older groups are now falling steeply. However, young adults have experienced frustratingly small decreases in CHD mortality rates since 1990. The drivers of these major differences in CHD mortality trends by age and sex merit urgent study. (***Circulation***. **2015;132:997-1002. DOI: 10.1161/CIRCULATIONAHA.115.015293.**)

Key Words: coronary disease ■ epidemiology ■ mortality ■ sex

Despite a remarkable decline in cardiovascular deaths over several decades, coronary heart disease (CHD) remains the leading cause of death in the United States. CHD mortality rates fell as much as 52% in men and 49% in women between 1980 and 2002.[1] However, these beneficial CHD mortality trends may not have been experienced by all demographic groups. In a previous analysis of US mortality, there was a dramatic slowing in the average annual rate of decline of CHD mortality among younger adults (35–54 years of age): in women from −5.4% in 1980 to 1989 to 1.5% in 2000 to 2002, and in men from −6.2% to −0.5%.[1] These worrisome trends reflecting a stagnation in or even an increase in CHD mortality in young adults have also been mirrored by statistics outside the United States.[2–5] In the United Kingdom, the CHD mortality decline in men and women 45 to 54 years of age slowed between 1984 and 2004. In addition, in 2002, CHD mortality rates in men 35 to 44 years of age increased for the first time in 2 decades.[3] Likewise, in Canada, younger individuals ≤55 years of age demonstrated a 1.7% annual increase in incident rates of acute myocardial infarction (AMI) hospitalization per year from 2000 to 2009.[5] Similarly, in Australia, an increase in the incidence of acute coronary syndromes (2.3%/y) and AMI (4.0%/y) was observed in women 35 to 54 years of age between 1996 and 2007.[4] Therefore, the purpose of our study was to examine US CHD mortality rates by age and sex from 1979 to 2011 and particularly to examine recent trends among young men and women.

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Clinical Perspective on p 1002

Methods

We obtained mortality data for all individuals ≥25 years of age in the United States between 1979 and 2011 from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.015293/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.015293**

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risk factor profiles in women is essential for improving their future morbidity and mortality.

Between 2001 and 2010 in the United States, there was no significant reduction in AMI hospitalization rates among young people (<55 years of age),[12] a stark contrast to Medicare population studies, which demonstrated >20% reduction in hospitalization rates in the same time period.[15] Consistent with our findings, recent trends in AMI hospitalization rates in young individuals show a similarly discouraging picture across Westernized nations. In Western Australia, hospitalizations for AMI between 1996 and 2007 declined in older individuals but did not change significantly in men <55 years of age and increased significantly in women in this age group by 4%/y.[4] In British Columbia, Canada, although hospitalizations for AMI between 2000 to 2009 declined significantly in older individuals, there was no significant change (0.3%/y) in young men ≤55 years old but a significant increase (1.7%) in young women.[5] These unfavorable trends in AMI hospitalization rates in young adults, especially women, contrast with declining hospital mortality rates among young people. Young women, in particular, have shown especially pronounced

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Time trends in statin utilisation and coronary mortality in Western European countries

Federico Vancheri,[1,2] Lars Backlund,[2] Lars-Erik Strender,[2] Brian Godman,[3,4] Björn Wettermark[5,6]

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ABSTRACT

Objectives: To determine whether there is a relation between statin utilisation and coronary heart disease (CHD) mortality in populations with different levels of coronary risk, and whether the relation changes over time.

Design: Ecological study using national databases of dispensed medicines and mortality rates.

Setting: Western European countries with similar public health systems.

Main outcome measures: Population CHD mortality rates (rate/100 000) as a proxy for population coronary risk level, and statin utilisation expressed as Defined Daily Dose per one Thousand Inhabitants per Day (DDD/TID), in each country, for each year between 2000 and 2012. Spearman's correlation coefficients between CHD mortality and statin utilisation were calculated. Linear regression analysis was used to assess the relation between changes in CHD mortality and statin utilisation over the years.

Results: 12 countries were included in the study. There was a wide range of CHD mortality reduction between the years 2000 and 2012 (from 25.9% in Italy to 57.9% in Denmark) and statin utilisation increase (from 121% in Belgium to 1263% in Denmark). No statistically significant relations were found between CHD mortality rates and statin utilisation, nor between changes in CHD and changes in statin utilisation in the countries over the years 2000 and 2012.

Conclusions: Among the Western European countries studied, the large increase in statin utilisation between 2000 and 2012 was not associated with CHD mortality, nor with its rate of change over the years. Factors different from the individual coronary risk, such as population ageing, health authority programmes, guidelines, media attention and pharmaceutical industry marketing, may have influenced the large increase in statin utilisation. These need to be re-examined with a greater emphasis on prevention strategies.

Strengths and limitations of this study

- This is the first study to examine the relation over time between statin utilisation and coronary heart disease (CHD) in Western European countries
- We conducted an ecological study investigating whether the rate of increase in statin utilisation was associated with the rate of decrease in CHD mortality among a sample of Western European countries in the period 2000–2012.
- The sample of countries had a wide range of CHD mortality rates and similar public health systems.
- CHD mortality was used as a proxy measure of population cardiovascular risk levels.
- Limitations include a small sample size and the lack of data regarding the patients' adherence to statin treatment, the indications for statin treatment—whether primary or secondary prevention—and the effects of pharmaceutical industry campaigns on doctors' decisions about statin treatment in different countries.

INTRODUCTION

A substantial decrease in coronary heart disease (CHD) mortality has been observed in Western European countries during the past four decades,[1 2] to a great extent attributable to reductions in major risk factors in the populations, mainly dyslipidaemia and hypertension.[3–5]

Statins reducing cholesterol synthesis were first used in the 1990s. Several clinical trials in both primary and secondary prevention have shown that statins reduce coronary events and mortality.[6 7] Since their introduction, the utilisation of statins has increased rapidly in all Western European countries, although the level of utilisation varies widely.[8–10] Current guidelines on CHD prevention propose that the decision to start statin treatment in primary prevention should be based on the assessment of the global risk of developing CHD in individual patients.[11 12] According to the guidelines, the treatment of high-risk individuals should be prioritised. This has resulted in multiple strategies among Western European

Conclusions: Among the Western European countries studied, the large increase in statin utilisation between 2000 and 2012 was not associated with CHD mortality, nor with its rate of change over the years. Factors different from the individual coronary risk, such as population ageing, health authority programmes, guidelines, media attention and pharmaceutical industry marketing, may have influenced the large increase in statin utilisation. These need to be re-examined with a greater emphasis on prevention strategies.

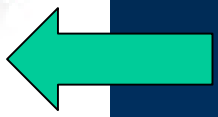
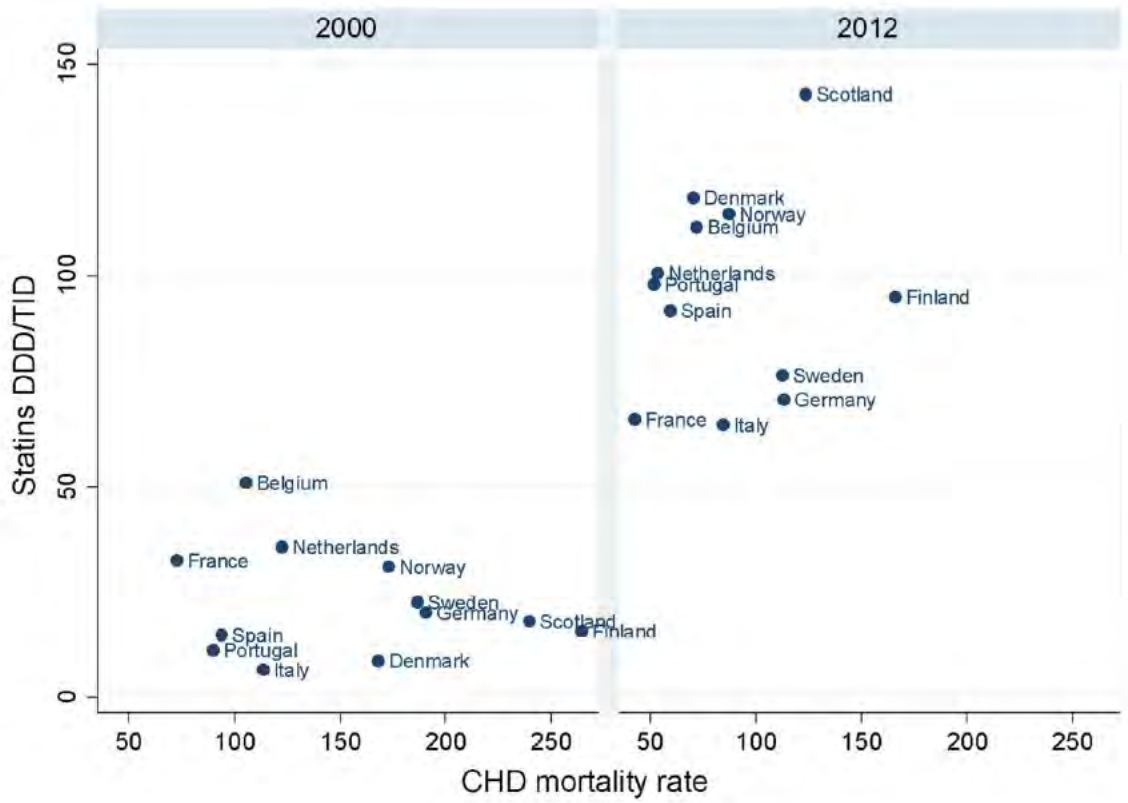


Figure 1 Statin utilisation and CHD mortality rates in the years 2000 and 2012. CHD mortality data from OECD Health Statistics 2014.[24] Italy missing data 2004–2005, Portugal missing data 2004–2006. Statin utilisation data from national databases on prescription sales in each country. Belgium data available from 2004 onwards, France until 2009. Statins data from databases on prescription sales. Belgium data available from 2004 onwards. France until 2009. Scotland until 2010. CHD, coronary heart disease; OECD, Organisation for Economic Co-operation and Development.



Nilsson et al. Journal of Negative Results in BioMedicine 2011, 10:6
http://www.jnrbm.com/content/10/1/6

JOURNAL OF NEGATIVE RESULTS IN BIOMEDICINE

RESEARCH Open Access

No connection between the level of exposition to statins in the population and the incidence/ mortality of acute myocardial infarction: An ecological study based on Sweden's municipalities

Staffan Nilsson[1,2*], Sigvard Mölstad[1,3], Catarina Karlberg[3], Jan-Erik Karlsson[4] and Lars-Göran Persson[3]

Abstract

Background: Randomised controlled trials have shown an excellent preventive effect of statins on ischemic heart disease. Our objective was to investigate if a relation can be detected between acute myocardial infarction- (AMI) mortality or incidence and statin utilisation, for men and women in different age-groups on a population basis.

Results: The utilisation rate of statins increased almost three times for both men and women between 1998 and 2002. During 1998-2000 the incidence of AMI decreased clearly for men but only slightly for women. Mortality decreased from 1998 to 2002. The change in statin utilisation from 1998 to 2000 showed no correlation to the change in AMI mortality from 2000 to 2002. Statin utilisation and AMI- incidence or mortality showed no correlations when adjusting for socio-economic deprivation, antidiabetic drugs and geographic coordinates.

Conclusions: Despite a widespread and increasing utilisation of statins, no correlation to the incidence or mortality of AMI could be detected. Other factors than increased statin treatment should be analysed especially when discussing the allocation of public resources.

Keywords: Myocardial infarction, Incidence, Antilipemic agents, Sweden, Population, Ecological study

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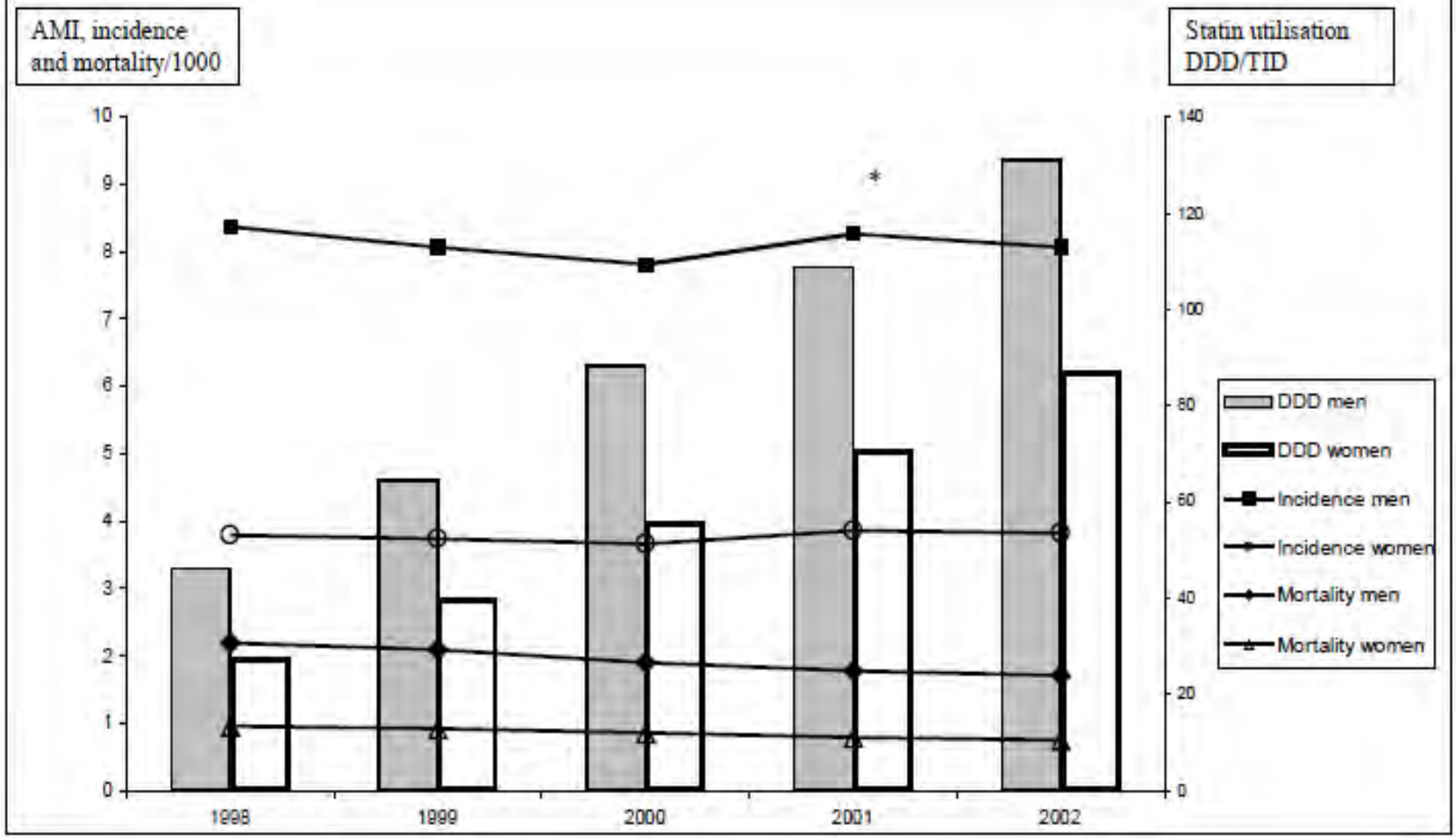


* Change of cut off level of Cardiac troponin T, troponin I or creatine kinase (CK-MB) for AMI.

Figure 1 Incidence and mortality of acute myocardial infarction (AMI) and statin utilisation in the Swedish population, 40-79 years old, 1998-2002. Utilisation of statins expressed in Defined Daily Doses per 1000 Inhabitants and Day (DDD/TID).

Articles

Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial

*Peter S Sever, Björn Dahlöf, Neil R Poulter, Hans Wedel, Gareth Beevers, Mark Caulfield, Rory Collins, Sverre E Kjeldsen, Arni Kristinsson, Gordon T McInnes, Jesper Mehlsen, Markku Nieminen, Eoin O'Brien, Jan Östergren, for the ASCOT investigators**

Summary

Background The lowering of cholesterol concentrations in individuals at high risk of cardiovascular disease improves outcome. No study, however, has assessed benefits of cholesterol lowering in the primary prevention of coronary heart disease (CHD) in hypertensive patients who are not conventionally deemed dyslipidaemic.

Methods Of 19 342 hypertensive patients (aged 40–79 years with at least three other cardiovascular risk factors) randomised to one of two antihypertensive regimens in the Anglo-Scandinavian Cardiac Outcomes Trial, 10 305 with non-coronary events (178 *vs* 247, 0·71 [0·59–0·86], p=0·0005) were also significantly lowered. There were 185 deaths in the atorvastatin group and 212 in the placebo group (0·87 [0·71–1·06], p=0·16). Atorvastatin lowered total serum cholesterol by about 1·3 mmol/L compared with placebo at 12 months, and by 1·1 mmol/L after 3 years of follow-up.

Interpretation The reductions in major cardiovascular events with atorvastatin are large, given the short follow-up time. These findings may have implications for future lipid-lowering guidelines.

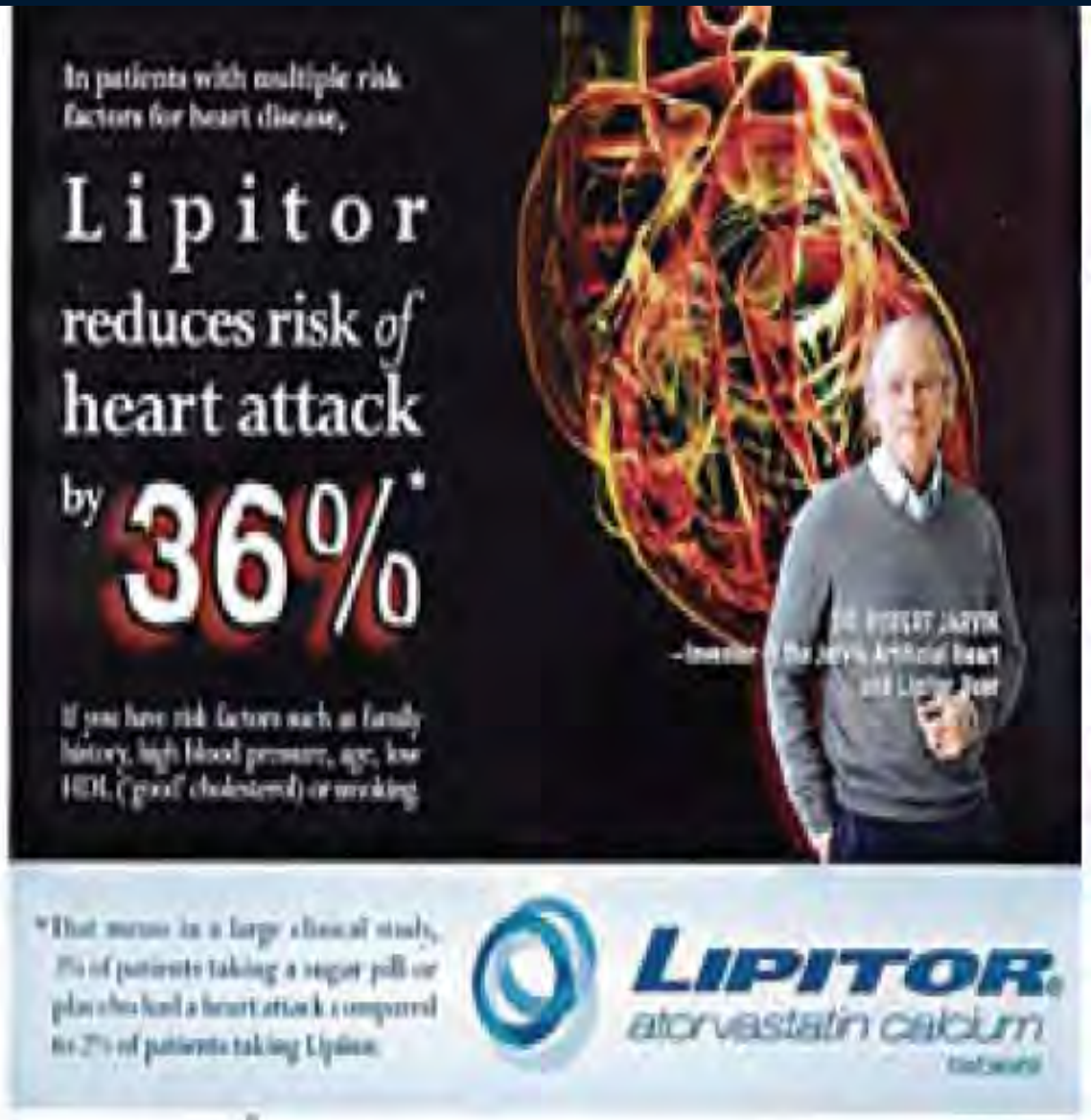
Lancet 2003; **361**: 1149–58. Published online April 2, 2003

N=10 305

	Atorvastatin		Placebo		Unadjusted hazard ratio (95% CI)	p
	n (%)	Rate*	n (%)	Rate*		
Primary endpoint†						
Non-fatal MI‡ plus fatal CHD	100 (1·9)	6·0	154 (3·0)	9·4	0·64 (0·50–0·83)	0·0005
Secondary endpoints†						
Total cardiovascular events and procedures	389 (7·5)	24·1	486 (9·5)	30·6	0·79 (0·69–0·90)	0·0005
Total coronary events	178 (3·4)	10·8	247 (4·8)	15·2	0·71 (0·59–0·86)	0·0005
Non-fatal MI§ plus fatal CHD	86 (1·7)	5·2	137 (2·7)	8·3	0·62 (0·47–0·81)	0·0005
All-cause mortality	185 (3·6)	11·1	212 (4·1)	12·8	0·87 (0·71–1·06)	0·1649
Cardiovascular mortality	74 (1·4)	4·4	82 (1·6)	4·9	0·90 (0·66–1·23)	0·5066
Fatal and non-fatal stroke	89 (1·7)	5·4	121 (2·4)	7·4	0·73 (0·56–0·96)	0·0236
Fatal and non-fatal heart failure	41 (0·8)	2·5	36 (0·7)	2·2	1·13 (0·73–1·78)	0·5794
Tertiary endpoints†						
Silent MI	14 (0·3)	0·8	17 (0·3)	1·0	0·82 (0·40–1·66)	0·5813
Unstable angina	21 (0·4)	1·3	24 (0·5)	1·4	0·87 (0·49–1·57)	0·6447
Chronic stable angina	33 (0·6)	2·0	56 (1·1)	3·4	0·59 (0·38–0·90)	0·0135
Peripheral arterial disease	42 (0·8)	2·5	41 (0·8)	2·5	1·02 (0·66–1·57)	0·9254
Life-threatening arrhythmias	10 (0·2)	0·6	3 (0·1)	0·2	3·31 (0·91–12·01)	0·0540
Development of diabetes mellitus	154 (3·0)	9·4	134 (2·6)	8·2	1·15 (0·91–1·44)	0·2493
Development of renal impairment	31 (0·6)	1·9	24 (0·5)	1·4	1·29 (0·76–2·19)	0·3513

MI=myocardial infarction. *Per 1000 patient-years. †Full definition of endpoints provided in reference 24. ‡Includes silent MI. §Excludes silent MI.

Table 3: **Hazard ratio of atorvastatin treatment on primary, secondary, and tertiary endpoints**



simplement assorti d'un astérisque qui renvoie à quelques lignes composées en petits caractères. Il y est précisé que « lors d'un important essai clinique », 2 % des patients sous Lipitor (1,9 %, en réalité) et 3 % des patients sous placebo ont subi une crise cardiaque. Conclusion : la probabilité *réelle* d'éviter un infarctus est de 1,1 %.

« Un virgule un pour cent divisé par 3 %, ça fait bien 36 %. Mais 36 % de rien, ça reste peu de chose ! La vérité, c'est que vous avez 99 chances sur 100 de ne pas bénéficier du médicament », sou-

ORIGINAL ARTICLE

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

S. Yusuf, J. Bosch, G. Dagenais, J. Zhu, D. Xavier, L. Liu, P. Pais, P. López-Jaramillo, L.A. Leiter, A. Dans, A. Avezum, L.S. Piegas, A. Parkhomenko, K. Keltai, M. Keltai, K. Sliwa, R.J.G. Peters, C. Held, I. Chazova, K. Yusoff, B.S. Lewis, P. Jansky, K. Khunti, W.D. Toff, C.M. Reid, J. Varigos, G. Sanchez-Vallejo, R. McKelvie, J. Pogue,* H. Jung, P. Gao, R. Diaz, and E. Lonn, for the HOPE-3 Investigators†

ABSTRACT

BACKGROUND

Previous trials have shown that the use of statins to lower cholesterol reduces the risk of cardiovascular events among persons without cardiovascular disease. Those trials have involved persons with elevated lipid levels or inflammatory markers and involved mainly white persons. It is unclear whether the benefits of statins can be extended to an intermediate-risk, ethnically diverse population without cardiovascular disease.

METHODS

In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years.

RESULTS

The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P=0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P=0.005).

CONCLUSIONS

Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Yusuf at the Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at yusufs@mcmaster.ca.

*Deceased.

†A complete list of the Heart Outcomes Prevention Evaluation (HOPE)–3 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 2, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1600176

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Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001
Secondary outcome — no. (%)	306 (4.8)	393 (6.2)	0.77 (0.66–0.89)	<0.001
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	154 (2.4)	171 (2.7)	0.89 (0.72–1.11)	
Myocardial infarction	45 (0.7)	69 (1.1)	0.65 (0.44–0.94)	
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52–0.95)	
Resuscitated cardiac arrest	4 (0.1)	4 (0.1)	0.99 (0.25–3.97)	
Revascularization	56 (0.9)	82 (1.3)	0.68 (0.48–0.95)	
Heart failure	21 (0.3)	29 (0.5)	0.72 (0.41–1.26)	
Angina with evidence of ischemia	56 (0.9)	64 (1.0)	0.87 (0.61–1.24)	
Death from any cause — no. (%)	334 (5.3)	357 (5.6)	0.93 (0.80–1.08)	0.32
New-onset diabetes — no. (%)	232 (3.9)	226 (3.8)	1.02 (0.85–1.23)	0.82
Coronary heart disease — no. (%)†	105 (1.7)	140 (2.2)	0.74 (0.58–0.96)	0.02
First and recurrent events of the second coprimary outcome‡				
No. of participants with ≥1 event	277	363		
No. of participants with ≥2 events	68	89		
No. of participants with ≥3 events	6	16		
Total no. of events	353	473	0.75 (0.64–0.89)	0.001
Hospitalizations — no. (%)§				
For cardiovascular causes	281 (4.4)	369 (5.8)	0.75 (0.64–0.88)	<0.001
For noncardiovascular causes	881 (13.9)	879 (13.9)	1.00 (0.91–1.10)	0.99

* The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization; and the secondary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with evidence of ischemia.

† Coronary heart disease was a post hoc outcome that included fatal or nonfatal myocardial infarction, coronary revascularization, and angina with evidence of ischemia.

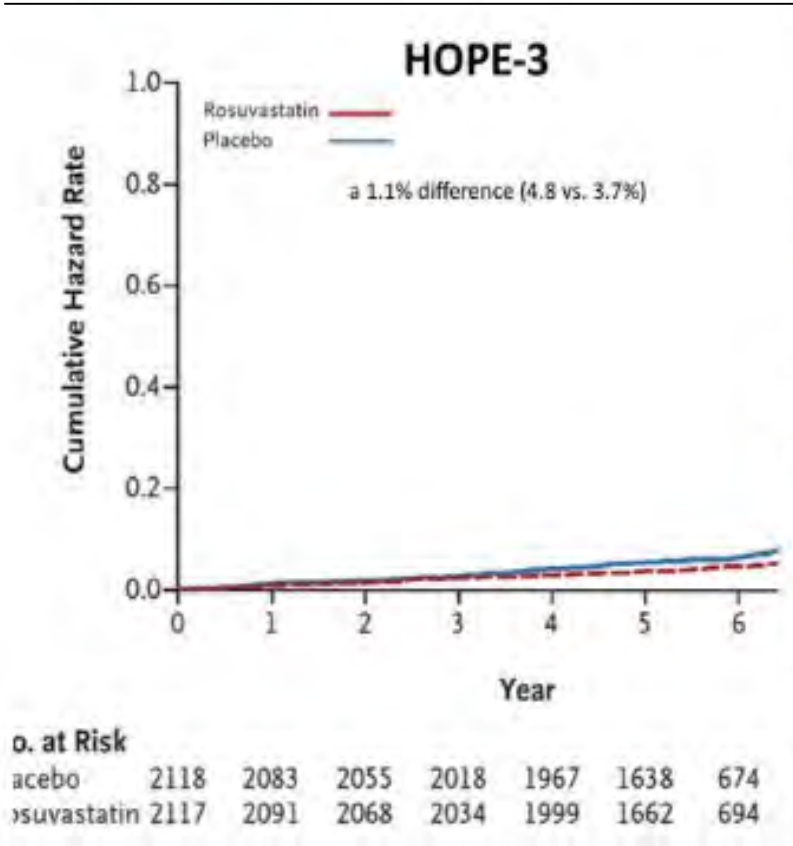
‡ The analysis of the recurrent events of the second coprimary outcome was a post hoc analysis that used a proportional-means model. The second coprimary outcome is shown because it comprises all events that were included in the first coprimary outcome as well as resuscitated cardiac arrest, heart failure, and revascularization.

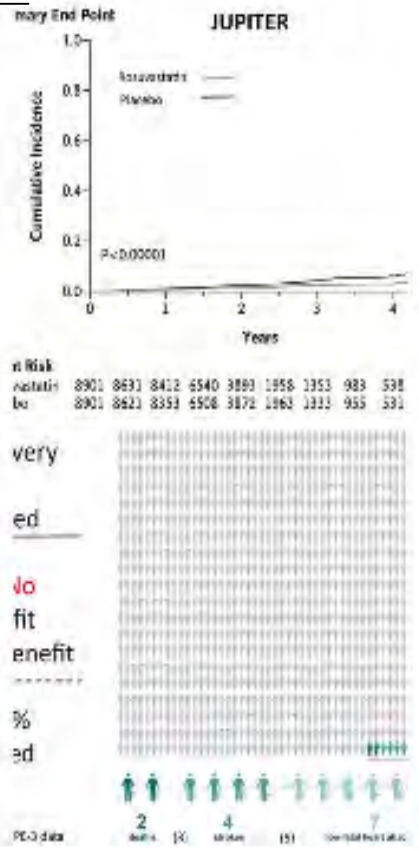
§ Hospitalizations were a prespecified safety outcome.

Eric Topol @EricTopol · Apr 3

A hard look at statins for primary prevention: 2 most recent & summary of all

~~tri~~als..can't we do better than this?





131 113

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known.

METHODS

We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS

The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group ($P<0.001$). The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; $P=0.016$). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital, and Harvard Medical School, Boston (C.P.C., R.P.G., A.M., K.I., E.A.B., S.D.W., E.B.); Duke Clinical Research Institute (DCRI), Durham, NC (M.A.B., J.A.W., C.R., R.M.C.); Montreal Heart Institute, Montreal (P.T.); Vivantes Neukölln Medical Center, Berlin (H.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Canisius-Wilhelmina Ziekenhuis, Nijmegen (T.O.O.), and the Netherlands Leiden University Medical Center, Leiden (J.W.J.) — both in the Netherlands; Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy (G.M.D.F.); National Institute of Cardiology, Warsaw, Poland (W.R.); and Merck, Kenilworth, NJ (P.D.L., A.M.T., T.A.M.). Address reprint requests to Dr. Cannon at the Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave., 1st Fl., Boston, MA 02115, or at cpcannon@partners.org.

*A complete list of investigators in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is provided in the Supplementary Appendix, available at NEJM.org.

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Table 2. Primary, Secondary, and Individual End Points.*

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11
Coronary revascularization ≥30 days after randomization	1793 (23.4)	1690 (21.8)	0.95 (0.89–1.01)	0.11
Urgent coronary revascularization ≥30 days after randomization	626 (8.6)	510 (7.0)	0.81 (0.72–0.91)	0.001
Any revascularization ≥30 days after randomization	1962 (25.6)	1871 (24.2)	0.96 (0.90–1.02)	0.18
Hospitalization for unstable angina	148 (1.9)	156 (2.1)	1.06 (0.85–1.33)	0.62
Other prespecified end points				
Death from cardiovascular causes, MI, or stroke	1704 (22.2)	1544 (20.4)	0.90 (0.84–0.96)	0.003
Major vascular events: death from coronary heart disease, MI, stroke, or coronary revascularization ≥30 days after randomization‡	2685 (34.0)	2498 (31.9)	0.928 (0.88–0.98)	0.007

* The database for the analysis presented here was locked on October 21, 2014. Percentages are 7-year Kaplan–Meier estimates. Major coro-

Original Investigation

Different Time Trends of Caloric and Fat Intake Between Statin Users and Nonusers Among US Adults

Gluttony in the Time of Statins?

Takehiro Sugiyama, MD, MSHS; Yusuke Tsugawa, MD, MPH; Chi-Hong Tseng, PhD; Yasuki Kobayashi, MD, PhD; Martin F. Shapiro, MD, PhD

Editor's Note page 1046

Supplemental content at jamainternalmedicine.com

IMPORTANCE Both dietary modification and use of statins can lower blood cholesterol. The increase in caloric intake among the general population is reported to have plateaued in the last decade, but no study has examined the relationship between the time trends of caloric intake and statin use.

OBJECTIVE To examine the difference in the temporal trends of caloric and fat intake between statin users and nonusers among US adults.

DESIGN, SETTING, AND PARTICIPANTS A repeated cross-sectional study in a nationally representative sample of 27 886 US adults, 20 years or older, from the National Health and Nutrition Examination Survey, 1999 through 2010.

EXPOSURES Statin use.

MAIN OUTCOMES AND MEASURES Caloric and fat intake measured through 24-hour dietary recall. Generalized linear models with interaction term between survey cycle and statin use were constructed to investigate the time trends of dietary intake for statin users and nonusers after adjustment for possible confounders. We calculated model-adjusted caloric and fat intake using these models and examined if the time trends differed by statin use. Body mass index (BMI) changes were also compared between statin users and nonusers.

RESULTS In the 1999-2000 period, the caloric intake was significantly less for statin users compared with nonusers (2000 vs 2179 kcal/d; $P = .007$). The difference between the groups became smaller as time went by, and there was no statistical difference after the 2005-2006 period. Among statin users, caloric intake in the 2009-2010 period was 9.6% higher (95% CI, 1.8-18.1; $P = .02$) than that in the 1999-2000 period. In contrast, no significant change was observed among nonusers during the same study period. Statin users also consumed significantly less fat in the 1999-2000 period (71.7 vs 81.2 g/d; $P = .003$). Fat intake increased 14.4% among statin users (95% CI, 3.8-26.1; $P = .007$) while not changing significantly among nonusers. Also, BMI increased more among statin users (+1.3) than among nonusers (+0.4) in the adjusted model ($P = .02$).

CONCLUSIONS AND RELEVANCE Caloric and fat intake have increased among statin users over time, which was not true for nonusers. The increase in BMI was faster for statin users than for nonusers. Efforts aimed at dietary control among statin users may be becoming less intensive. The importance of dietary composition may need to be reemphasized for statin users.

Author Affiliations: Author affiliations are listed at the end of this article.

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JAMA Intern Med. 2014;174(7):1038-1045. doi:10.1001/jamainternmed.2014.1927

Table 3. Model-Adjusted[a] Relative Changes in Caloric and Fat Intake Among US Adults by Statin Use, 1999-2010

Characteristic	Change From 1999-2000 to 2009-2010, % (95% CI)		*P* Value for Difference in Trends[b]
	Statin User	Statin Nonuser	
Caloric Intake			
1999-2000	0 [Reference]	0 [Reference]	.001
2001-2002	1.7 (−5.6 to 9.5)	0.8 (−2.0 to 3.6)	
2003-2004	6.0 (−1.2 to 13.7)	1.7 (−1.0 to 4.5)	
2005-2006	7.1 (0.2 to 14.8)	0.1 (−3.2 to 3.6)	
2007-2008	4.4 (−3.4 to 12.8)	−2.0 (−5.2 to 1.3)	
2009-2010	9.6 (1.8 to 18.1)	−1.9 (−4.6 to 0.9)	
Fat Intake			
1999-2000	0 [Reference]	0 [Reference]	<.001
2001-2002	2.8 (−6.9 to 13.6)	1.8 (−1.4 to 5.1)	
2003-2004	10.9 (−0.1 to 23.0)	3.8 (0.5 to 7.2)	
2005-2006	14.2 (3.9 to 25.4)	2.5 (−1.8 to 6.9)	
2007-2008	12.1 (1.6 to 23.6)	−0.2 (−4.0 to 3.8)	
2009-2010	14.4 (3.8 to 26.1)	−2.3 (−5.6 to 1.1)	

[a] Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

[b] Significance of interaction terms between survey cycle (continuous) and statin use (binary).

Original Investigation

Statins and Physical Activity in Older Men The Osteoporotic Fractures in Men Study

David S. H. Lee, PharmD, PhD; Sheila Markwardt, BS; Leah Goeres, PharmD; Christine G. Lee, MD; Elizabeth Eckstrom, MD, MPH; Craig Williams, PharmD; Rongwei Fu, PhD; Eric Orwoll, MD; Peggy M. Cawthon, PhD; Marcia L. Stefanick, PhD; Dawn Mackey, PhD; Douglas C. Bauer, MD; Carrie M. Nielson, PhD

IMPORTANCE Muscle pain, fatigue, and weakness are common adverse effects of statin medications and may decrease physical activity in older men.

OBJECTIVE To determine whether statin use is associated with physical activity, longitudinally and cross-sectionally.

DESIGN, SETTING, AND PARTICIPANTS Men participating in the Osteoporotic Fractures in Men Study (N = 5994), a multicenter prospective cohort study of community-living men 65 years and older, enrolled between March 2000 and April 2002. Follow-up was conducted through 2009.

EXPOSURES Statin use as determined by an inventory of medications (taken within the last 30 days). In cross-sectional analyses (n = 4137), statin use categories were users and nonusers. In longitudinal analyses (n = 3039), categories were prevalent users (baseline use and throughout the study), new users (initiated use during the study), and nonusers (never used).

MAIN OUTCOMES AND MEASURES Self-reported physical activity at baseline and 2 follow-up visits using the Physical Activity Scale for the Elderly (PASE). At the third visit, an accelerometer measured metabolic equivalents (METs [kilocalories per kilogram per hour]) and minutes of moderate activity (METs ≥3.0), vigorous activity (METs ≥6.0), and sedentary behavior (METs ≤1.5).

RESULTS At baseline, 989 men (24%) were users and 3148 (76%) were nonusers. The adjusted difference in baseline PASE between users and nonusers was −5.8 points (95% CI, −10.9 to −0.7 points). A total of 3039 men met the inclusion criteria for longitudinal analysis: 727 (24%) prevalent users, 845 (28%) new users, and 1467 (48%) nonusers. PASE score declined by a mean (95% CI) of 2.5 (2.0 to 3.0) points per year for nonusers and 2.8 (2.1 to 3.5) points per year for prevalent users, a nonstatistical difference (0.3 [−0.5 to 1.0] points). For new users, annual PASE score declined at a faster rate than nonusers (difference of 0.9 [95% CI, 0.1 to 1.7] points). A total of 3071 men had adequate accelerometry data, 1542 (50%) were statin users. Statin users expended less METs (0.03 [95% CI, 0.02-0.04] METs less) and engaged in less moderate physical activity (5.4 [95% CI, 1.9-8.8] fewer minutes per day), less vigorous activity (0.6 [95% CI, 0.1-1.1] fewer minutes per day), and more sedentary behavior (7.6 [95% CI, 2.6-12.4] greater minutes per day).

CONCLUSIONS AND RELEVANCE Statin use was associated with modestly lower physical activity among community-living men, even after accounting for medical history and other potentially confounding factors. The clinical significance of these findings deserves further investigation.

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Invited Commentary

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ORIGINAL INVESTIGATIONS

Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men

A Population-Based Prospective Cohort Study

Agneta Åkesson, PhD, Susanna C. Larsson, PhD, Andrea Discacciati, MSc, Alicja Wolk, DMSc

TABLE 3 Effect of Combined Low-Risk Behaviors in Relation to Risk of Myocardial Infarction*

Group	Low-Risk Group No. of Events (% Men)	Age-Standardized Incidence Rate† (95% CI)	Compared With High-Risk Group‡ RR (95% CI)	Compared With the Remainder of the Study Population RR (95% CI)	Population Attributable Risk§ % (95% CI)
1 low-risk factor: healthy diet (RFS top quintile)	177 (18)	495 (417-572)	0.74 (0.58-0.96)	0.82 (069-0.96)	16 (4-35)
2 low-risk factors‖: healthy diet (RFS top quintile), alcohol consumption 10-30 g/day	74 (8.7)	429 (321-537)	0.65 (0.48-0. 87)	0.75 (0.59-0.95)	23 (4-39)
3 low-risk factors¶: healthy diet (RFS top quintile), alcohol consumption 10-30 g/day, no smoking	36 (5.4)	321 (208-433)	0.36 (0.25-0.53)	0.54 (0.39-0.76)	44 (23-49)
4 low-risk factors#: healthy diet (RFS top quintile), alcohol consumption 10-30 g/day, no smoking, physically active (≥40 min/day of walking/ bicycling and ≥1 h/week of exercise)	9 (1.7)	218 (73-363)	0.24 (0.12-0.47)	0.36 (0.19-0.69)	64 (30-81)
5 low-risk factors: healthy diet (RFS top quintile), alcohol consumption 10-30 g/day, no smoking, physically active (≥40 min/day of walking/ bicycling and ≥1 h/week of exercise), waist circumference <95 cm	3 (1.0)	131 (0-279)	0.14 (0.04-0.43)	0.21 (0.07-0.66)	79 (34-93)

*All relative risks were adjusted for age (continuous), educational achievement (≤9, 10 to 12, >12 years), family history of myocardial infarction (yes/no), use of aspirin (yes/no), marital status (unmarried, married, divorced, widowed), non-Recommended Food Score (quintiles), and total energy intake (continuous). †Per 100,000 person-years. ‡The high-risk group (8.3% of the study population and 166 cases of myocardial infarction [age-standardized incidence rate 979 cases per 100,000 person-years]) included men with no low-risk factors and was characterized by the following: median 2.9 servings/day of vegetables and fruit, 3.0 servings/day of whole grains, and 1.4 servings/week of fish; 24 pack-years of tobacco smoking (55% reported to be current smokers); 36% reported neither ≥40 min of daily walking/bicycling nor ≥1 h per week of exercise; and a median waist circumference 101 cm. §Estimated compared with the remainder of the total study population, representing 91.3%, 94.6%, 98.3%, and 99%, respectively, for each additional low-risk factor. ‖The model was also adjusted for smoking, physical activity, and waist circumference. ¶The model was also adjusted for physical activity and waist circumference. #The model was also adjusted for waist circumference.

RFS = Recommended Food Score; other abbreviations as in Table 2.

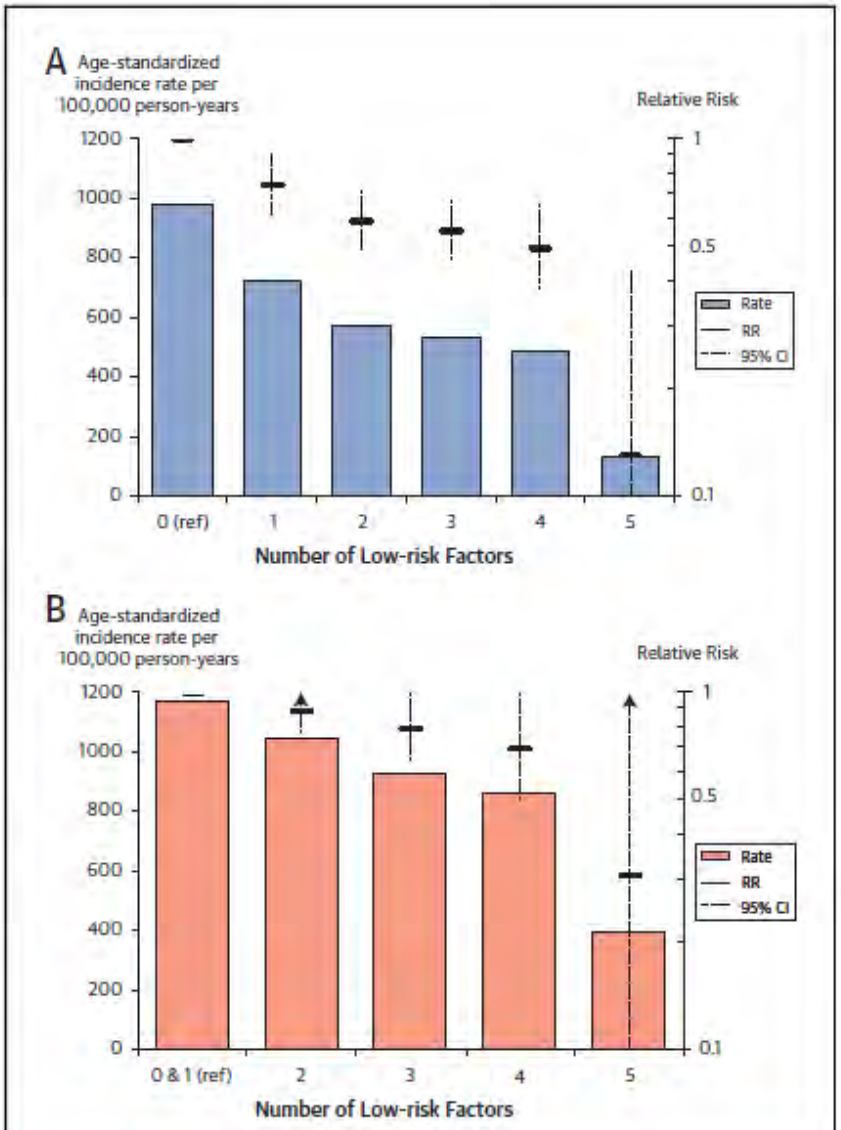

FIGURE 1 **MI Incidence for the Addition of Any Low-Risk Behavior**

Age-standardized incidence rates and multivariable-adjusted relative risks of MI for the addition of any single low-risk factor compared with the high-risk group for men without hypertension and high cholesterol (n = 20,721), p for trend < 0.001 **(A)**, and men with hypertension and high cholesterol (n = 7,139), p for trend = 0.002 (3 and 4 statistically

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Combined Impact of Health Behaviours and Mortality in Men and Women: The EPIC-Norfolk Prospective Population Study

Kay-Tee Khaw[1]*, Nicholas Wareham[2], Sheila Bingham[3], Ailsa Welch[1], Robert Luben[1], Nicholas Day[1]

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Funding: EPIC-Norfolk is supported by programme grants from Medical Research Council and Cancer Research United Kingdom with additional support from the Stroke Association, British Heart Foundation, Research Into Ageing, and the Academy of Medical Science. The sponsors had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, and preparation, review, or approval of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Published: January 8, 2008

Abbreviations: CI, confidence interval; ICD, International Classification of Disease; RR, relative risk

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ABSTRACT

Background

There is overwhelming evidence that behavioural factors influence health, but their combined impact on the general population is less well documented. We aimed to quantify the potential combined impact of four health behaviours on mortality in men and women living in the general community.

Methods and Findings

We examined the prospective relationship between lifestyle and mortality in a prospective population study of 20,244 men and women aged 45–79 y with no known cardiovascular disease or cancer at baseline survey in 1993–1997, living in the general community in the United Kingdom, and followed up to 2006. Participants scored one point for each health behaviour: current non-smoking, not physically inactive, moderate alcohol intake (1–14 units a week) and plasma vitamin C >50 mmol/l indicating fruit and vegetable intake of at least five servings a day, for a total score ranging from zero to four. After an average 11 y follow-up, the age-, sex-, body mass–, and social class–adjusted relative risks (95% confidence intervals) for all-cause mortality(1,987 deaths) for men and women who had three, two, one, and zero compared to four health behaviours were respectively, 1.39 (1.21–1.60), 1.95 (1.70–2.25), 2.52 (2.13–3.00), and 4.04 (2.95–5.54) $p < 0.001$ trend. The relationships were consistent in subgroups stratified by sex, age, body mass index, and social class, and after excluding deaths within 2 y. The trends were strongest for cardiovascular causes. The mortality risk for those with four compared to zero health behaviours was equivalent to being 14 y younger in chronological age.

Conclusions

Four health behaviours combined predict a 4-fold difference in total mortality in men and women, with an estimated impact equivalent to 14 y in chronological age.

The Editors' Summary of this article follows the references.

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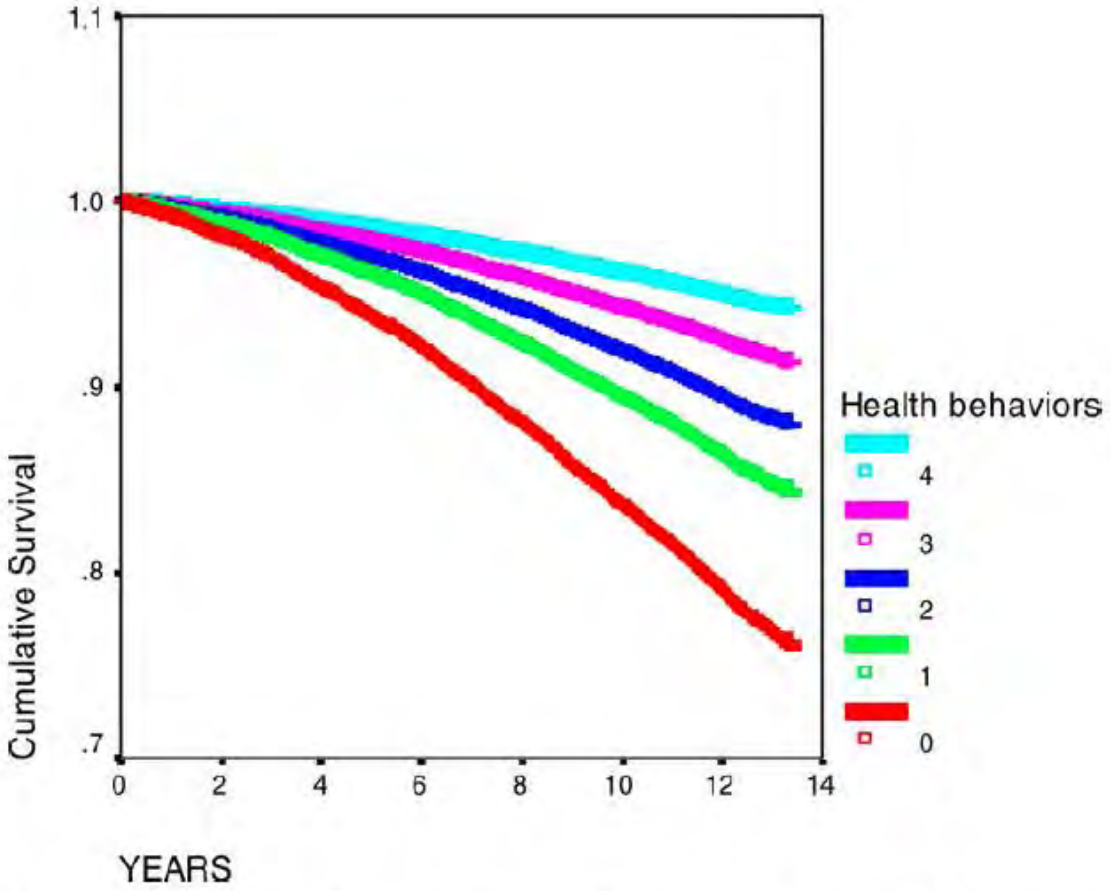


Figure 1. Survival Function According to Number of Health Behaviours in Men and Women Aged 45–79 Years without Known Cardiovascular Disease or Cancer, Adjusted for Age, Sex, Body Mass Index and Social Class, EPIC-Norfolk 1993–2006

doi:10.1371/journal.pmed.0050012.g001

EDITORIAL COMMENT

The Promise of Lifestyle for Cardiovascular Health

Time for Implementation*

Dariush Mozaffarian, MD, DrPH

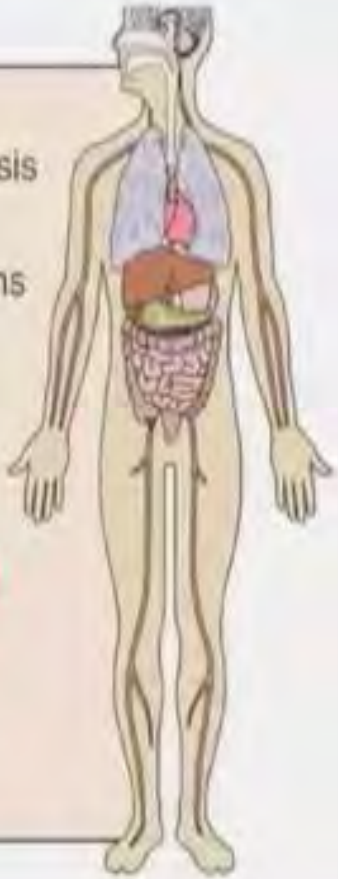
and of abdominal obesity to 4 in 5 MIs. These findings highlight the primacy of healthy lifestyle. For both individual patients and populations, lifestyle goals should not be formulated solely for control of weight or blood pressure, cholesterol, and glucose levels. Although lifestyle has major benefits on these physiological factors, a healthier diet, greater activity, and nonsmoking influence numerous other pathways of risk and produce substantial additional benefits for cardiovascular and noncardiovascular health (5). For example, in the present investigation among >20,000 Swedish men, the combination of a healthier diet

an end and instead recognizing the relevance of lifestyle as a primary target for health. It is time for medical educators, clinicians, health administrators, and insurance providers to follow suit by designing and implementing a comprehensive, ambitious agenda to incorporate measures of and targets for dietary quality, physical activity, smoking, and central obesity into every aspect of the health system (9). Patients should enter their doctor's office and not simply ask "How are my blood pressure, cholesterol, and glucose levels?" but also ask "How are my dietary habits, physical activity level, smoking, and waist measurement?"

Diet & Health: Modern Science

Refined grains, starches, sugars
Fruits, vegetables, nuts
Whole grains, legumes
Yogurt, cheese, milk
Fish, shellfish
Processed meats, red meats
Vegetable oils, specific fatty acids
Coffee, tea, alcohol
Sugary beverages, juice
Minerals, antioxidants, phytochemicals
Food-based dietary patterns
Food processing, preparation methods

Blood pressure
Glucose-insulin homeostasis
Liver fat synthesis
Blood lipids, apolipoproteins
Endothelial function
Systemic inflammation
Brain reward, craving
Gut microbiome
Satiety, hunger, obesity
Adipocyte function
Cardiac function
Thrombosis, coagluation
Vasular adhesion



Mozaffarian D, Circulation 2016

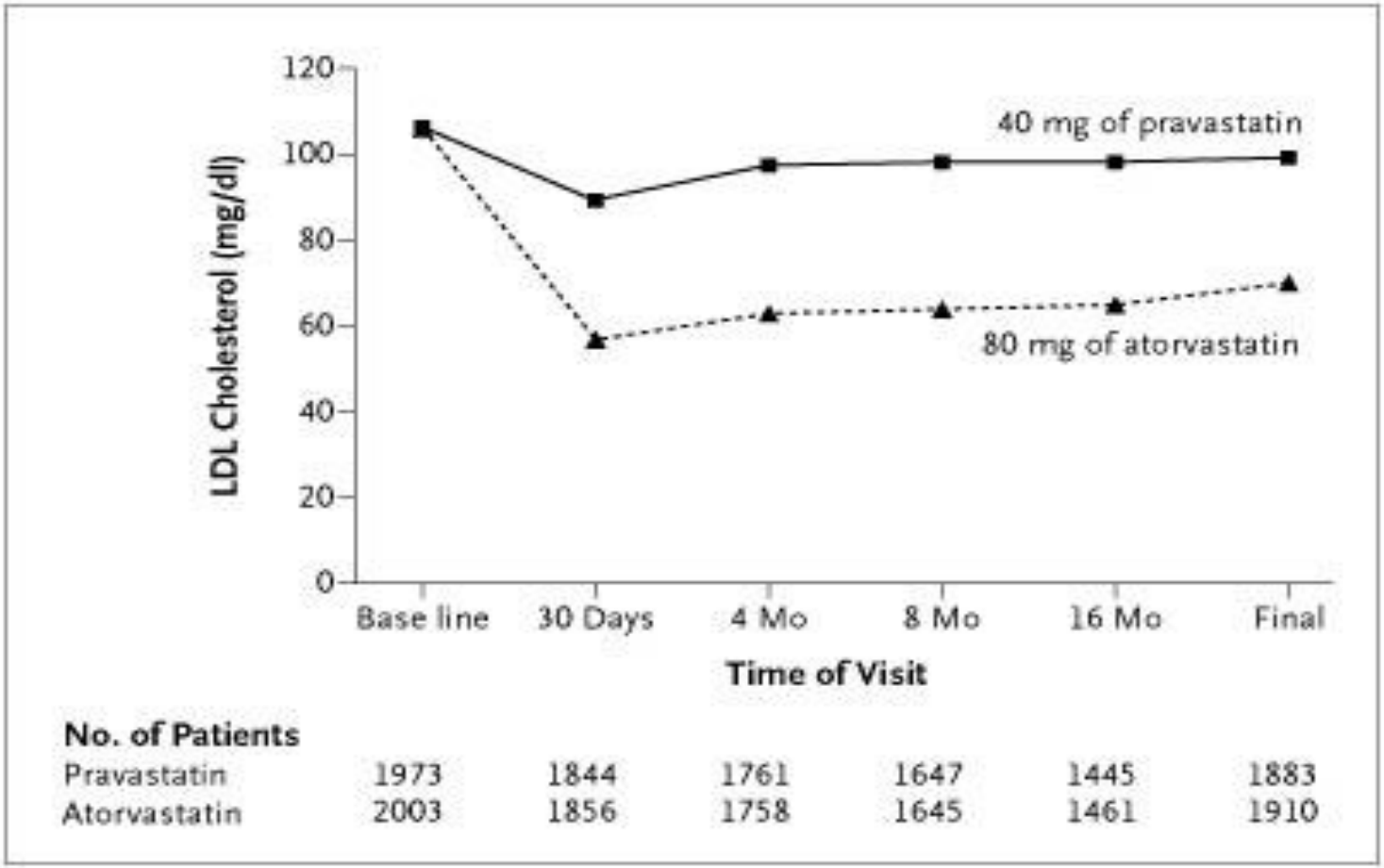
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*

Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Cannon, C. et al. N Engl J Med 2004;350:1495-1504

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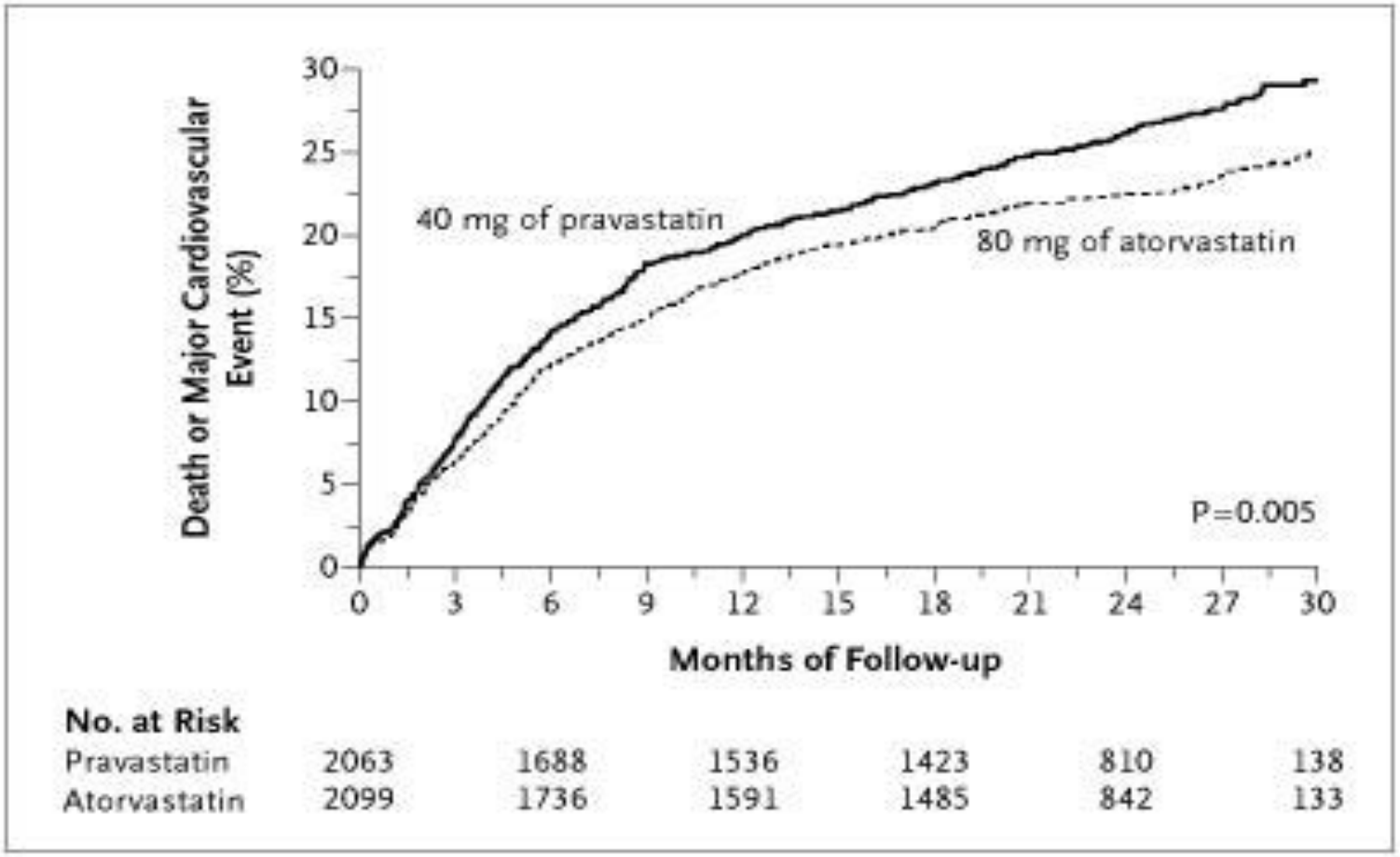
Kaplan-Meier Estimates of the Incidence of the Primary End Point of Death from Any Cause or a Major Cardiovascular Event



Cannon, C. et al. N Engl J Med 2004;350:1495-1504

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Association of Diet, Exercise, and Smoking Modification With Risk of Early Cardiovascular Events After Acute Coronary Syndromes

Clara K. Chow, MBBS, FRACP, PhD; Sanjit Jolly, MD, MSc, FRCPC; Purnima Rao-Melacini, MSc; Keith A.A. Fox, BSc (Hons), MB, ChB, FRCP, FESC, FMedSci; Sonia S. Anand, MD, PhD, FRCPc; Salim Yusuf, DPhil, FRCPC, FRSC

Background—Although preventive drug therapy is a priority after acute coronary syndrome, less is known about adherence to behavioral recommendations. The aim of this study was to examine the influence of adherence to behavioral recommendations in the short term on risk of cardiovascular events.

Methods and Results—The study population included 18 809 patients from 41 countries enrolled in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 randomized clinical trial. At the 30-day follow-up, patients

(*Circulation*. 2010;121:750-758.

Table 6. Relationship Between Diet/Exercise Modification and Repeat Cardiovascular Events in Patients With ACS

	Risk of MI		Risk of Stroke		Risk of Death		Risk of Death/MI/Stroke	
Category	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
No diet/exercise	Reference		Reference		Reference		Reference	
Diet only	0.93 (0.74–1.16)	0.5137	0.84 (0.54–1.31)	0.4357	0.91 (0.73–1.13)	0.3986	0.91 (0.77–1.07)	0.2605
Exercise only	0.78 (0.56–1.1)	0.1547	0.94 (0.52–1.68)	0.8256	0.61 (0.42–0.88)	0.0091	0.69 (0.54–0.89)	0.0037
Both diet and exercise	0.52 (0.40–0.69)	<0.0001	0.46 (0.26–0.82)	0.0079	0.45 (0.33–0.60)	<0.0001	0.46 (0.38–0.57)	<0.0001

Models were adjusted for age; sex; region; history of hypertension, diabetes, and prior MI; body mass index; creatinine; PCI/CABG before 30 days; and use of β-blockers, statins, antiplatelets, and ACE/ARB drugs at 30 days.


UNE
TEMPÊTE PARFAITE
SE PROFILE À L'HORIZON
25 JANVIER 2010
BULLETIN DE SANTÉ 2010 DES CANADIENS ET DES CANADIENNES
DE LA FONDATION DES MALADIES DU CŒUR
FONDATION
DES MALADIES
DU CŒUR
À la conquête de solutions.

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HOMMES

1981	COMPOSITION CORPORELLE	2007-2009
173,0 cm (5 pi 8 po)	Taille	175,3 cm (5 pi 9 po)
77,4 kg (171 livres)	Poids	86,6 kg (191 livres)*
25,7 kg/m^2 - embonpoint	Indice de masse corporelle	27,9 kg/m^2* - embonpoint
90,6 cm (35,7 po) - faible risque	Circonférence de la taille	97,0 cm (38,2 po)* - risque accru
99,0 cm (39,0 po)	Circonférence des hanches	102,7 cm (40,4 po)*
0,91	Rapport taille-hanches	0,95*
	TESTS DE CONDITION PHYSIQUE	
104 kg - très bonne	Force de préhension	94 kg* - bonne
23,1 cm - passable	Flexion du tronc	26,7 cm* - bonne
–	Puissance aérobie maximale prévue (VO_2max)	39,2 ml•(kg•min)$^{-1}$ - bonne

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FEMMES

1981	COMPOSITION CORPORELLE	2007-2009
161,5 cm (5 pi 4 po)	Taille	162,3 cm (5 pi 4 po)
63,2 kg (139 livres)	Poids	68,4 kg (151 livres)*
24,1 kg/m^2 - poids normal	Indice de masse corporelle	25,8 kg/m^2* - embonpoint
76,3 cm (30,0 po) - faible risque	Circonférence de la taille	83,4 cm (32,8 po)* - risque accru
98,5 cm (38,8 po)	Circonférence des hanches	102,5 cm (40,4 po)*
0,77	Rapport taille-hanches	0,81*
	TESTS DE CONDITION PHYSIQUE	
62 kg - très bonne	Force de préhension	56 kg* - bonne
30,2 cm - bonne	Flexion du tronc	31,5 cm - bonne
–	Puissance aérobie maximale prévue (VO_2max)	32,8 ml•(kg•min)$^{-1}$ - bonne

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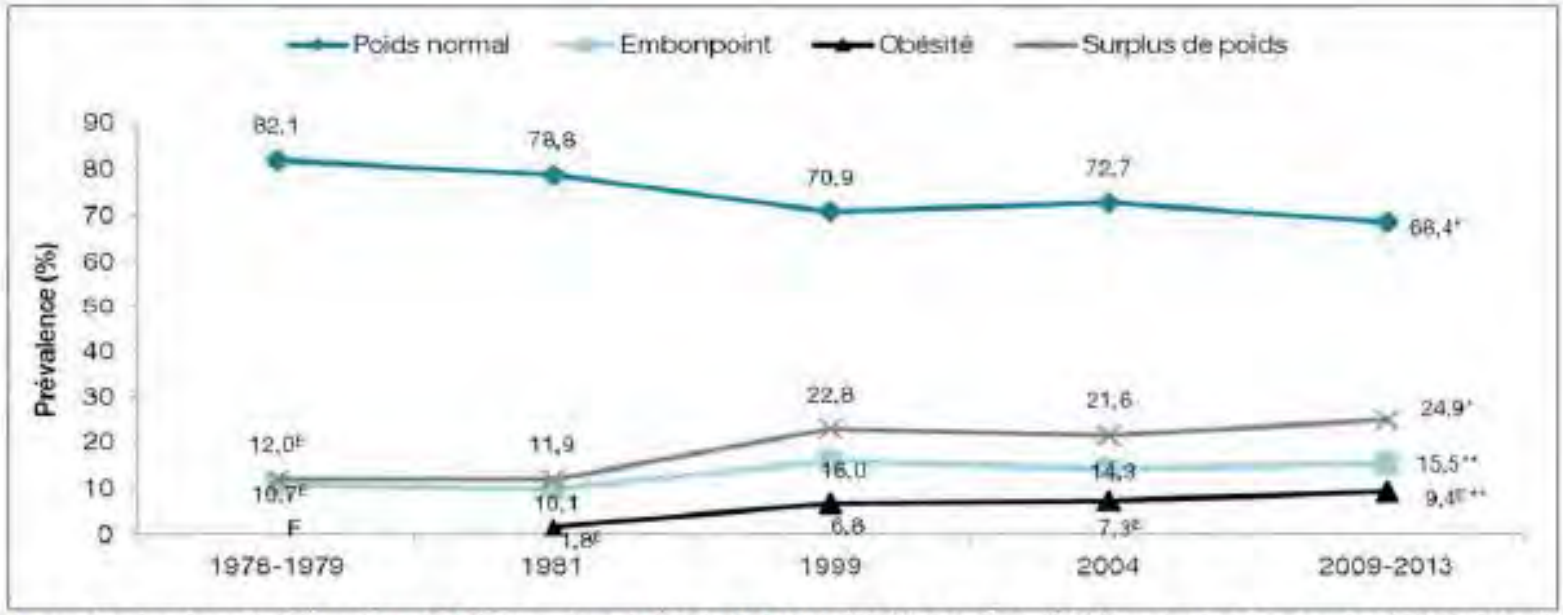
Figure 2 **Statut pondéral chez les jeunes québécois âgés de 6 à 17 ans, Québec, 1978-1979, 1981[a], 1999[b], 2004 et 2009-2013**



Source des données : Statistique Canada, fichiers maîtres de l'ESC 1978-1979, l'ESCC-2.2, 2004, l'ECMS cycles 2 et 3 fusionnés 2009-2013. Institut de la statistique du Québec, fichier maître de l'ESSEA – volet nutrition 1999. Fichier de microdonnées de l'ECPC 1981.
Analyses statistiques : INSPQ, 2015.

[a] La population ciblée dans l'ECPC de 1981 était les Canadiens de 7 à 69 ans, les résultats présentés sont représentatifs des jeunes québécois âgés de 7 à 17 ans en l'absence des 6-17 ans.

[b] La population ciblée dans l'ESSEA – volet nutrition de 1999 était les jeunes québécois âgés de 6 à 16 ans, les résultats présentés sont représentatifs des jeunes québécois âgés de 6 à 16 ans en l'absence des 6-17 ans.

[E] CV compris entre 16,6 % et 33,3 % (interpréter avec prudence).

[F] CV supérieur à 33,3 % (donnée non diffusée).

* Valeur significativement différente de l'estimation de l'ESC 1978-1979. ** Valeur significativement différente de l'estimation de l'ECPC 1981 pour les 7-17 ans.

Epidemiology of cardiovascular disease in young individuals

Charlotte Andersson[1,2] and Ramachandran S. Vasan[1,3]

Abstract | In the past 2 decades, a high prevalence of risk factors for cardiovascular disease, such as obesity, physical inactivity, and poor diet, has been observed among young individuals living in developed countries. The rate of substance abuse (opioids, cocaine, electronic cigarettes, and anabolic steroids) is also increasing among young adults, whereas cigarette smoking might be declining. Among younger individuals (aged 18–50 years), the incidence of cardiovascular diseases over the same time period has either been steady or has increased, in contrast to the trend towards a lower incidence of cardiovascular disease in adults aged >50 years. Current observations might, therefore, be used to forecast a potential epidemic of cardiovascular disease in the near future as the younger segment of the population ages. In this Review, we discuss the burden of risk factors for ischaemic heart disease, heart failure, atrial fibrillation, and sudden cardiac death among young adults aged 18–45 years. Furthermore, we discuss the prevalence, incidence, and temporal trends of various cardiovascular diseases among this young segment of the population.

Cardiovascular diseases among young adults (defined in general as individuals aged 18–45 years) comprise a heterogeneous group of disorders that can be either congenital or acquired. The incidence and prevalence of both congenital and acquired cardiovascular diseases seem to be increasing over the past few decades in the Western world, secondary to changing risk factor profiles among children and young adults. This Review discusses the risk factors, incidence, prevalence, and temporal trends of acquired cardiovascular diseases, including ischaemic heart disease, heart failure, atrial fibrillation, and sudden cardiac death, among young individuals.

Risk factor burden

The high prevalence of risk factors among individuals living in the USA has led the AHA to identify seven key health metrics ('ideal health factors') to reduce the future burden of cardiovascular disease (TABLE 1). These ideal health factors have been linked with lower levels of several biomarkers of subclinical atherosclerosis (such as carotid intima–media thickness)[1,2] and are linearly associated with the risk of developing cardiovascular disease and the risk of all-cause and cardiovascular mortality[3–5]. Ideal levels of key cardiovascular health factors are also important in reducing the risk of premature cardiovascular-related death (defined as the onset of cardiovascular disease in individuals aged <60 years)[3]. FIGURE 1 presents the prevalence of each cardiovascular health metric for younger (aged 20–49 years) versus the prevalence in older individuals (aged ≥50 years) based on estimates from the NHANES study[6]. High blood pressure, BMI, and levels of blood cholesterol and blood glucose were more common overall in older than in younger individuals because these risk factors tend to accumulate and increase with age. By contrast, both smoking and the consumption of unhealthy foods were more common in younger than in older individuals. Very few individuals in the USA, including children, have an ideal health profile[6].

Obesity. Over the past 40 years, the global age-adjusted prevalence of obesity has risen by nearly threefold from 3.2% to 10.8% in men and from 6.4% to 14.9% in women[7]. Between 1980 and 2013, the prevalence of children who are overweight or obese has increased from 16% to 23% in developed countries and from 8% to 10% in developing countries[8]. However, in some developing countries, particularly those in South Asia, the high prevalence of children who are underweight remains as much of a major health issue as obesity[7]. Although BMI increases with age, steeper increases in weight have been observed for more recent birth cohorts (particularly since the 1960s) in both developing and developed countries[8]. However, analyses of more recent cohorts of the NHANES study have suggested that the previous sharp increases in obesity prevalence among individuals in the USA are levelling off[9]. A comprehensive review from 2010 similarly concluded that whereas obesity rates are stabilizing in many Western countries, including the USA and Europe, obesity might still be on

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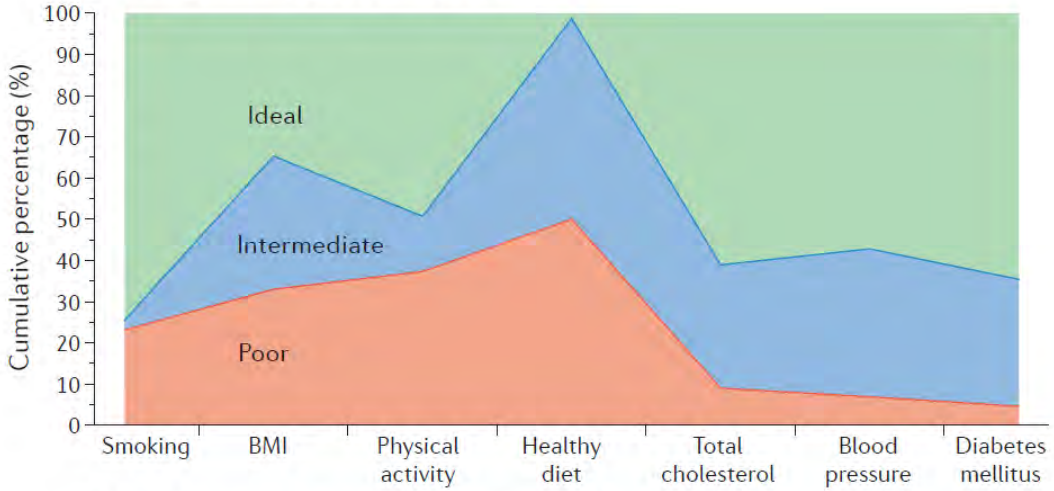


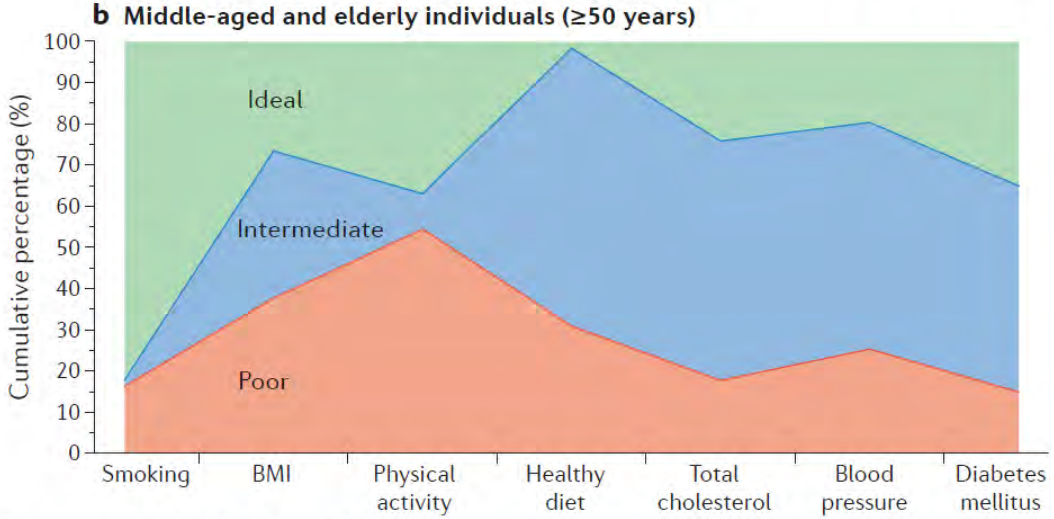
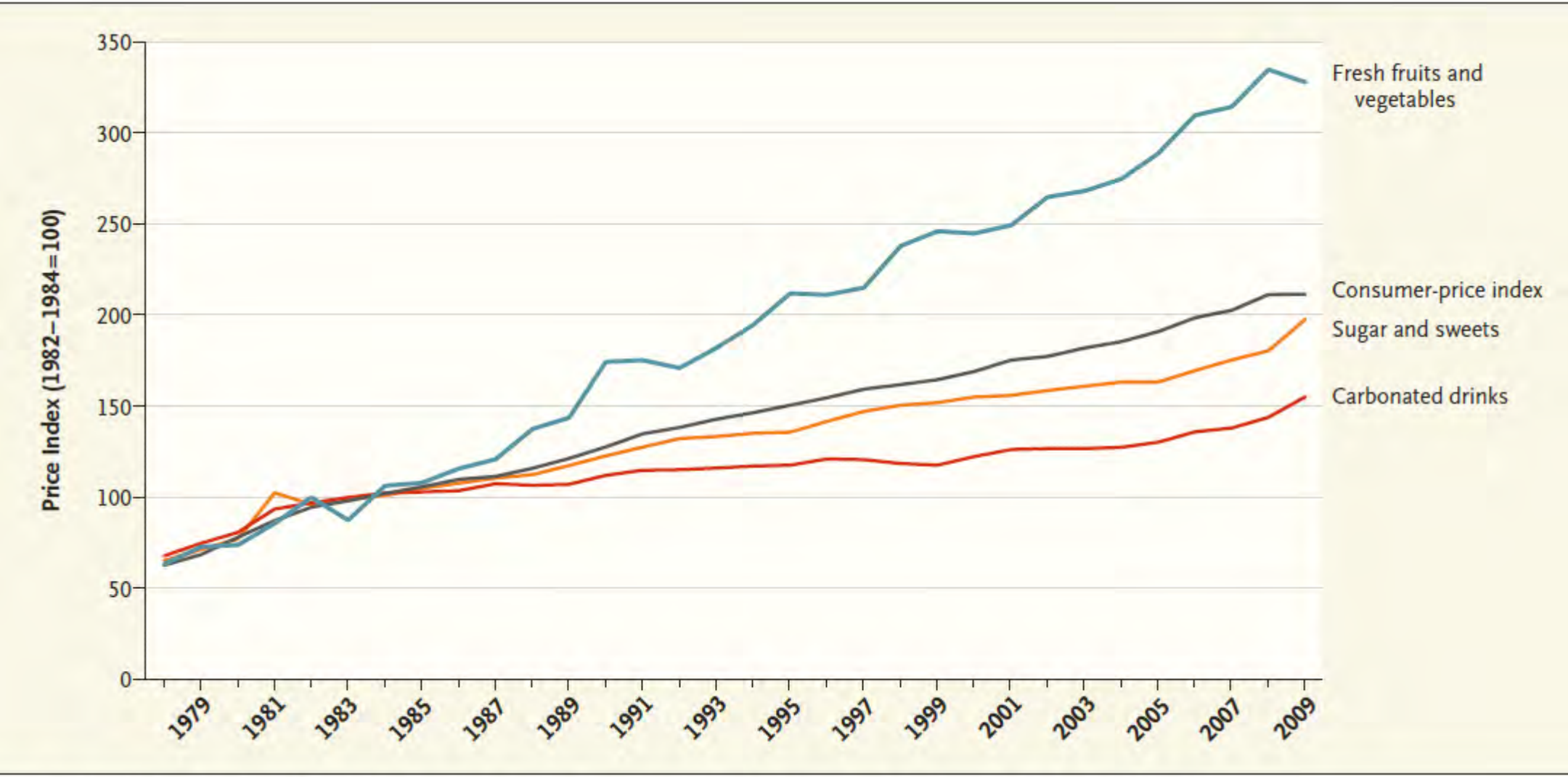


Figure 1 | **Levels of various risk factors stratified by age groups (20–49 years and ≥50 years) in the NHANES[6]. a** | Young individuals (aged 20–49 years). **b** | Middle-aged and older individuals (aged ≥50 years). Red represents poor risk factor levels, blue represents intermediate risk factor levels, and green represents ideal risk factor levels.



Relative Price Changes for Fresh Fruits and Vegetables, Sugars and Sweets, and Carbonated Drinks, 1978–2009.

Original Investigation

Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults

Quanhe Yang, PhD; Zefeng Zhang, MD, PhD; Edward W. Gregg, PhD; W. Dana Flanders, MD, ScD; Robert Merritt, MA; Frank B. Hu, MD, PhD

IMPORTANCE Epidemiologic studies have suggested that higher intake of added sugar is associated with cardiovascular disease (CVD) risk factors. Few prospective studies have examined the association of added sugar intake with CVD mortality.

OBJECTIVE To examine time trends of added sugar consumption as percentage of daily calories in the United States and investigate the association of this consumption with CVD mortality.

DESIGN, SETTING, AND PARTICIPANTS National Health and Nutrition Examination Survey (NHANES, 1988-1994 [III], 1999-2004, and 2005-2010 [n = 31 147]) for the time trend analysis and NHANES III Linked Mortality cohort (1988-2006 [n = 11 733]), a prospective cohort of a nationally representative sample of US adults for the association study.

Invited Commentary

Supplemental content at jamainternalmedicine.com

Table 3. Adjusted HR of CVD Mortality Comparing Percentage of Calories From Added Sugar Greater Than or Equal to 10% or 25% With Less Than 10%[a]

Characteristic	Midvalue of Usual Percentage of Calories From Added Sugar[b]			*P* Value[c]
	5.0%	17.5%	28.7%	
Range (0-100)/usual percentage, %	0 to <10.0	10.0 to <25.0	≥25.0	
HR (95% CI)				
Adjusted only for age, sex, race/ethnicity	1 [Ref]	1.39 (1.20 to 1.62)	3.55 (2.00 to 6.29)	<.001
Fully adjusted[d]	1 [Ref]	1.30 (1.09 to 1.55)	2.75 (1.40 to 5.42)	.004

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; Ref, reference.

calories from added sugar and CVD mortality based on the Satterthwaite

F test; all tests are 2 tailed

JAMA Internal Medicine | Special Communication

Sugar Industry and Coronary Heart Disease Research
A Historical Analysis of Internal Industry Documents

Cristin E. Kearns, DDS, MBA; Laura A. Schmidt, PhD, MSW, MPH; Stanton A. Glantz, PhD

Early warning signals of the coronary heart disease (CHD) risk of sugar (sucrose) emerged in the 1950s. We examined Sugar Research Foundation (SRF) internal documents, historical reports, and statements relevant to early debates about the dietary causes of CHD and assembled findings chronologically into a narrative case study. The SRF sponsored its first CHD research project in 1965, a literature review published in the *New England Journal of Medicine*, which singled out fat and cholesterol as the dietary causes of CHD and downplayed evidence that sucrose consumption was also a risk factor. The SRF set the review's objective, contributed articles for inclusion, and received drafts. The SRF's funding and role was not disclosed. Together with other recent analyses of sugar industry documents, our findings suggest the industry sponsored a research program in the 1960s and 1970s that successfully cast doubt about the hazards of sucrose while promoting fat as the dietary culprit in CHD. Policymaking committees should consider giving less weight to food industry–funded studies and include mechanistic and animal studies as well as studies appraising the effect of added sugars on multiple CHD biomarkers and disease development.

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Invited Commentary
Author Audio Interview
Supplemental content

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In the 1950s, disproportionately high rates of coronary heart disease (CHD) mortality in American men led to studies of the role of dietary factors, including cholesterol, phytosterols, excessive calories, amino acids, fats, carbohydrates, vitamins, and minerals in influencing CHD risk.[1] By the 1960s, 2 prominent physiologists were championing divergent causal hypotheses of CHD[2,3]: John Yudkin identified added sugars as the primary agent, while Ancel Keys identified total fat, saturated fat, and dietary cholesterol. However, by the 1980s, few scientists believed that added sugars played a significant role in CHD, and the first *1980 Dietary Guidelines for Americans*[4] focused on reducing total fat, saturated fat, and dietary cholesterol for CHD prevention.

Although the contribution of dietary sugars to CHD is still debated, what is clear is that the sugar industry, led by the Sugar Association, the sucrose industry's Washington, DC–based trade association,[5] steadfastly denies that there is a relationship between added sugar consumption and CVD risk.[6,7] This Special Communication uses internal sugar industry documents to describe how the industry sought to influence the scientific debate over the dietary causes of CHD in the 1950s and 1960s, a debate still reverberating in 2016.

Methods

The Sugar Association evolved from the Sugar Research Foundation (SRF), founded in 1943.[8] We located correspondence between the SRF and Roger Adams, a professor who served on the SRF's scientific advisory board (SAB) between 1959 and 1971, in the University of Illinois Archives[9] (319 documents totaling 1551 pages). We located correspondence between the SRF and D. Mark Hegsted, professor of nutrition at the Harvard School of Public Health and codirector of the SRF's first CHD research project from 1965 to 1966,[10] in the Harvard Medical Library[11] (27 documents totaling 31 pages).

We collected additional SRF materials through a WorldCat search including annual reports, symposium proceedings, and internal reviews of research. We reviewed historical reports and statements contextualizing scientific debates in the 1950s and 1960s on dietary factors causally related to CHD published by the National Academy of Sciences–National Research Council (NAS-NRC), US Public Health Service, the American Heart Association (AHA), and American Medical Association (AMA). Findings were assembled chronologically into a narrative case study.

Results

SRF's Interest in Promoting a Low-Fat Diet to Prevent CHD

Sugar Research Foundation president Henry Hass's 1954 speech, "What's New in Sugar Research,"[12] to the American Society of Sugar Beet Technologists identified a strategic opportunity for the sugar industry: increase sugar's market share by getting Americans to eat a lower-fat diet: "Leading nutritionists are pointing out the chemical connection between [American's] high-fat diet and the formation of cholesterol which partly plugs our arteries and capillaries, restricts the flow of blood, and causes high blood pressure and heart trouble... if you put [the middle-aged man] on a low-fat diet, it takes just five days for the blood cholesterol to get down to where it should be... If the carbohydrate industries were to recapture this 20

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Invited Commentary

HEALTH CARE POLICY AND LAW

Food Industry Funding of Nutrition Research

The Relevance of History for Current Debates

Marion Nestle, PhD, MPH

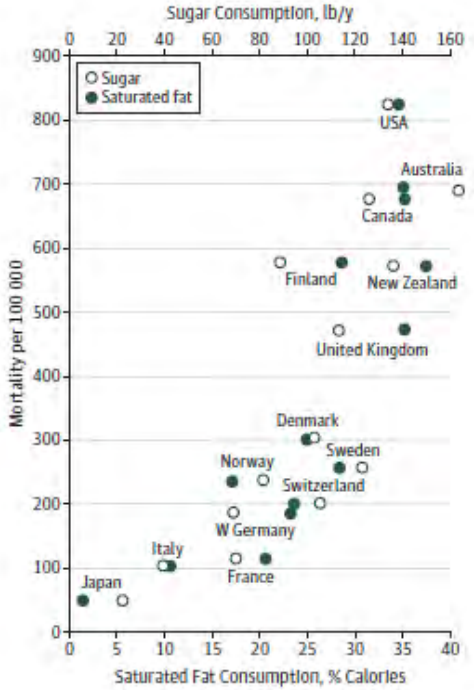
Industry-sponsored nutrition research, like that of research sponsored by the tobacco, chemical, and pharmaceutical industries, almost invariably produces results that confirm the benefits or lack of harm of the sponsor's products, even when independently sponsored research comes to opposite conclusions.[1] Although considerable evidence demonstrates that those industries deliberately influenced the design, results, and interpretation of the studies they paid for,[2] much less is known about the influence of food-company sponsorship on nutrition research. Typically, the disclosure statements of sponsored nutrition studies state that the funder had no role in their design, conduct, interpretation, writing, or publication. Without a "smoking gun" it is difficult to prove otherwise.

Author Audio Interview

Related article

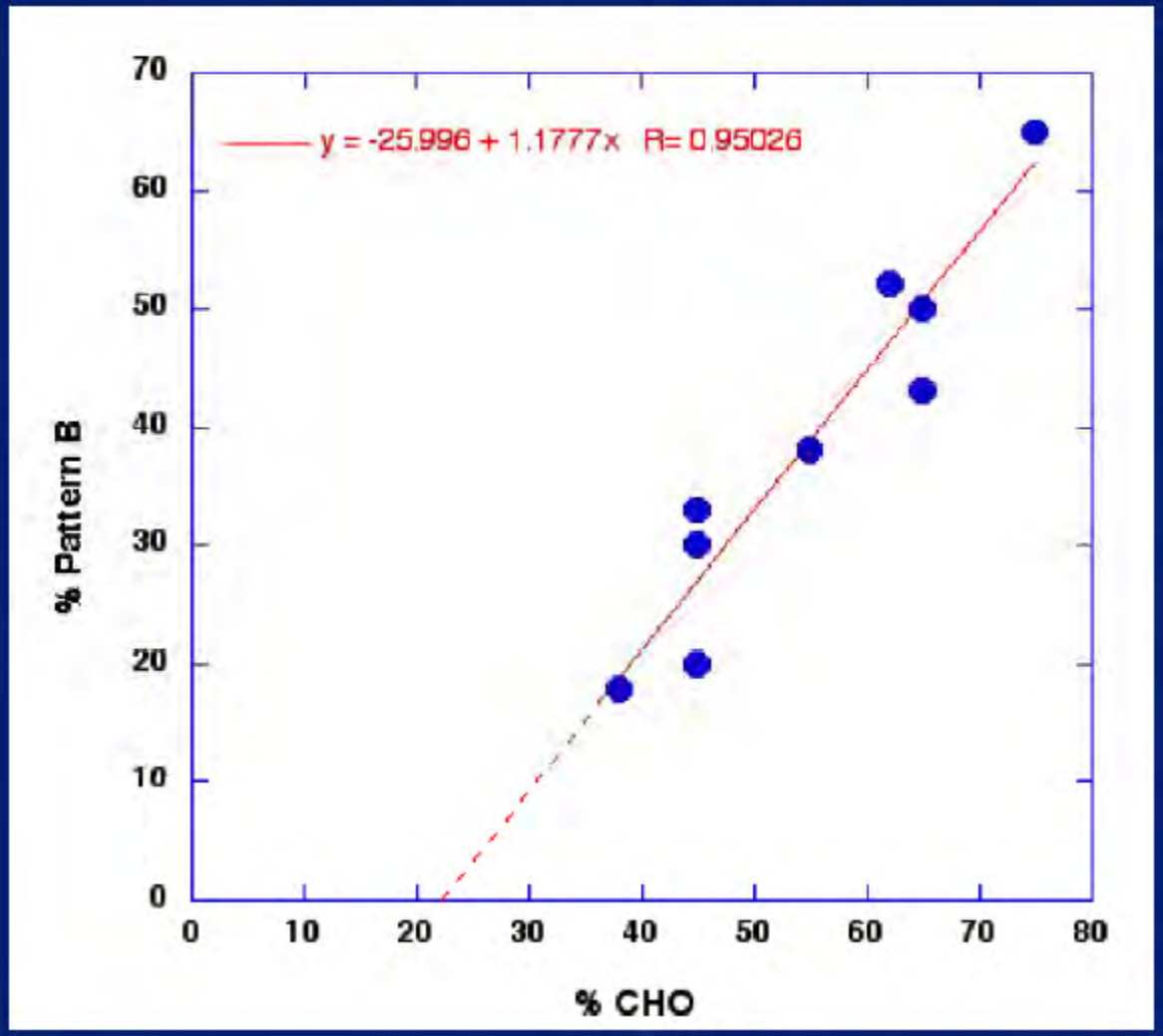
In this issue of *JAMA Internal Medicine*, Kearns and colleagues[3] report on having found a smoking gun. From a deep dive into archival documents from the 1950s and 1960s, they have produced compelling evidence that a sugar trade association not only paid for but also initiated and influenced research expressly to exonerate sugar as a major risk factor for coronary heart disease (CHD). Although studies at that time indicated a relationship between high-sugar diets and CHD risk, the sugar association preferred scientists and policymakers to focus on the role of dietary fat and cholesterol. The association paid the equivalent of more than $48 000 in today's dollars to 2 nutrition professors, at Harvard no less, to

Figure. Close Epidemiological Correlations Between Sugar and Saturated Fat "Consumption" and Mortality in 14 Countries



Adapted from the article by McGandy et al[4] and used with permission. Courtesy of Domingo Piñero, PhD.

LDL particle size is responsive to dietary CHO



Krauss, J Nutr 131:340S, 2001

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Dietary Sugars Intake and Cardiovascular Health: A Scientific Statement From the American Heart Association

Rachel K. Johnson, Lawrence J. Appel, Michael Brands, Barbara V. Howard, Michael Lefevre, Robert H. Lustig, Frank Sacks, Lyn M. Steffen, Judith Wylie-Rosett and on behalf of the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention

Circulation 2009;120:1011-1020; originally published online Aug 24, 2009;

"There's no question that sedentary lifestyles have caused the obesity crisis to get out of control."

- Indra Nooyi, CEO PepsiCo

"active balanced lifestyle" Coca-Cola

"balanced active lifestyle"

"a balanced and healthy lifestyle" General Mills

"a balanced lifestyle" PEPSICO

"a balanced diet and lifestyle" Unilever

"a well-balanced lifestyle" MARS incorporated

"a balanced lifestyle" Nestlé


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runjumpthrow
HERSHEY / Athletics Canada

Français

Athletics Canada Announces Expansion of Run Jump Throw Program through Partnership with The Hershey Company

Athletics Canada announced today a new five-year partnership with The Hershey Company that aims to get children excited about physical activity

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FOR CLINICIANS
FOR EMPLOYERS
Heart Conditions
Drugs & Treatments
Heart Basics
Healthy Living
Connect With Others
News & Events
My Dashboard
News & Events
Coca-Cola Family Field Day
Members of the CardioSmart team will be in Atlanta on Aug. 17 to help promote an active lifestyle and provide tips on heart health.
Aug 17, 2013, 8:00 AM - 1:00 PM
The World Of Coca-Cola at Pemberton Place 121 Baker St NW Atlanta, GA 30313
Coca-Cola family field day
CardioSmart is participating in Coca-Cola Family Field Day, which looks to inspire families and teens to rediscover the joy of being active to create long-term healthy habits. The day is filled with fun, light-hearted competition where teams of four complete six field day events striving for the best overall time to win an exciting grand prize. Events will be slightly challenging while also being humorous (there's a tricycle race!) Other activities during the field day include:
* Health & Wellness Expo where attendees can pick up heart healthy information and great CardioSmart giveaways
* Kids Zone
* Coca-Cola Open Happiness Truck
* Coca-Cola Recycling Truck
For more information and to register for the event, visit Coca-Cola's Family Field Day page.
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Join CardioSmart Now
Earn CardioSmart Points
10 Points Per Day
Track Your Activity
Earn CardioSmart Points for logging your daily activity
Calculate Your Heart Disease Risk
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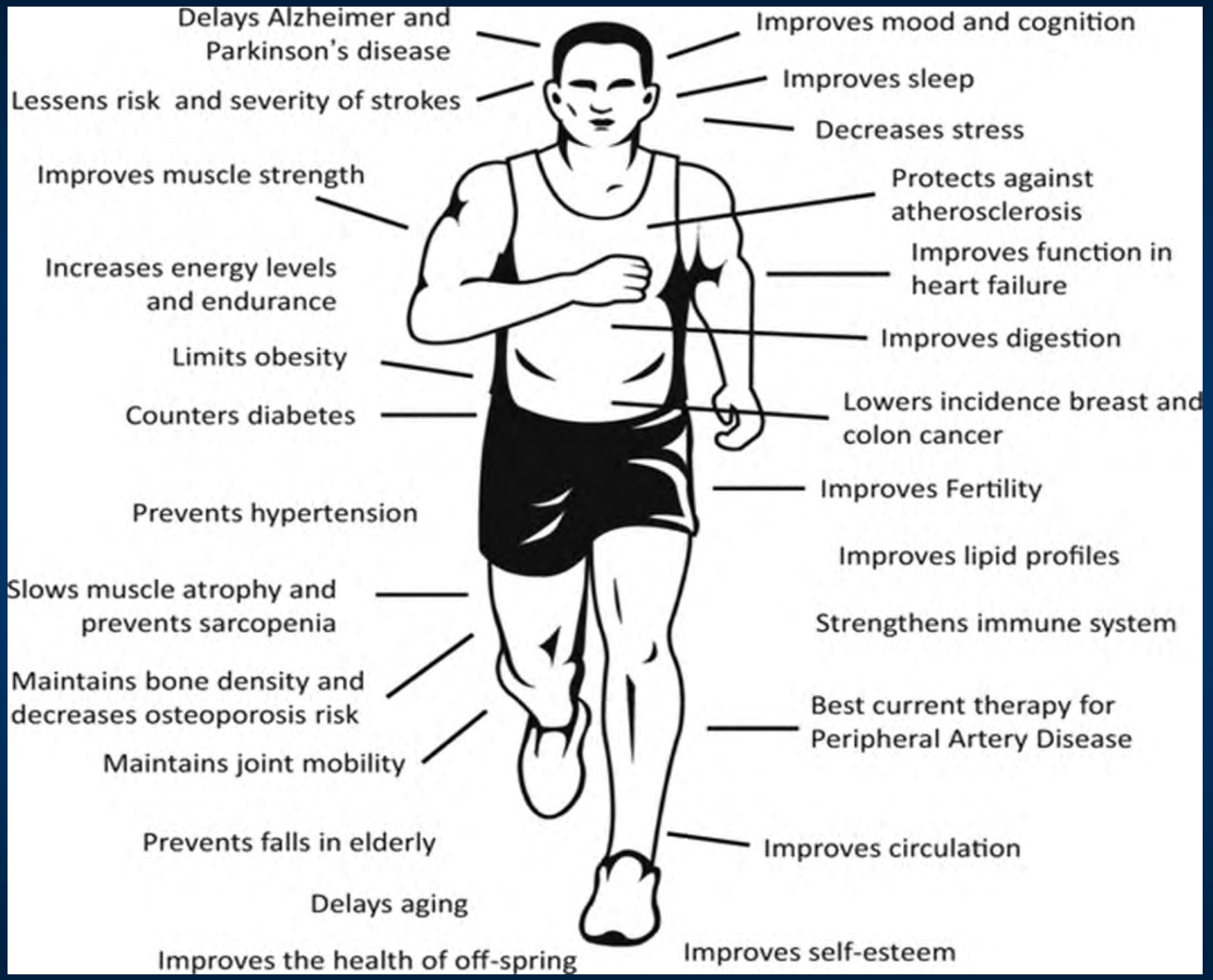

Rowe G et al. Circulation 2014;129:798-810

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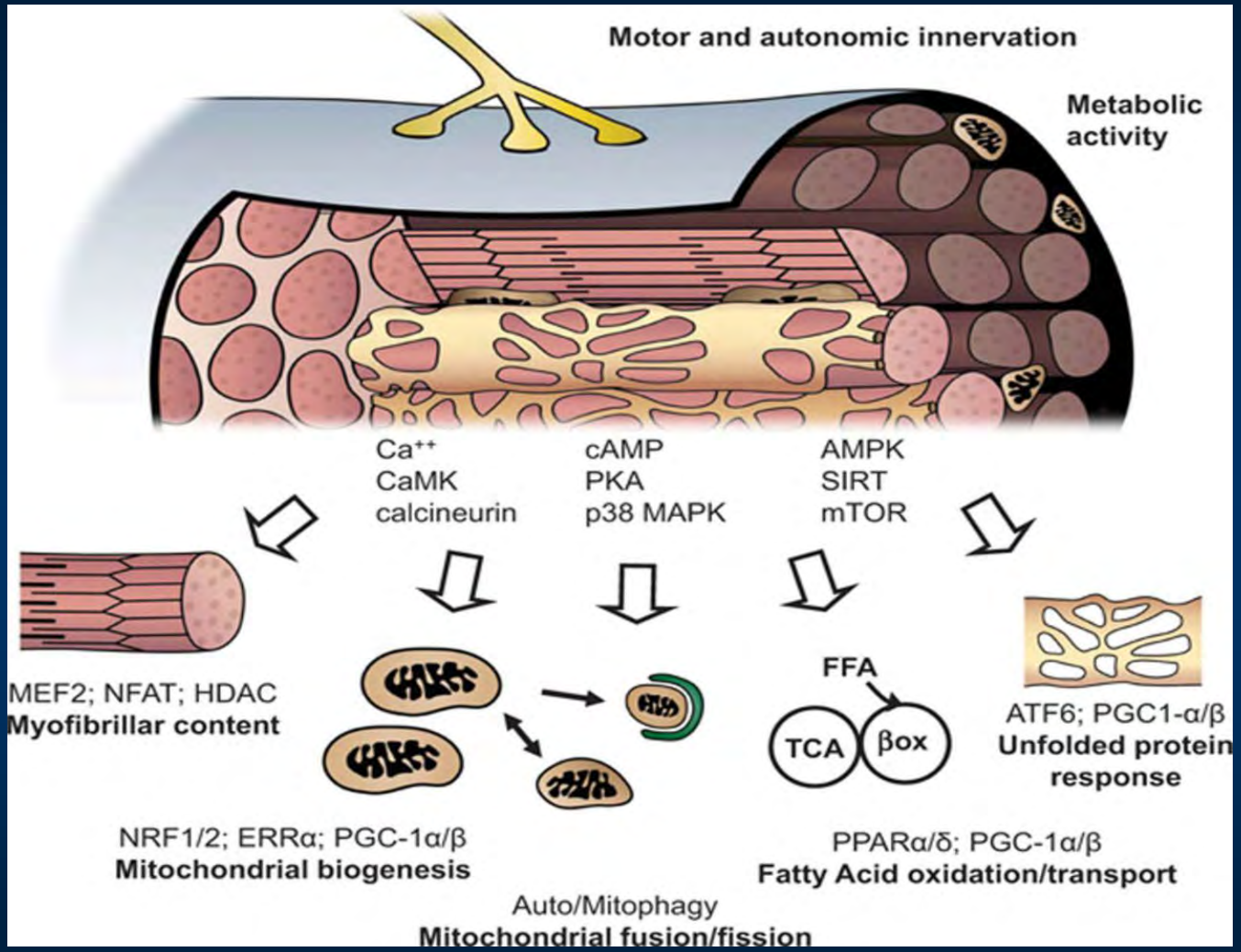
Modular signaling pathways that underpin muscular adaptations to endurance exercise.



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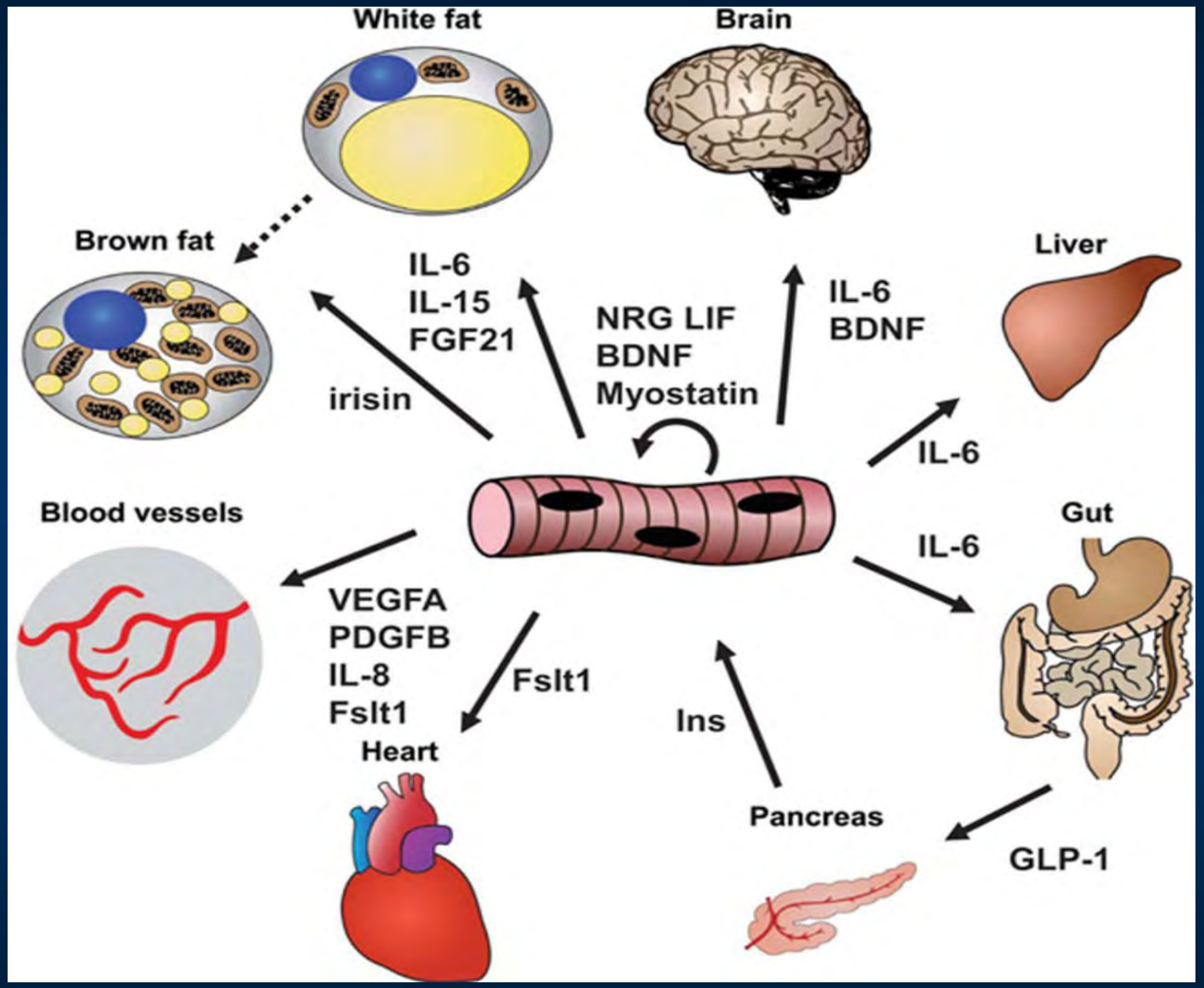
Muscle as an endocrine organ.



Rowe G et al. Circulation 2014;129:798-810

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Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

The effect of physical activity or exercise on key biomarkers in atherosclerosis — A systematic review

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ABSTRACT

Objective: This systematic review aimed to summarize published papers on the effect of physical activity (PA)/exercise on key atherosclerotic factors in patients with risk factors for or established cardiovascular disease (CVD).

Methods: Studies involving PA and cytokines, chemokines, adhesion molecules, CRP and angiogenic factors were searched for in Medline and Cochrane library. Original human studies of more than 2 weeks of PA intervention were included. Study quality was assessed according to the GRADE system of evidence.

Results: Twenty-eight papers fulfilled the inclusion criteria. PA decreases the cytokines, tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and interferon-γ IFN-γ (high, moderate and low evidence, respectively). The effect of PA on chemokines; stromal derived factor-1 (SDF-1), interleukin-8 (IL-8) (insufficient evidence) and monocyte chemoattractant protein-1 (MCP-1) (low evidence) was inconclusive. Aerobic exercise decreased the adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (moderate and high evidence, respectively), while effects of PA on E- and P-selectin were inconclusive. PA decreases C-reactive protein (CRP) (high evidence). The angiogenic actors, endothelial progenitor cells (EPCs) are increased (high evidence) and VEGF is decreased (moderate evidence) by PA. The effect of PA on these factors seems to depend on the type and duration of exercise intervention and patient factors, such as presence of ischemia.

Conclusion: As presented in this review, there is a high level of evidence that physical activity positively affects key players in atherosclerosis development. These effects could partly explain the scientifically proven anti-atherogenic effects of PA, and do have important clinical implications.

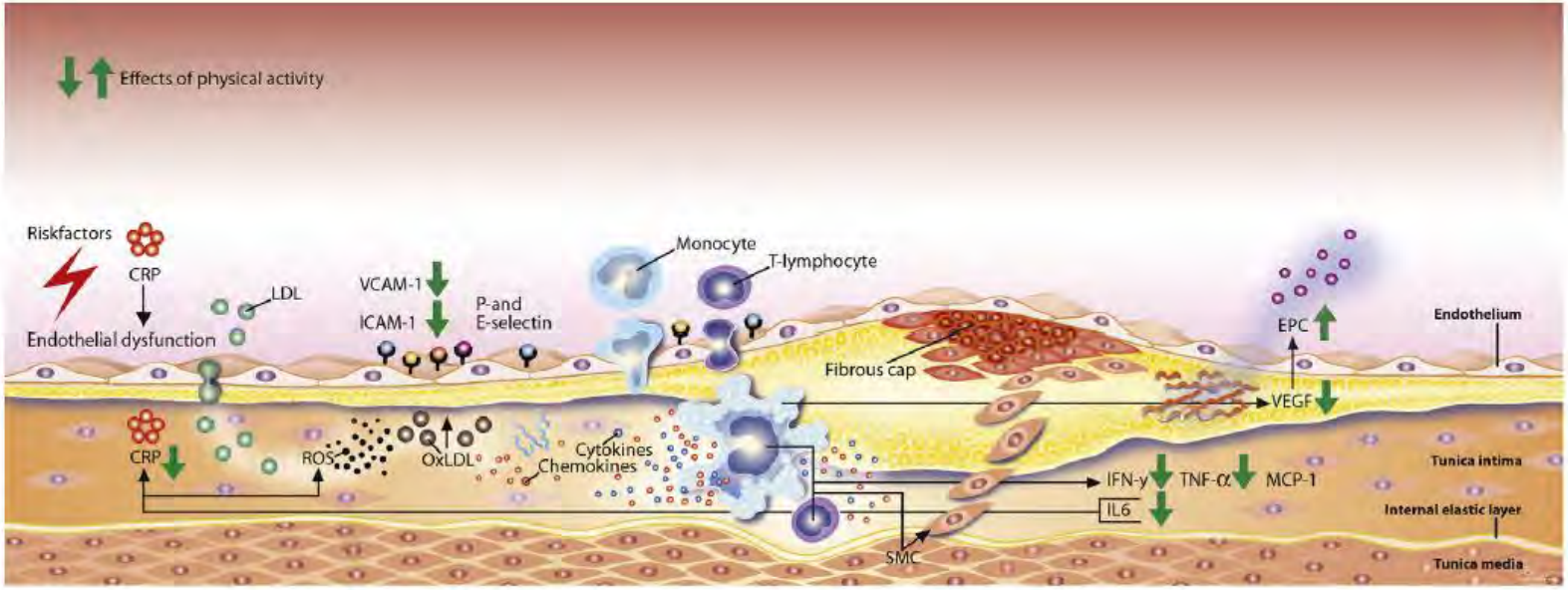

Fig. 2. An overview over the effect of physical activity/exercise on key factors in the atherosclerotic process. The green arrows show the effect of physical activity/exercise (CRP = C-reactive protein, LDL = low density lipoprotein, OxLDL = oxidized LDL, ROS = reactive oxygen species, VCAM-1 = vascular cell adhesion molecule-1, ICAM-1 = intracellular adhesion molecule-1, MCP-1 = monocyte chemoattractant protein-1, IFN-γ = interferon-γ, TNF-α = tumor necrosis factor-α, IL-6 = interleukin-6, EPC = endothelial progenitor cell, VEGF = vascular endothelial growth factor).

Figure II

Relation « quantité-bénéfices » illustrant le lien entre la dépense hebdomadaire d'énergie et les bénéfices attendus pour la santé chez les personnes sédentaires

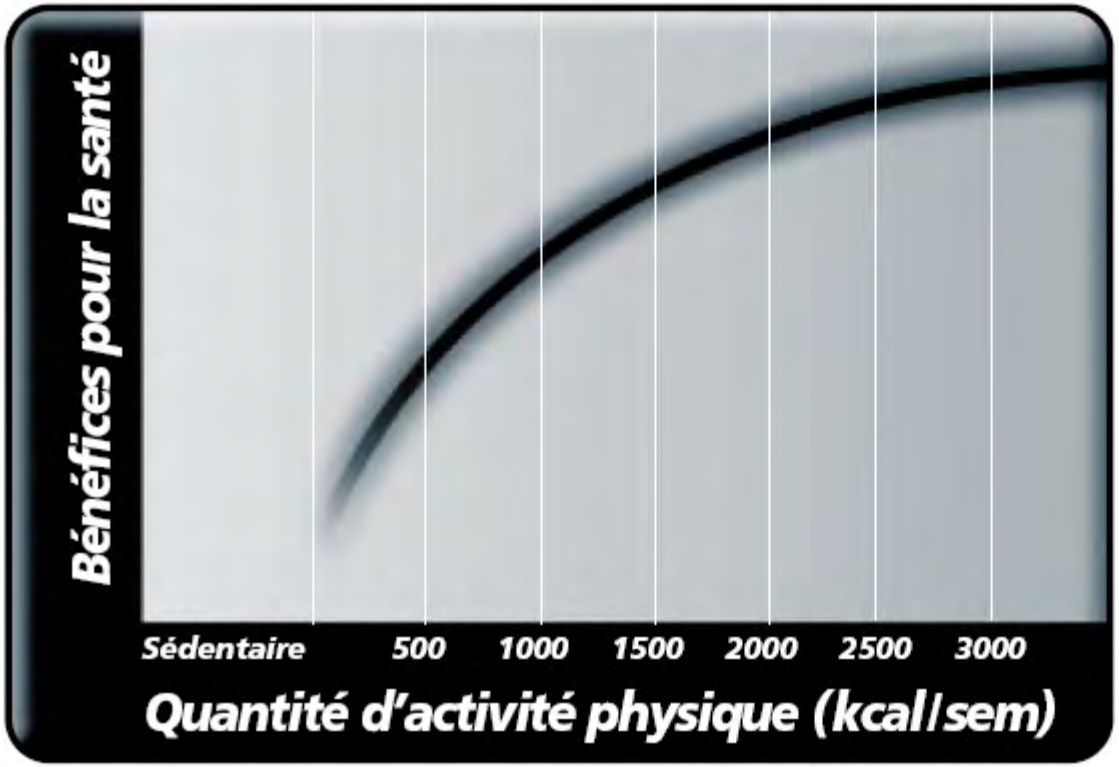

Tableau 3

Durée et fréquence nécessaires pour une activité physique de différentes intensités afin de dépenser environ 1000 kcal par semaine

Intensité (catégorie)[1]	Fréquence (nombre de fois par semaine)	Durée (min)	kcal/séance
Faible	7	60	150
	4	90 à 120	250
Modérée	7	30	150
	4	45	250
Élevée	7	20	150
	4	30	250

1. L'intensité faible correspond à une dépense énergétique inférieure à 4 kcal·min^{-1}, l'intensité modérée, à une dépense énergétique variant entre 4 et 8 kcal·min^{-1} et l'intensité élevée, à une dépense énergétique supérieure à 8 kcal·min^{-1}.

Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi Pang Wen, Jackson Pui Man Wai*, Min Kuang Tsai, Yi Chen Yang, Ting Yuan David Cheng, Meng-Chih Lee, Hui Ting Chan, Chwen Keng Tsao, Shan Pou Tsai, Xifeng Wu*

Summary

Background The health benefits of leisure-time physical activity are well known, but whether less exercise than the recommended 150 min a week can have life expectancy benefits is unclear. We assessed the health benefits of a range of volumes of physical activity in a Taiwanese population.

Methods In this prospective cohort study, 416 175 individuals (199 265 men and 216 910 women) participated in a standard medical screening programme in Taiwan between 1996 and 2008, with an average follow-up of 8·05 years

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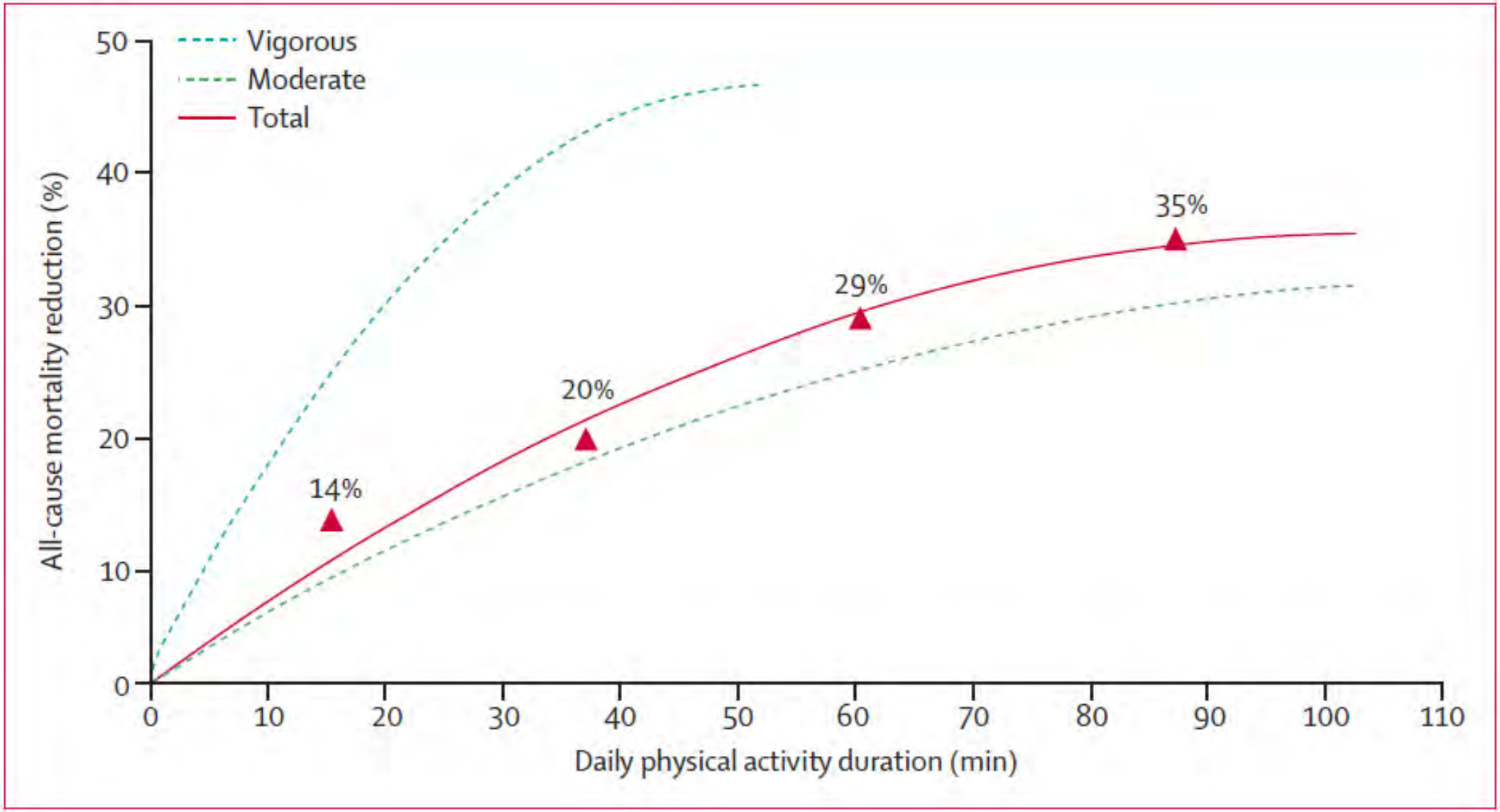
See Online/Comment DOI:10.1016/S0140-6736(11)61029-5


Vigorous
Moderate
Total
All-cause mortality reduction (%)
50
40
30
20
10
0
14%
20%
29%
35%
0
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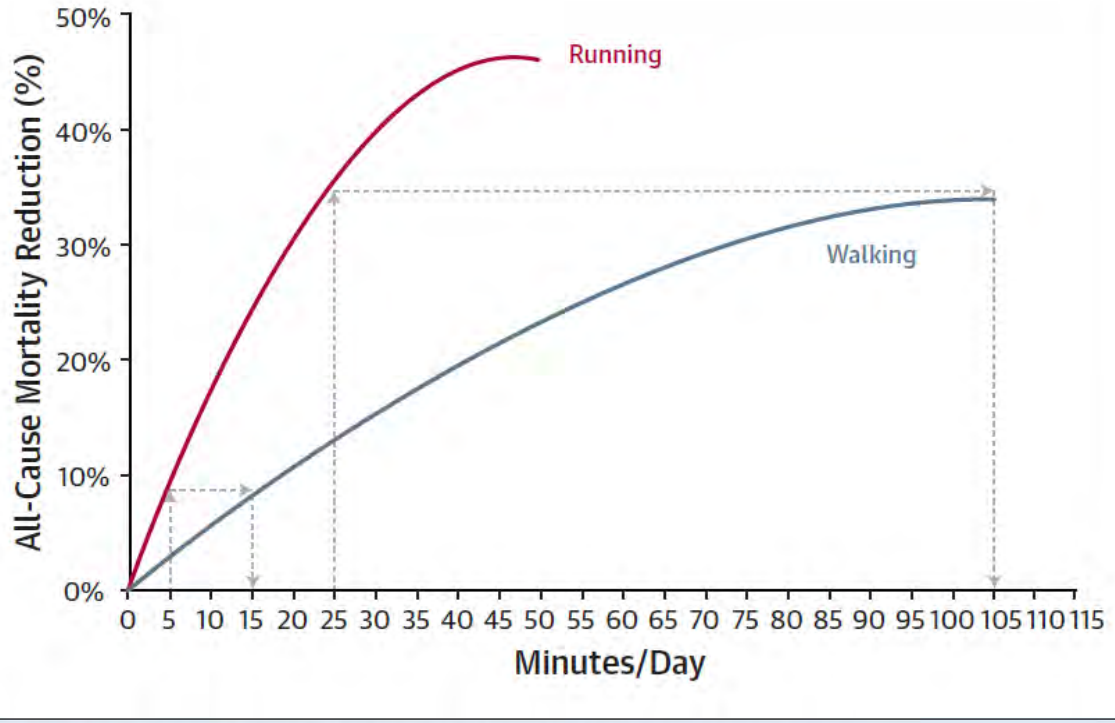

FIGURE 1 Comparison of Benefits Between Walking and Running

A 5-min run generates the same benefits as a 15-min walk, and a 25-min run is equivalent to a 105-min walk.

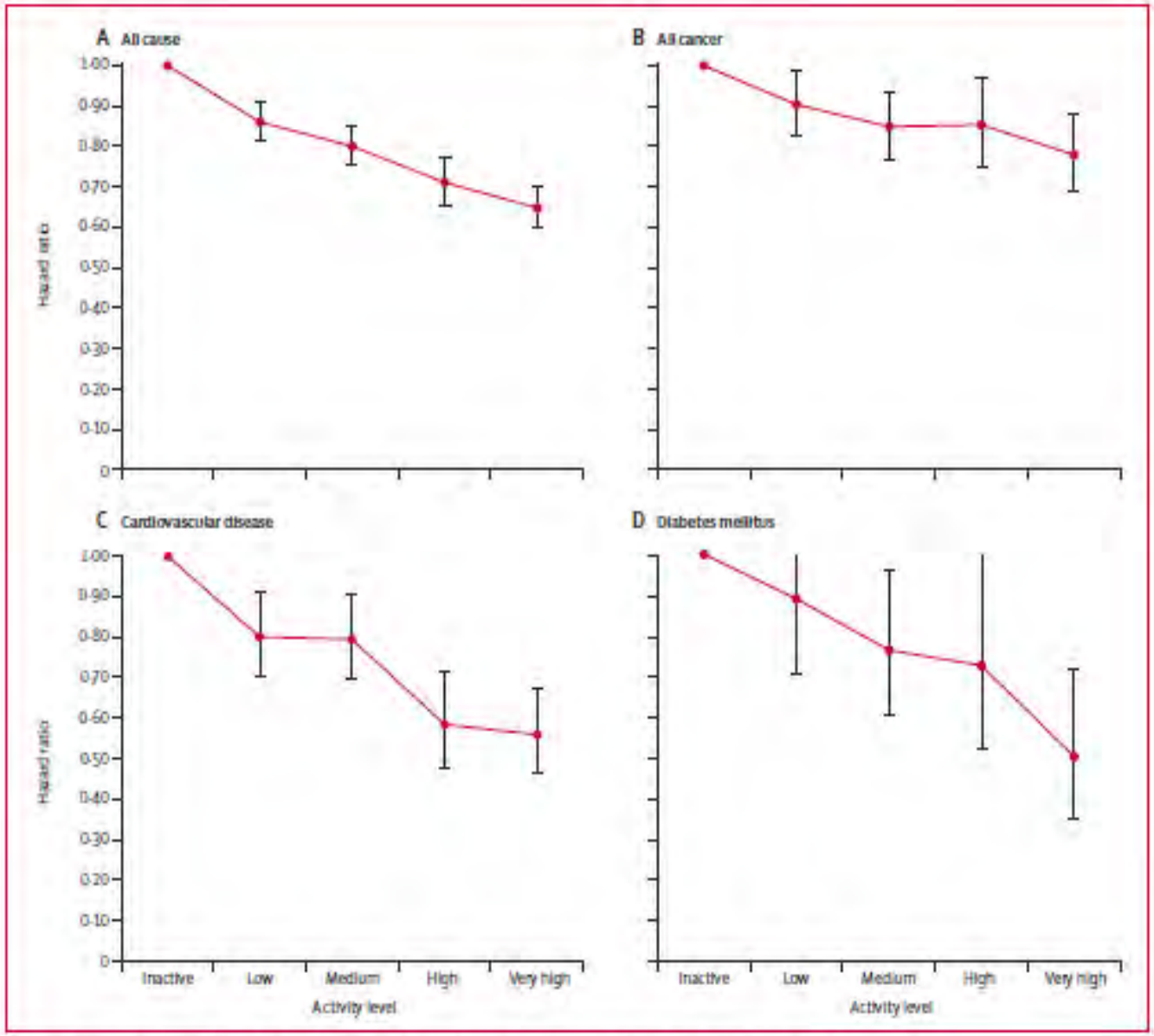

Figure 1: Relation between physical activity volume and mortality reduction compared with individuals in the inactive group
Bars show 95% CIs.

*Anil Nigam, Martin Juneau
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Survival benefit associated with low-level physical activity

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In *The Lancet*, Chi Pang Wen and colleagues[1] report their findings from a very large observational study, showing that a small amount of leisure-time physical activity reduces total mortality, mortality from cardiovascular disease, and mortality from cancer. Although the ability of physical activity in moderate amounts to reduce mortality from all causes has been well documented,[2–4] the public-health recommendation in most countries is to do the equivalent of at least 30 min per day of walking, most days of the week—ie, 150 min per week.[5,6] Wen and colleagues' study shows that half this amount of physical activity (15 min per day for 6 days a week) reduces all-cause mortality by 14%, cancer mortality by 10%, and mortality from cardiovascular disease by 20%. To our knowledge, this is the first observational study of this size to report important and global health benefits at such a low volume of leisure-time physical activity with this degree of precision. The benefits of physical activity follow a dose-response curve (figure), which clearly shows that although a little amount of physical activity is good, more is better. In an ideal world, people would benefit greatly from 300 min of moderate-intensity physical activity per week, but data from most countries show that this amount of physical activity is achieved by only a small proportion of the population.[5,7] The reason for this reality is multifactorial and complex, and individual, psychosocial, and environmental factors all play a part.[8] Repeated, simple advice from a physician—as Wen and colleagues suggest—is one of many interventions that can effectively contribute to increased physical activity.[9] We agree that this advice is very simple and probably easily achievable.

Because of its observational nature, Wen and colleagues' study cannot establish causality, but their results are entirely consistent with the findings of prospective randomised trials in secondary cardiovascular prevention that show a clear mortality benefit from regular exercise.[10–13] As such, the direct health benefits of exercise are irrefutable. Exercise can reduce cardiovascular mortality and, in particular, coronary mortality by many mechanisms, including improvements in endothelial function, autonomic tone, inflammation, and risk-factor control. The final common pathways of cardiovascular risk reduction presumably operate through both improved endothelial function and improved autonomic regulation of cardiovascular function.[13] Improved endothelial function leads to the prevention and stabilisation of coronary atherosclerosis, thereby reducing the risk of acute coronary syndromes. Improved autonomic function leads to a reduced risk of sudden cardiac death. Cancer, like coronary heart disease, is also to an extent preventable and shares several common risk factors such as poor nutrition, obesity, inflammation, and physical inactivity. Therefore, improvements in some of these risk factors with regular exercise could plausibly explain the cancer mortality benefits recorded by Wen and colleagues. The oncoprotective effects of exercise are certainly an expanding topic of research in cancer.[13]

Finally, noteworthy from a public health perspective, 54% of individuals in the Taiwanese cohort studied were inactive, with another 22% doing low levels of leisure-time physical activity only. Rural-to-urban migration across the Asia-Pacific region through rapid economic growth and industrialisation during the past few decades could explain these low levels of physical activity and the concomitant epidemics of obesity and diabetes that are being witnessed.[14] The knowledge that as little as 15 min per day of exercise on most days of the week can substantially reduce an individual's risk of dying could encourage many more individuals to incorporate a small amount of physical activity into their busy lives. Governments and health professionals both have major roles to play to spread this good news story and convince people of the importance of being at least minimally active.

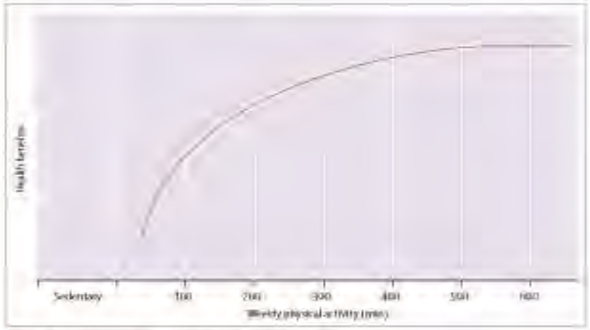

Figure: Relation between health benefits and physical activity

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The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study

Scott A Lear, Weihong Hu, Sumathy Rangarajan, Danijela Gasevic, Darryl Leong, Romaina Iqbal, Amparo Casanova, Sumathi Swaminathan, RM Anjana, Rajesh Kumar, Annika Rosengren, Li Wei, Wang Yang, Wang Chuangshi, Liu Huaxing, Sanjeev Nair, Rafael Diaz, Harry Swidon, Rajeev Gupta, Noushin Mohammadifard, Patricio Lopez-Jaramillo, Aytekin Oguz, Katarzyna Zatonska, Pamela Seron, Alvaro Avezum, Paul Poirier, Koon Teo, Salim Yusuf

Summary

Background Physical activity has a protective effect against cardiovascular disease (CVD) in high-income countries, where physical activity is mainly recreational, but it is not known if this is also observed in lower-income countries, where physical activity is mainly non-recreational. We examined whether different amounts and types of physical activity are associated with lower mortality and CVD in countries at different economic levels.

Methods In this prospective cohort study, we recruited participants from 17 countries (Canada, Sweden, United Arab Emirates, Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa, China, Colombia, Iran, Bangladesh, India, Pakistan, and Zimbabwe). Within each country, urban and rural areas in and around selected cities and towns were identified to reflect the geographical diversity. Within these communities, we invited individuals aged between 35 and 70 years who intended to live at their current address for at least another 4 years. Total physical activity was assessed using the International Physical Activity Questionnaire (IPQA). Participants with pre-existing CVD were excluded from the analyses. Mortality and CVD were recorded during a mean of 6·9 years of follow-up. Primary clinical outcomes during follow-up were mortality plus major CVD (CVD mortality, incident myocardial infarction, stroke, or heart failure), either as a composite or separately. The effects of physical activity on mortality and CVD were adjusted for sociodemographic factors and other risk factors taking into account household, community, and country clustering.

Findings Between Jan 1, 2003, and Dec 31, 2010, 168916 participants were enrolled, of whom 141945 completed the IPAQ. Analyses were limited to the 130 843 participants without pre-existing CVD. Compared with low physical activity (<600 metabolic equivalents [MET]× minutes per week or <150 minutes per week of moderate intensity physical activity), moderate (600–3000 MET× minutes or 150–750 minutes per week) and high physical activity (>3000 MET× minutes or >750 minutes per week) were associated with graded reduction in mortality (hazard ratio 0·80, 95% CI 0·74–0·87 and 0·65, 0·60–0·71; p<0·0001 for trend), and major CVD (0·86, 0·78–0·93; p<0·001 for trend). Higher physical activity was associated with lower risk of CVD and mortality in high-income, middle-income, and low-income countries. The adjusted population attributable fraction for not meeting the physical activity guidelines was 8·0% for mortality and 4·6% for major CVD, and for not meeting high physical activity was 13·0% for mortality and 9·5% for major CVD. Both recreational and non-recreational physical activity were associated with benefits.

Interpretation Higher recreational and non-recreational physical activity was associated with a lower risk of mortality and CVD events in individuals from low-income, middle-income, and high-income countries. Increasing physical activity is a simple, widely applicable, low cost global strategy that could reduce deaths and CVD in middle age.

Funding Population Health Research Institute, the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, Ontario SPOR Support Unit, Ontario Ministry of Health and Long-Term Care, AstraZeneca, Sanofi-Aventis, Boehringer Ingelheim, Servier, GSK, Novartis, King Pharma, and national and local organisations in participating countries that are listed at the end of the Article.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide[1] and a major economic global burden.[2] Despite reductions in CVD mortality in high-income countries, global CVD mortality increased by 41% between 1990 and 2013, largely driven by rises in low-income and lower-middle-income countries.[3] Indeed, 70% of global CVD deaths come from low-income and middle-income countries, where it is the commonest cause of death.[4,5] 23% of the world's population is estimated to be insufficiently active[6] and WHO has recommended a decrease in insufficient physical activity of 10% (of the aforementioned 23%) by 2020.[7]

Many studies from high-income countries have reported significant inverse associations of physical activity with mortality and CVD morbidity,[8] but such data from low-

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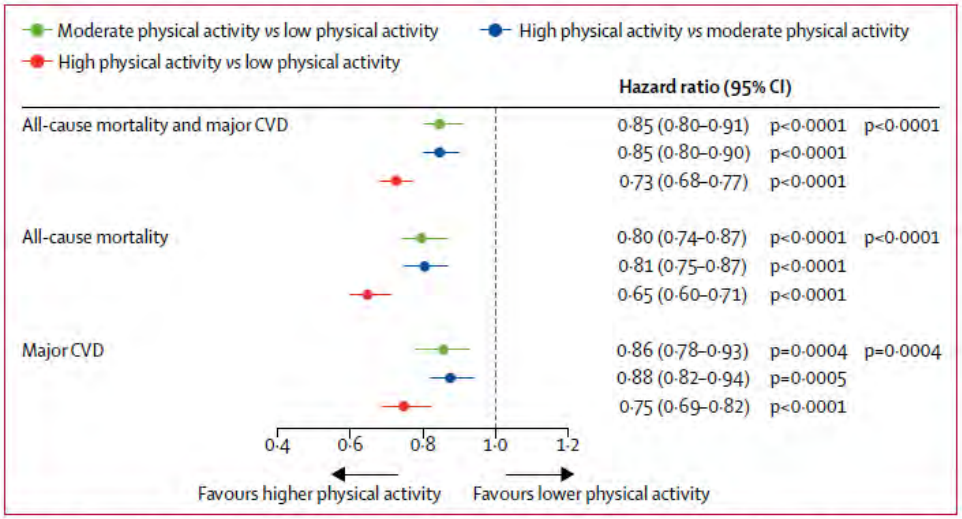

***Figure 1*: Hazard ratios and 95% CI for all-cause mortality and major CVD, all-cause mortality, or major CVD by level of physical activity**

Data adjusted for age, sex, education, country income level, urban or rural residency, family history of CVD, and smoking status; taking into account household, community, and country clustering. There were 3155 events for all-cause mortality and major CVD, 2041 events for all-cause mortality, and 1723 events for major CVD. The p values of the first column show the significance of each comparison. p values of the second column show the significance of the overall effect of physical activity. Low physical activity=<600 MET × min per week. Moderate physical activity=600–3000 MET × min per week. High physical activity=>3000 MET × min per week. CVD=cardiovascular disease. Major CVD=CVD mortality plus incident myocardial infarction, stroke, or heart failure. MET=metabolic equivalents.

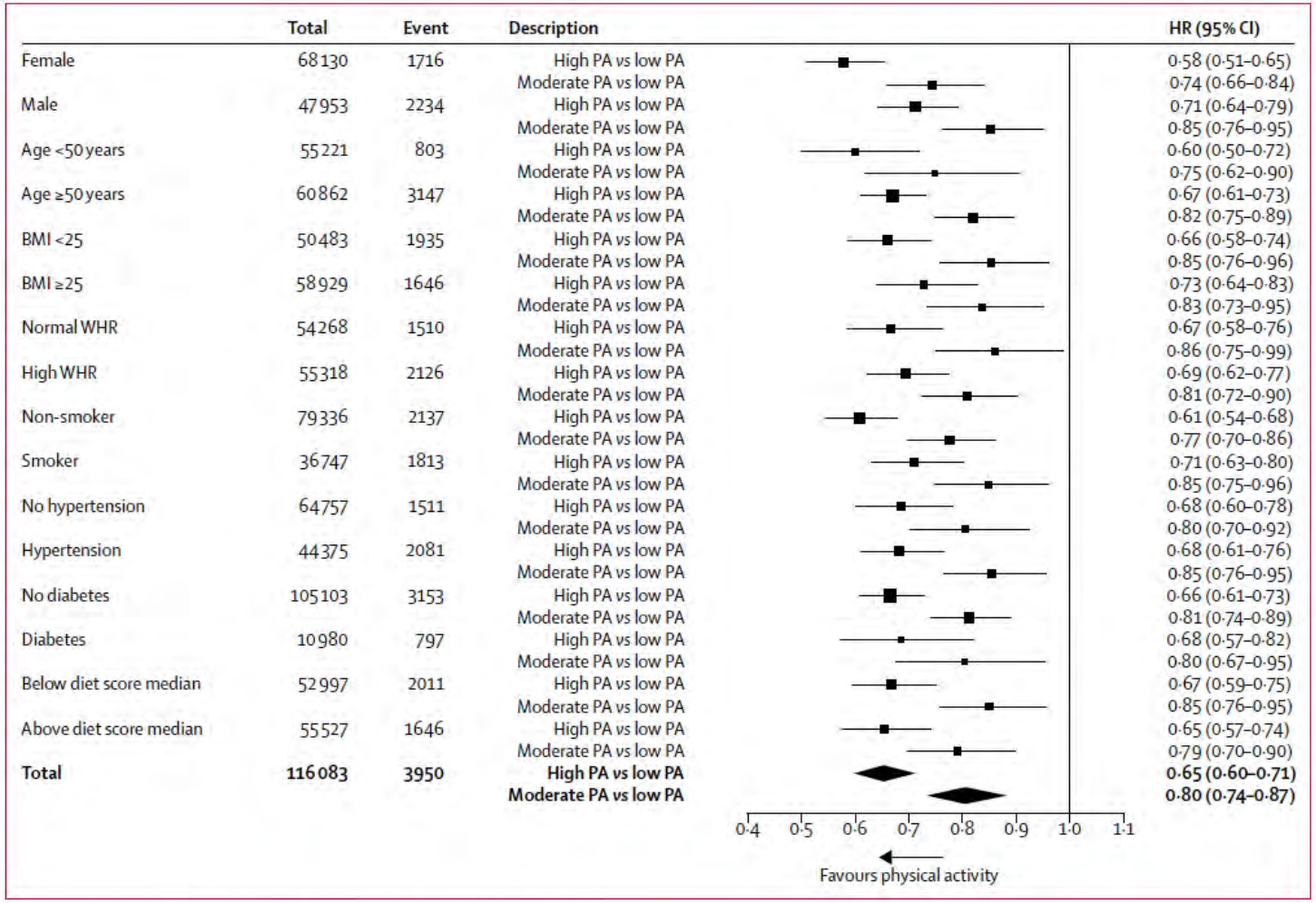

Figure 2: **Hazard ratios and 95% CI of total physical activity for mortality**

Adjusted for age, sex, education, country income level, urban or rural residency, family history of cardiovascular disease, and smoking status taking into account household, community, and country clustering. Based on data for 115 436 participants with complete data. Low physical activity (<600 MET × min per week) is the reference group. Moderate physical activity=600–3000 MET × min per week. High physical activity=>3000 MET × min per week. PA=physical activity. HR=hazard ratio. MET=metabolic equivalents. BMI=body-mass index. WHR=waist-to-hip ratio (high WHR was defined as above 0·85 for women and girls and above 0·9 for men and boys).

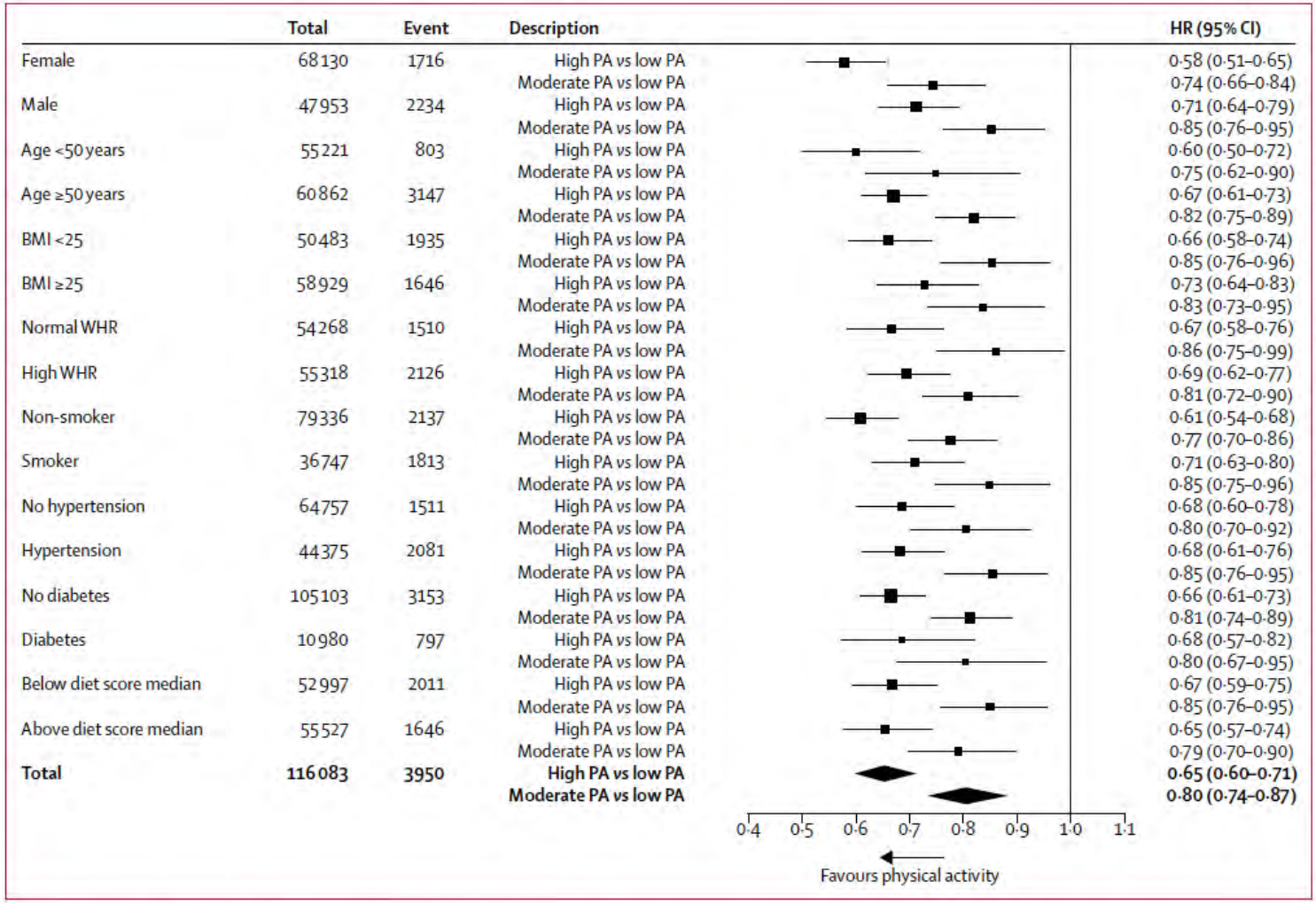

Figure 2: **Hazard ratios and 95% CI of total physical activity for mortality**

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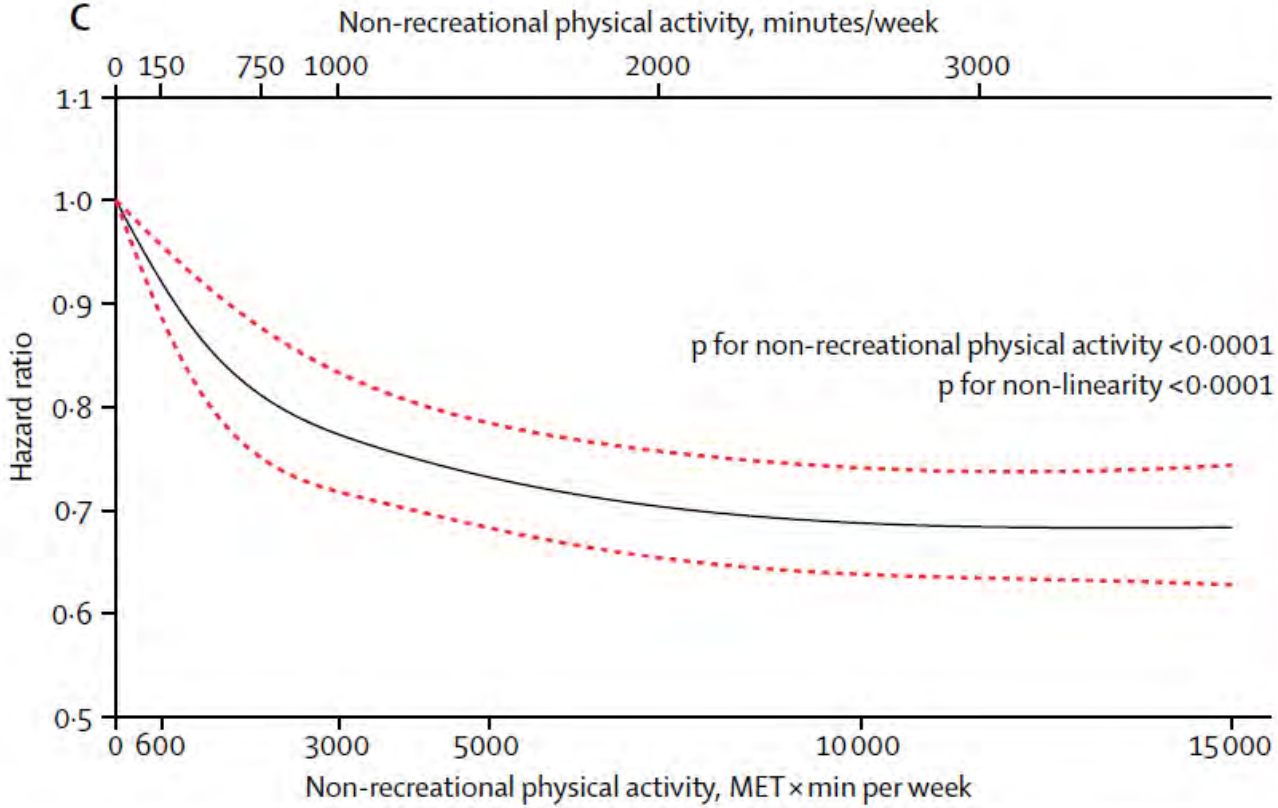
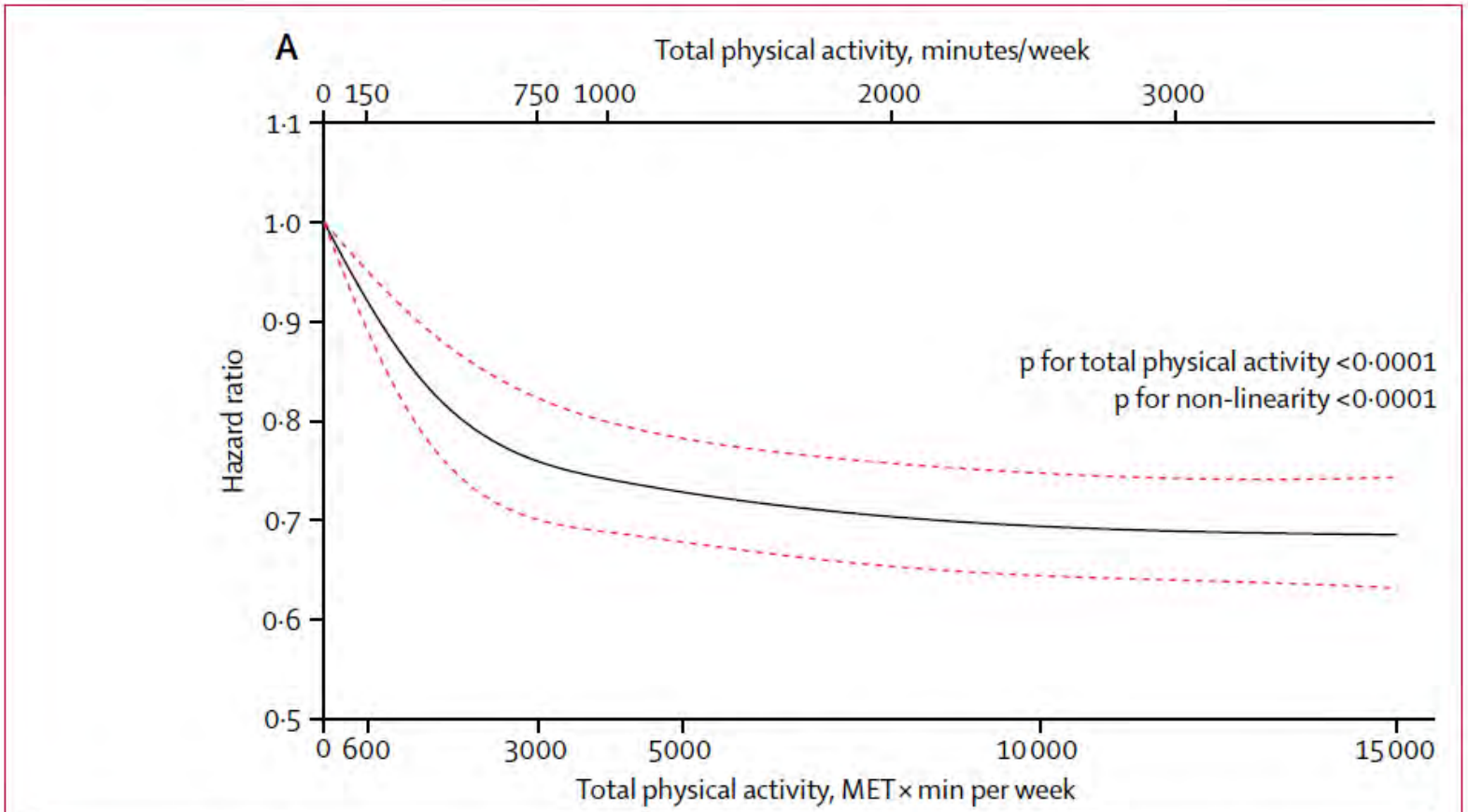
Recreational physical activity, MET × min per week

Interval (MET × min per week)	0–600	600–3000	>3000
Total	94893	24177	3597
Number of events	6647	1342	187

C



Interval (MET × min per week)	0–600	600–3000	3000–5000	5000–10000	10000–15000	>15000
Total	27968	47964	15571	17547	7597	6020
Number of events	2384	2964	873	1077	459	419



Interval (MET × min per week)	0–600	600–3000	3000–5000	5000–10 000	10 000–15 000	>15 000
Total	21 690	46 409	18 781	20 801	8566	6420
Number of events	1941	3007	1028	1247	507	446

The New England
Journal of Medicine

VOLUME 346 MARCH 14, 2002 NUMBER 11

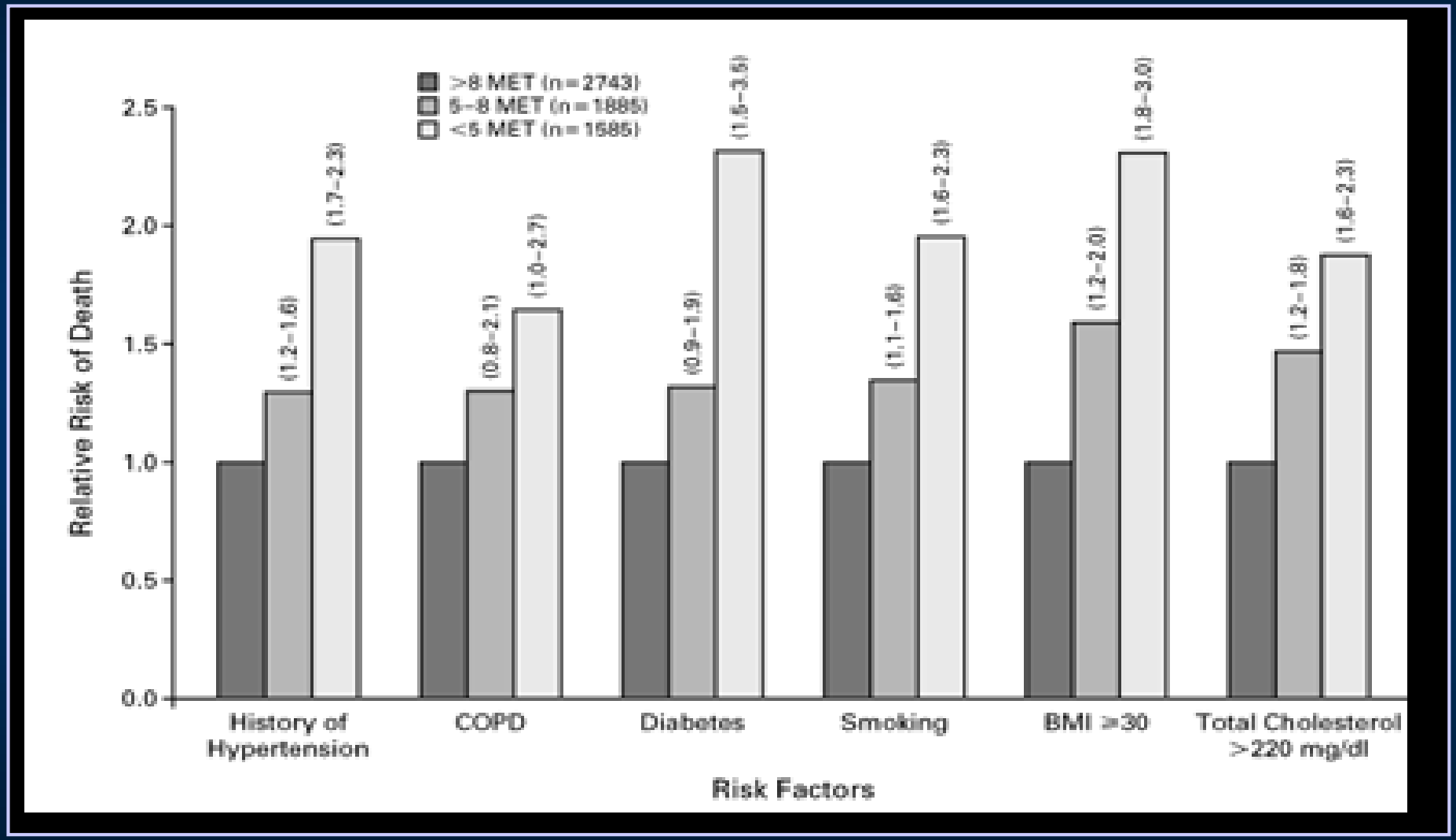
EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING

JONATHAN MYERS, PH.D., MANISH PRAKASH, M.D., VICTOR FROELICHER, M.D., DAT DO, M.D., SARA PARTINGTON, B.SC., AND J. EDWIN ATWOOD, M.D.

ABSTRACT

Background Exercise capacity is known to be an important prognostic factor in patients with cardiovascular disease, but it is uncertain whether it predicts mortality equally well among healthy persons. There is also uncertainty regarding the predictive power of

DURING the past two decades, exercise capacity and activity status have become well-established predictors of cardiovascular and overall mortality.[1,2] The fact that exercise capacity is a strong and independent predictor of outcomes supports the value of the exercise test as a clin-


≥8 MET (n = 2743)
5–8 MET (n = 1885)
<5 MET (n = 1585)
Relative Risk of Death
2.5
2.0
1.5
1.0
0.5
0.0
(1.2–1.6)
(1.7–2.3)
(0.8–2.1)
(1.0–2.7)
(0.9–1.9)
(1.5–3.5)
(1.1–1.6)
(1.6–2.3)
(1.2–2.0)
(1.8–3.0)
(1.2–1.8)
(1.6–2.3)
History of Hypertension
COPD
Diabetes
Smoking
BMI ≥30
Total Cholesterol >220 mg/dl
Risk Factors

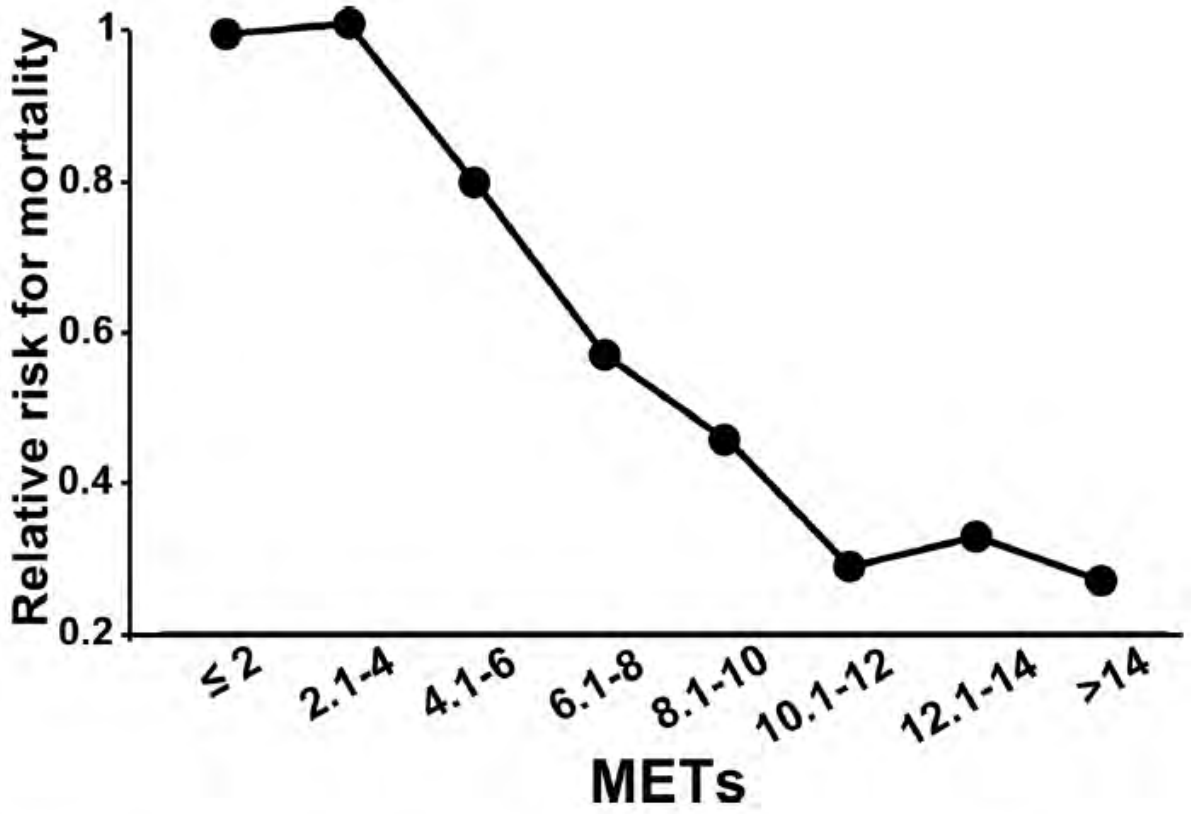
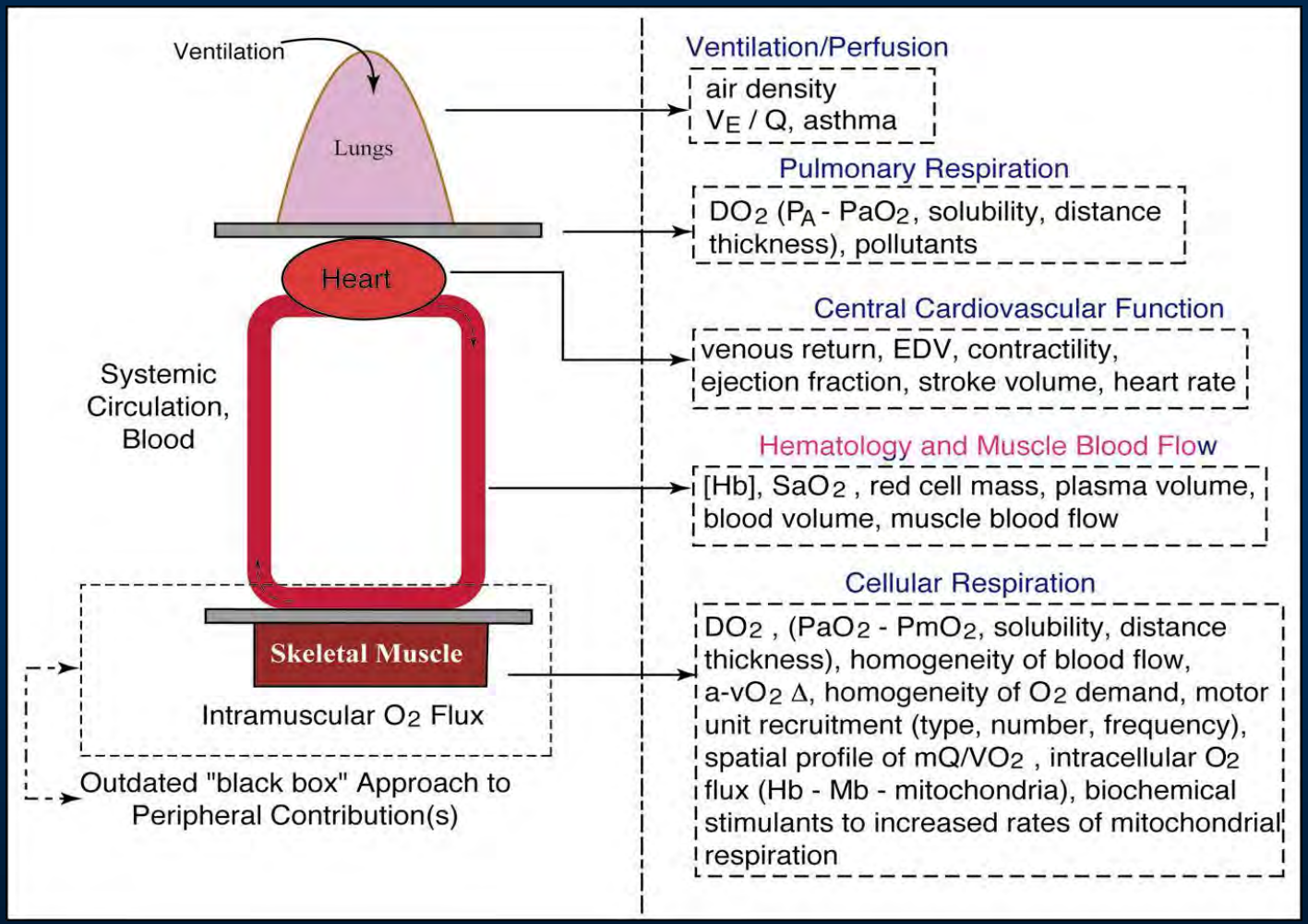


Figure 7 Mortality risk at different exercise capacities. Significant reductions in mortality do not occur less than 4 metabolic equivalents of resting metabolism (METs), become less at approximately 4 to 6 METs and an asymptote occurring at approximately 10 METs in 15,000 US veterans of wars. [Reproduced, with permission, from reference (277, 279)].

Limitations de la capacité maximale:



(Wasserman et al 2005, Robergs 2001, ATS/ACCP Statement CPET 2003)

Table 1 Estimated Historical Reductions in Daily Steps By Humans

Population year	Steps per day	References
Paleolithic (~20,000 BC)	~13,200-21,120 (men); ~10,560 (women)	(384)
Amish (2002)	18,425 (men); 14,196 (women)	(27)
Mean of 26 studies (1966-2007)	7473 (mainly women)	(63)
Colorado (2002)	6733 (men); 6384 (women)	(572)
US adults (2010)	5340 (men); 4912 (women)	(26)

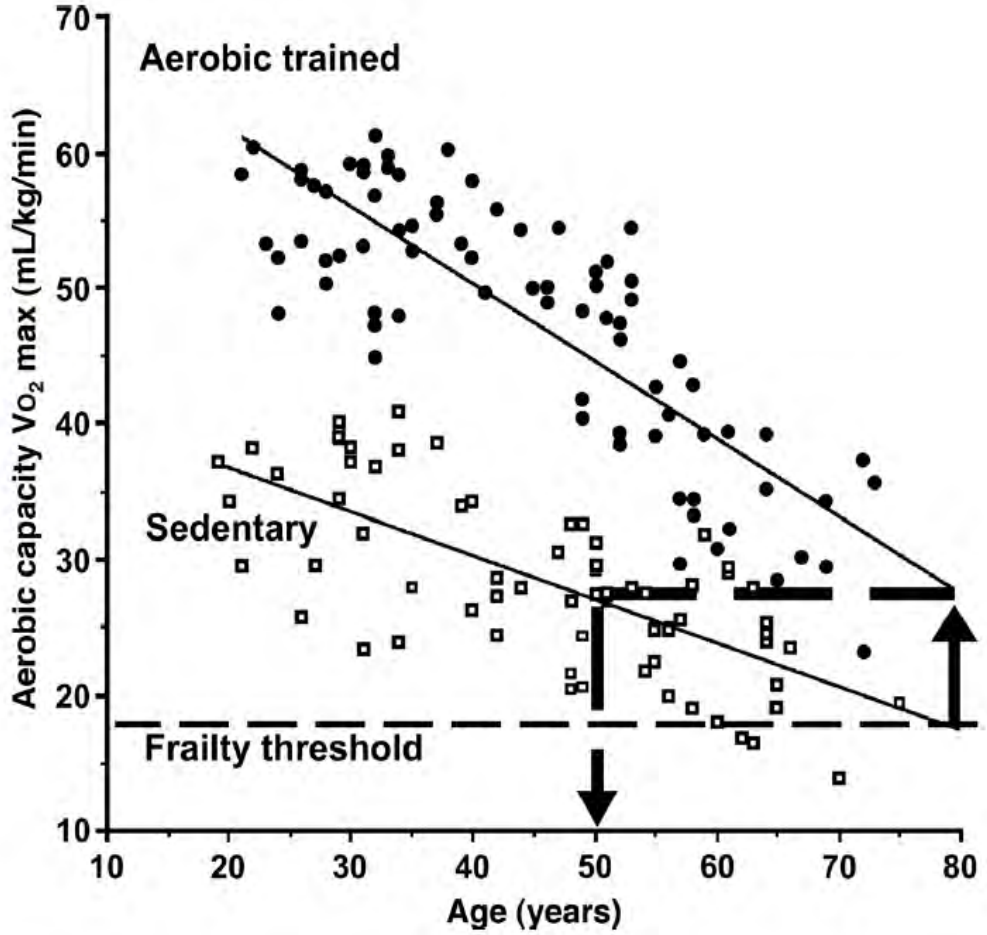


Figure 4 Best-fit linear lines are shown for aerobic capacities of two cross-sectional groups (aerobic trained and sedentary) as a function of their increasing chronological age. At the chronological age of 80 years, a horizontal line is extended from the endurance-trained line to the left where it intersects the sedentary line at age 50 years. Subjects were women who had been aerobically trained for at least 2 years with road-racing competition (closed circles) versus women who were sedentary (open squares) who performed no regular exercise and had body mass indexes (BMIs) more than 35 kg/m^2 (aerobic-trained

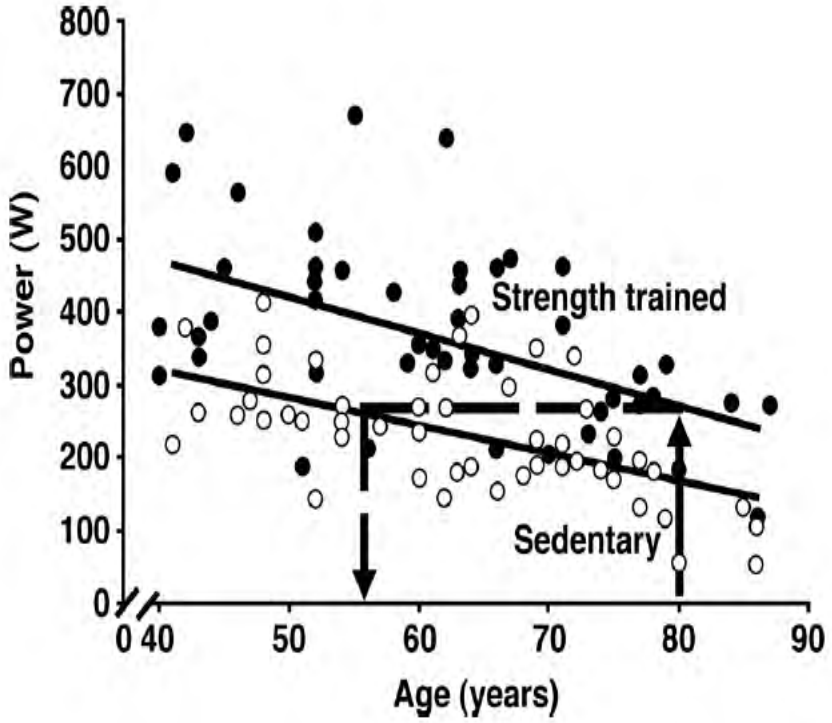


Figure 6 Best-fit linear lines are shown for power of two cross-sectional groups (strength trained and sedentary) as a function of their increasing chronological age. At the chronological age of 80 years, a horizontal line is extended from the power-trained line to the left where it intersects the sedentary line at age 56 years. The cross-sectional strength-trained subjects are shown in closed circles and sedentary in open circles. [Reproduced, with permission, from reference (401)].

Measuring and Monitoring Success in Compressing Morbidity

James F. Fries, MD

The Compression of Morbidity paradigm, introduced in 1980, maintains that if the average age at first infirmity, disability, or other morbidity is postponed and if this postponement is greater than increases in life expectancy, then cumulative lifetime morbidity will decrease—compressed between a later onset and the time of death. The National Long-Term Care Survey, the National Health Interview Survey, and other data now document declining disability trends beginning in 1982 and accelerating more recently. The decline is about 2% per year, contrasted with a decline in mortality rates of about 1% per year, thereby documenting compression of morbidity in the United States at the population level. Longitudinal studies now link good health risk status with long-term reductions in cumulative lifetime disability; persons with few behavioral health risks have only one-fourth the disability of those who have more risk factors, and the onset of disability is postponed from 7 to 12 years, far more than any increases in longevity in the groups. Randomized, controlled trials of health enhancement programs in elderly populations show reduction in health risks, improved health status, and decreased medical care utilization. Health policy initiatives now being undertaken have promise of increasing and consolidating health gains for the elderly.

Ann Intern Med. 2003;139:455-459. www.annals.org

For author affiliation, see end of text.

The Compression of Morbidity paradigm, which was presented as an hypothesis in 1980 (1), noted that most illness was chronic and occurred in later life and postulated that the lifetime burden of illness could be reduced if the onset of chronic illness could be postponed and if this postponement could be greater than increases in life expectancy. Figure 1 illustrates this concept. Estimated present lifetime morbidity is portrayed with three possible future scenarios: life extension, shift-to-the-right, and compression of morbidity. The lines represent the length of life, and the shaded triangles depict lifetime morbidity. Two arrows are shown for each scenario: The left arrow represents the median age at onset of chronic morbidity

been rising with the emergence of chronic illnesses, but it could be argued that this period was ending with declining incidences of major chronic illnesses, such as cardiovascular disease (1).

The Compression paradigm focuses attention on the quality of life over its quantity and considers morbidity as a lifetime cumulative area-under-the-curve concept rather than just a cross-sectional particular point of time, such as a specific age. It suggests that the national burden of illness may be reduced by postponing the onset of infirmity. Thus, the national illness burden that is increasing because of the growing number of elderly persons in the population may be offset, at least in part, by a lower average illness

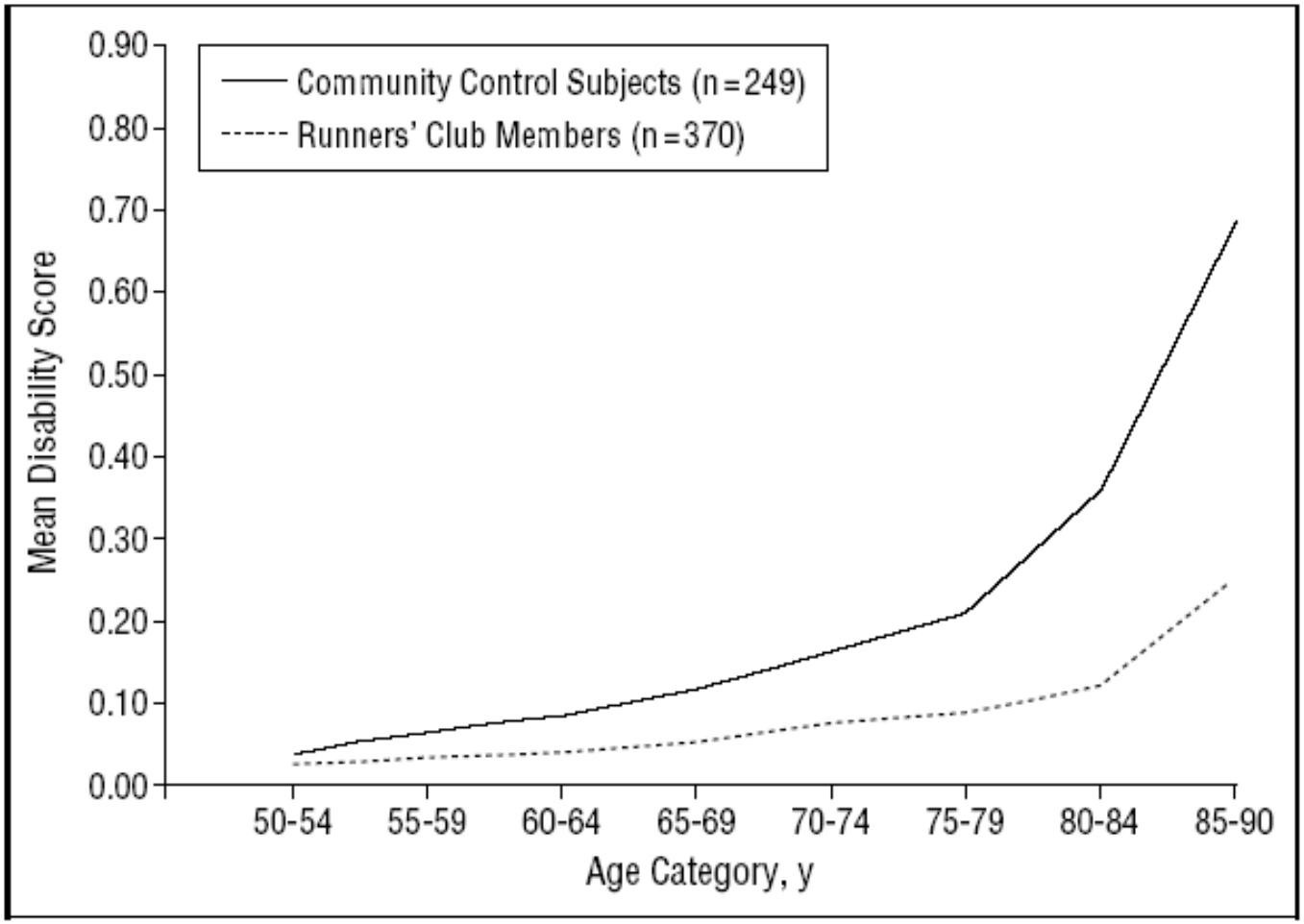


Figure 4. Mean disability scores by age category (at the 1997 questionnaire) and runner status. Subjects contributed one mean disability score to each age group when more than one score was available.

- En moyenne, les Canadiens ont regardé 28 heures de télévision par semaine, nombre plus élevé que la moyenne de 26,5 heures en 2009. Cette augmentation est attribuable à l'utilisation d'un nouvel outil de mesure, plus précis.

Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality

A Meta-analysis

Anders Grøntved, MPH, MSc
Frank B. Hu, MD, PhD

Context Prolonged television (TV) viewing is the most prevalent and pervasive sedentary behavior in industrialized countries and has been associated with morbidity and mortality. However, a systematic and quantitative assessment of published studies is not available.

Objective To perform a meta-analysis of all prospective cohort studies to determine the association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality.

Data Sources and Study Selection Relevant studies were identified by searches of the MEDLINE database from 1970 to March 2011 and the EMBASE database from 1974 to March 2011 without restrictions and by reviewing reference lists from retrieved articles. Cohort studies that reported relative risk estimates with 95% confidence intervals (CIs) for the associations of interest were included.

Data Extraction Data were extracted independently by each author and summary estimates of association were obtained using a random-effects model.

Data Synthesis Of the 8 studies included, 4 reported results on type 2 diabetes (175 938 individuals; 6428 incident cases during 1.1 million person-years of follow-up), 4 reported on fatal or nonfatal cardiovascular disease (34 253 individuals; 1052 incident cases), and 3 reported on all-cause mortality (26 509 individuals; 1879 deaths during 202 353 person-years of follow-up). The pooled relative risks per 2 hours of TV viewing per day were 1.20 (95% CI, 1.14-1.27) for type 2 diabetes, 1.15 (95% CI, 1.06-1.23) for fatal or nonfatal cardiovascular disease, and 1.13 (95% CI, 1.07-1.18) for all-cause mortality. While the associations between time spent viewing TV and risk of type 2 diabetes and cardiovascular disease were linear, the risk of all-cause mortality appeared to increase with TV viewing duration of greater than 3 hours per day. The estimated absolute risk differences per every 2 hours of TV viewing per day were 176 cases of type 2 diabetes per 100 000 individuals per year, 38 cases of fatal cardiovascular disease per 100 000 individuals per year, and 104 deaths for all-cause mortality per 100 000 individuals per year.

Conclusion Prolonged TV viewing was associated with increased risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.

JAMA. 2011;305(23):2448-2455 www.jama.com

TELEVISION (TV) VIEWING IS THE most commonly reported daily activity apart from working and sleeping in many populations around the world.[1-3] On average, 40% of daily free time is occupied by TV viewing within several European countries[1] and 30% in Australia.[2] This corresponds to a daily TV viewing time of about 3.3 to 4.0 hours. In the United States, the average number of daily hours of TV viewing has recently been reported to be 3 hours.[3]

Beyond altering energy expenditure by displacing time spent on physical activities, TV viewing is associated with unhealthy eating (eg, higher intake of fried foods, processed meat, and sugar-sweetened beverages and lower intake of fruits, vegetables, and whole grains) in both children and adults.[4-7] Furthermore, TV viewing may be associated with the intake of foods and beverages that are advertised on TV[4] and could attract some individuals to begin smoking.[4]

Physical inactivity, various dietary factors, and smoking are well-established independent risk factors of type 2 diabetes, cardiovascular disease, and all-cause mortality. Because

CME available online at www.jamaarchivescme.com and questions on p 2476.

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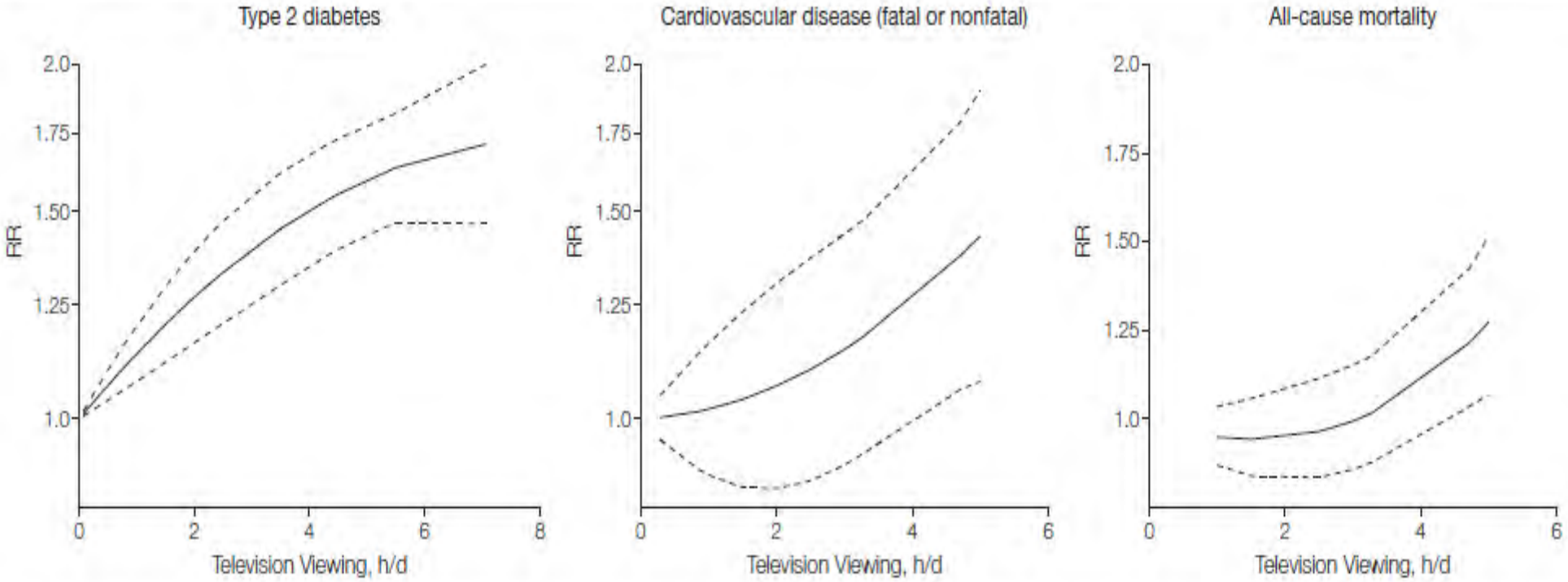
Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mdm603@northwestern.edu.

Figure 3. Dose-Response Relationship Between Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, All-Cause Mortality



Dotted lines represent the 95% confidence intervals for the fitted trend. The dose-response relationship plot between television (TV) viewing (hours per day) and risk of type 2 diabetes (4 studies), cardiovascular disease (4 studies), and all-cause mortality (3 studies) was estimated with random-effects meta-regression,[10] which allowed for a nonlinear response by including a quadratic term of TV viewing time. The test for a nonlinear relationship was only significant for all-cause mortality ($P = .007$). In subsequent piecewise regression, the best model fit was obtained at an inflection point of 3 hours of TV viewing per day ($P = .01$ for difference in slopes).

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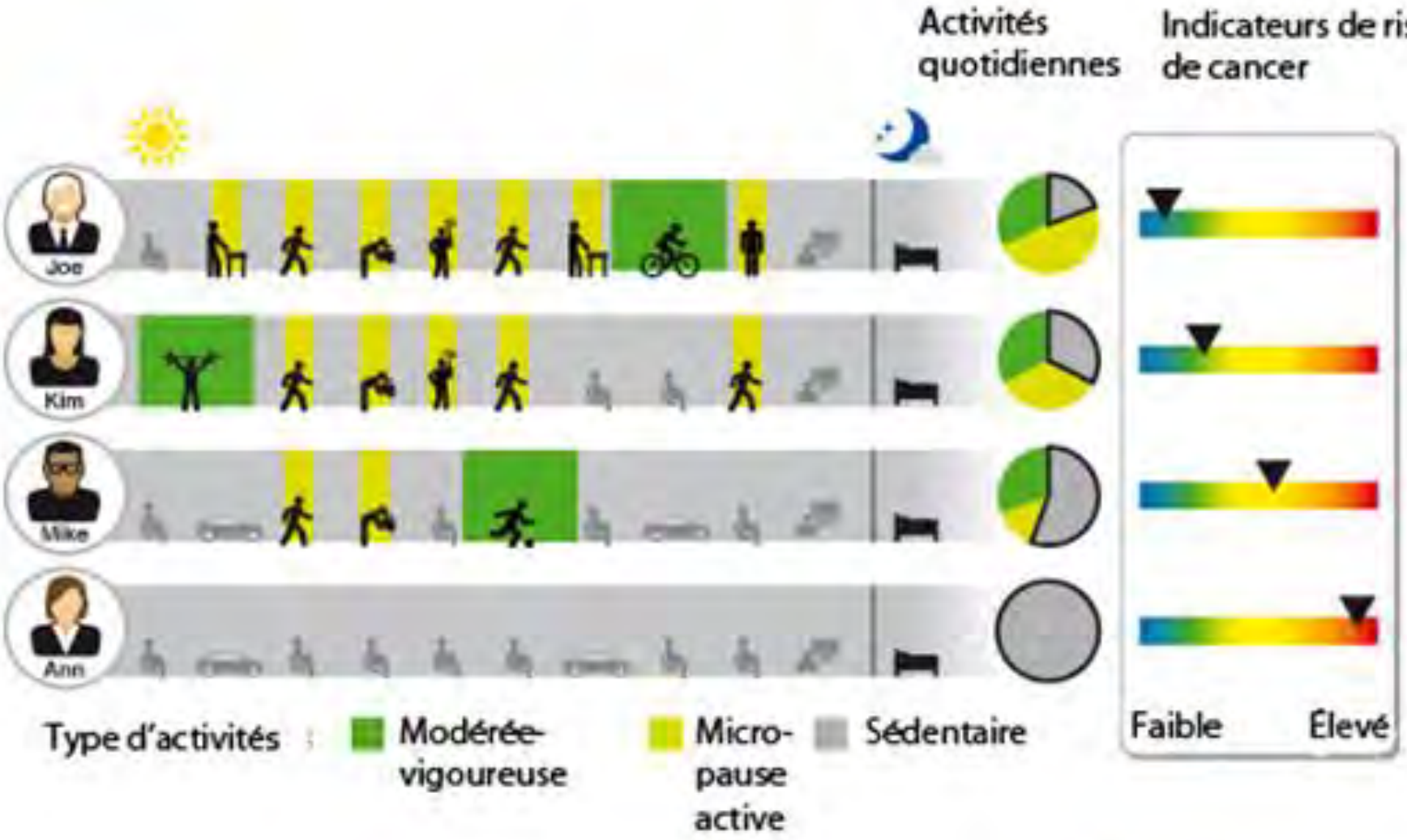
Relationship of Sedentary Behavior and Physical Activity to Incident Cardiovascular Disease

Results From the Women's Health Initiative

Andrea K. Chomistek, ScD,* JoAnn E. Manson, MD, DrPH,† Marcia L. Stefanick, PhD,‡
Bing Lu, MD, DrPH,† Megan Sands-Lincoln, PhD,§ Scott B. Going, PhD,‖ Lorena Garcia, PhD,¶
Matthew A. Allison, MD,# Stacy T. Sims, PhD,‡ Michael J. LaMonte, PhD,**
Karen C. Johnson, MD,†† Charles B. Eaton, MD‡‡§§

Boston, Massachusetts; Stanford, Davis, and San Diego California; Philadelphia, Pennsylvania; Tucson, Arizona; Buffalo, New York; Memphis, Tennessee; and Providence and Pawtucket, Rhode Island

Objectives The aim of this study was to examine the independent and joint associations of sitting time and physical activity with risk of incident cardiovascular disease (CVD).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Indicateurs de risque de cancer
Joe
Kim
Mike
Ann
Type d'activités :
Modérée-vigoureuse
Micro-pause active
Sédentaire
Faible
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AMERICAN INSTITUTE for CANCER RESEARCH

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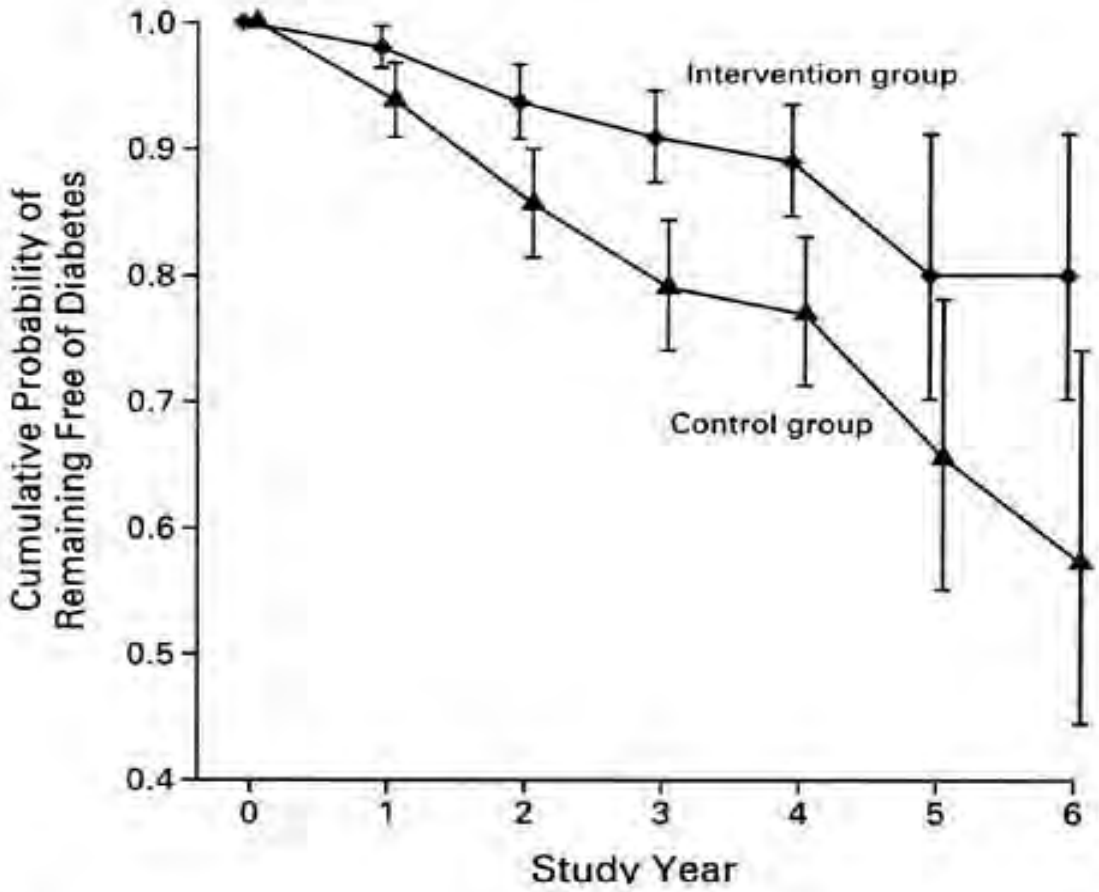
VOLUME 344 MAY 3, 2001 NUMBER 18

PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

Proportion of Subjects without Diabetes during the Trial.



Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Walking and Dementia in Physically Capable Elderly Men

Robert D. Abbott, PhD
Lon R. White, MD
G. Webster Ross, MD
Kamal H. Masaki, MD
J. David Curb, MD
Helen Petrovitch, MD

Context Evidence suggests that physical activity may be related to the clinical expression of dementia. Whether the association includes low-intensity activity such as walking is not known.

Objective To examine the association between walking and future risk of dementia in older men.

Design Prospective cohort study.

Setting and Participants Distance walked per day was assessed from 1991 to 1993 in 2257 physically capable men aged 71 to 93 years in the Honolulu-Asia Aging Study. Follow-up for incident dementia was based on neurological assessment at 2 repeat examinations (1994-1996 and 1997-1999).

Main Outcome Measures Overall dementia, Alzheimer disease, and vascular dementia.

Results During the course of follow-up, 158 cases of dementia were identified (15.6/1000 person-years). After adjusting for age, men who walked the least (<0.25 mile/d) experienced a 1.8-fold excess risk of dementia compared with those who walked more than 2 mile/d (17.8 vs 10.3/1000 person-years; relative hazard [RH], 1.77; 95% confidence interval [CI], 1.04-3.01). Compared with men who walked the most (>2 mile/d), an excess risk of dementia was also observed in those who walked 0.25 to 1 mile/d (17.6 vs 10.3/1000 person-years; RH, 1.71; 95% CI, 1.02-2.86). These associations persisted after accounting for other factors, including the possibility that limited amounts of walking could be the result of a decline in physical function due to preclinical dementia.

Conclusions Findings suggest that walking is associated with a reduced risk of dementia. Promoting active lifestyles in physically capable men could help late-life cognitive function.

JAMA. 2004;292:1447-1453 www.jama.com

PHYSICAL AND ENVIRONMENTAL factors associated with the risk of dementia remain largely undefined. Although equivocal, evidence suggests that physical activity may have a relationship with the clinical expression of dementia.[1-7] Whether the association includes low-intensity activity such as regular walking is not known. One study showed that a composite measure of physical activity, partially based on walking histories, is associated with a reduced risk of dementia.[1] In a large cohort of women, those who walked more had significantly smaller declines in a modified Mini-Mental State Examination score over a 6- to 8-year

ORIGINAL RESEARCH | Annals of Internal Medicine

The Association Between Midlife Cardiorespiratory Fitness Levels and Later-Life Dementia

A Cohort Study

Laura F. DeFina, MD; Benjamin L. Willis, MD, MPH; Nina B. Radford, MD; Ang Gao, MS; David Leonard, PhD; William L. Haskell, PhD; Myron F. Weiner, MD; and Jarett D. Berry, MD, MS

Table 2. Cox Proportional Hazards Model for Incident Alzheimer Disease and Related Types of Dementia

Effect, by Model Adjustment	Hazard Ratio (95% CI)	*P* Value
Adjustment 1 (n = 19 458)*		
Quintile 1 (reference)	1.00	–
Quintile 2	0.87 (0.75–1.01)	0.069
Quintile 3	0.78 (0.67–0.91)	0.001
Quintile 4	0.70 (0.60–0.81)	<0.001
Quintile 5	0.64 (0.54–0.76)	<0.001

Review

Neurophysiological and epigenetic effects of physical exercise on the aging process

Perla Kaliman[a,*], Marcelina Párrizas[a], Jaume F. Lalanza[b,c], Antoni Camins[d], Rosa Maria Escorihuela[c,*], Mercè Pallàs[d,*]

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Epigenetics

ABSTRACT

Aging is a gradual process during which molecular and cellular processes deteriorate progressively, often leading to such pathological conditions as vascular and metabolic disorders and cognitive decline. Although the mechanisms of aging are not yet fully understood, inflammation, oxidative damage, mitochondrial dysfunction, functional alterations in specific neuronal circuits and a restricted degree of apoptosis are involved. Physical exercise improves the efficiency of the capillary system and increases the oxygen supply to the brain, thus enhancing metabolic activity and oxygen intake in neurons, and increases neurotrophin levels and resistance to stress. Regular exercise and an active lifestyle during adulthood have been associated with reduced risk and protective effects for mild cognitive impairment and Alzheimer's disease. Similarly, studies in animal models show that physical activity has positive physiological and cognitive effects that correlate with changes in transcriptional profiles. According to numerous studies, epigenetic events that include changes in DNA methylation patterns, histone modification and alterations in microRNA profiles seem to be a signature of aging. Hence, insight into the epigenetic

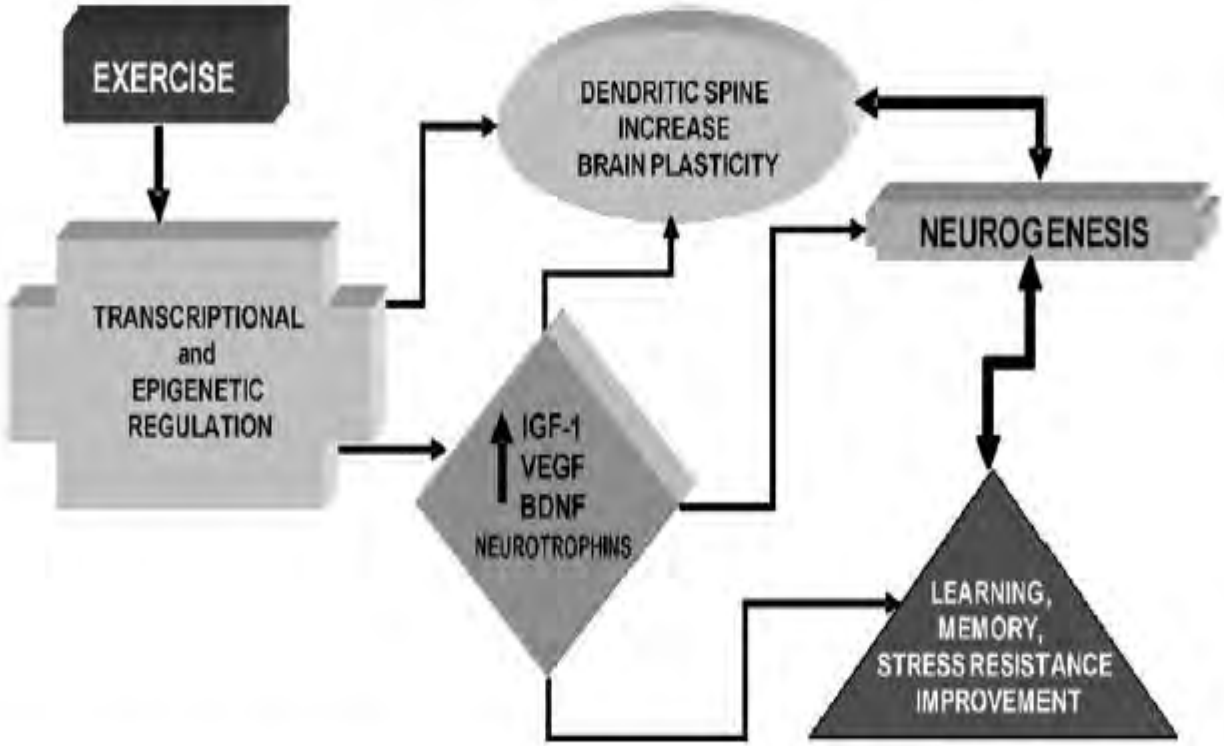


Fig. 1. A model for the effect of exercise on molecular, neuroplastic and cognitive parameters. Physical activity has positive neurophysiological effects mediated by changes in the transcriptional profiles of growth and neurotrophic factors such as VEGF, IGF-1 and BDNF that lead to improved efficiency of the capillary system and neuroplastic mechanisms in the brain. Although the precise molecular pathways that sustain these processes are unknown, recent data have described the epigenetic impact of physical exercise in peripheral tissues and in the brain. In mice such changes have been correlated with cognitive enhancement and increased stress resistance.

J Rehabil Med

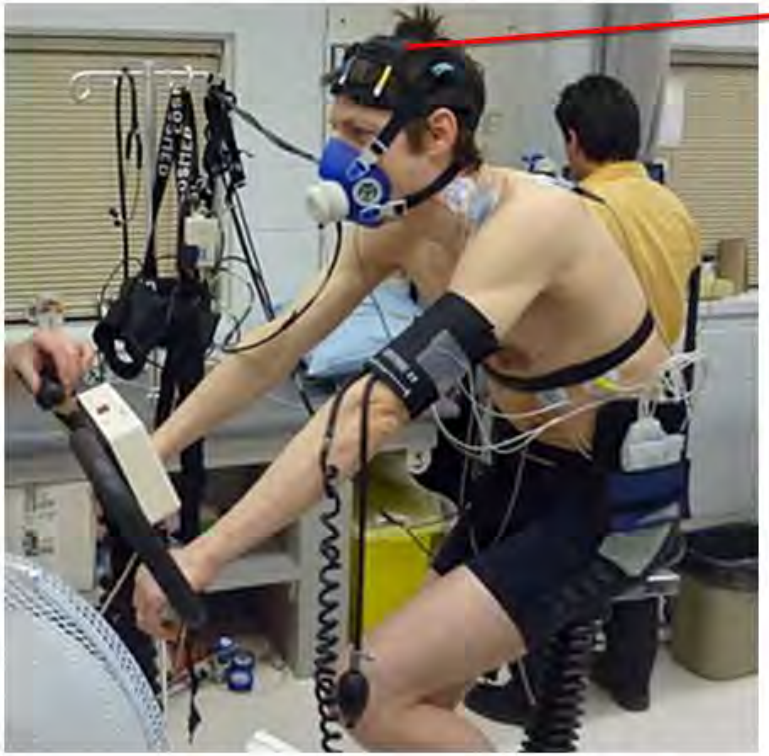
SHORT COMMUNICATION

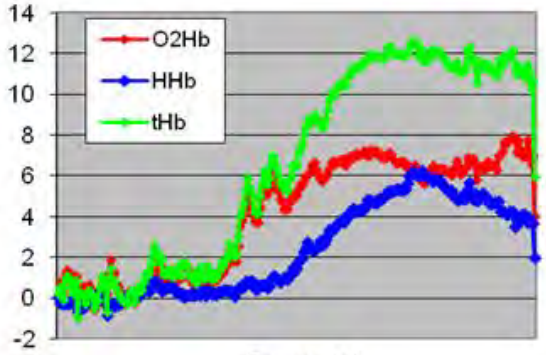
EFFECT OF INTERVAL TRAINING ON COGNITIVE FUNCTIONING AND CEREBRAL OXYGENATION IN OBESE PATIENTS: A PILOT STUDY

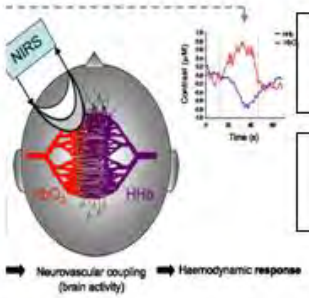
Joffrey Drigny, MSc[1], Vincent Gremeaux, MD, PhD[1–3,4], Olivier Dupuy, PhD[1,5–7], Mathieu Gayda, PhD[1–3], Louis Bherer, PhD[5,6], Martin Juneau, MD[1–3] and Anil Nigam, MD[1–3]

From the [1]Cardiovascular Prevention and Rehabilitation Centre (ÉPIC), [2]Research Center, Montreal Heart Institute and "Université de Montréal", [3]Department of Medicine, Faculty of Medicine, "Université de Montréal", Montreal, Canada, [4]Plateforme d'investigation technologique, INSERM CIC 1432, CHU Dijon, Dijon, France, [5]PERFORM Centre, Department of Psychology, Concordia University, Montréal, Québec and [6]Laboratoire LESCA, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal, Canada and [7]Faculté des Sciences du Sport, Laboratoire MOVE, Université de Poitiers, France

Epreuve d'effort triangulaire







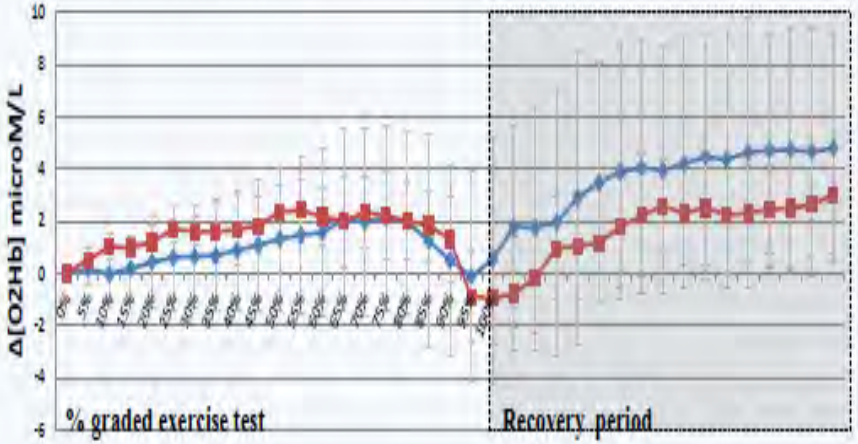
Activation :
↑ O2Hb et ↓ /stabilité HHb

Désactivation :
↓ O2Hb et ↑ HHb

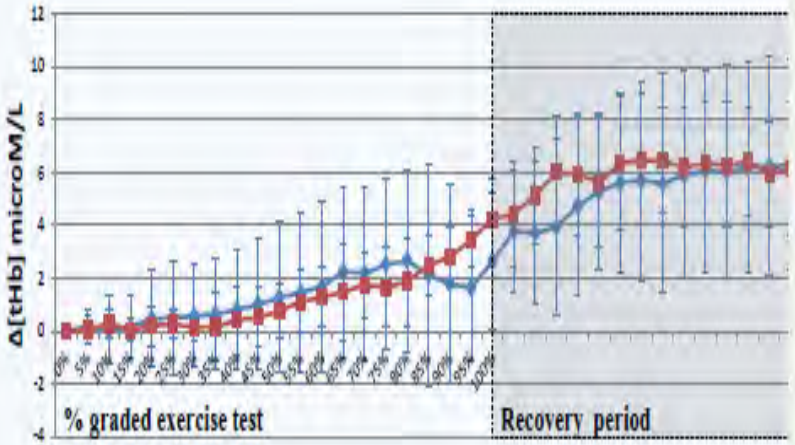
Oxygénation cérébrale: NIRS
Oxymon, Artinis, Netherlands

re 2- Changes in cerebral oxygenation during maximal exercise testing

O2Hb



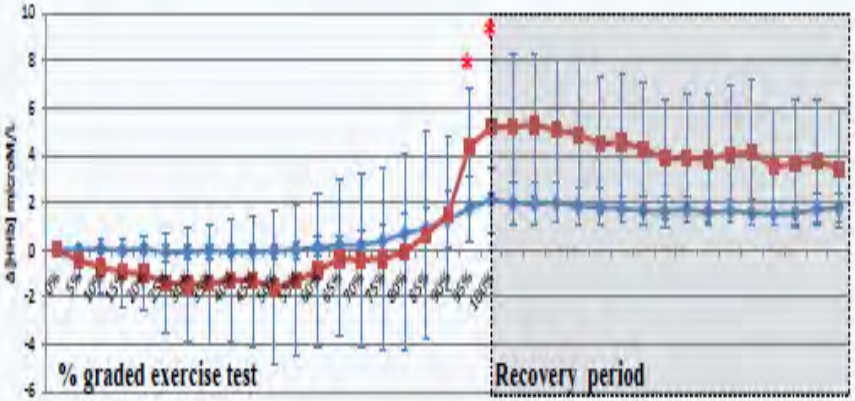
tHb



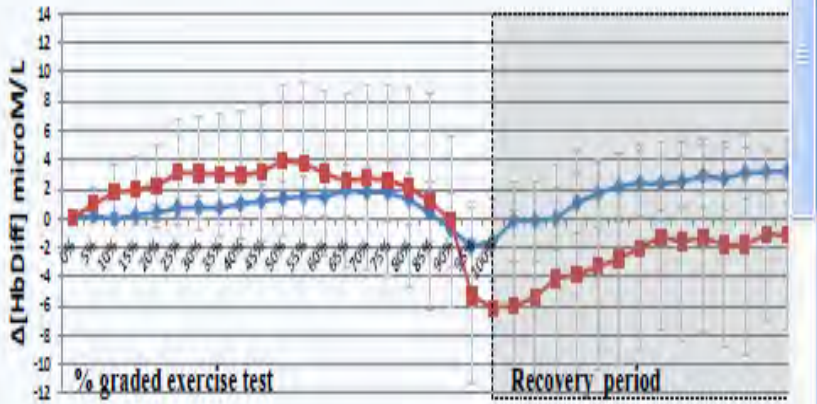
before

after

HHb



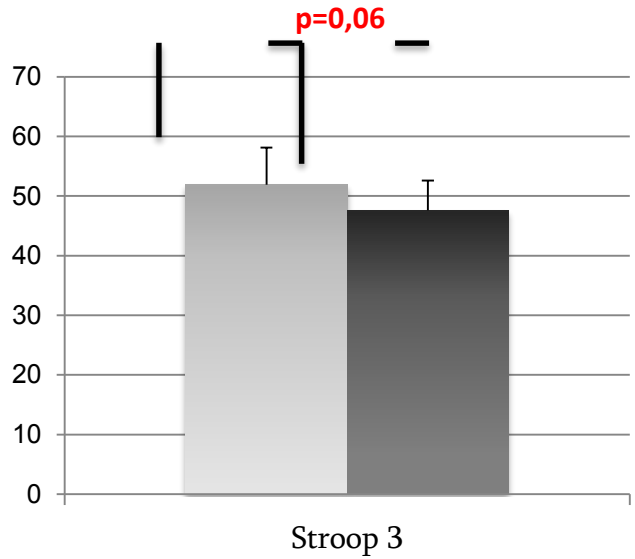
HbDiff



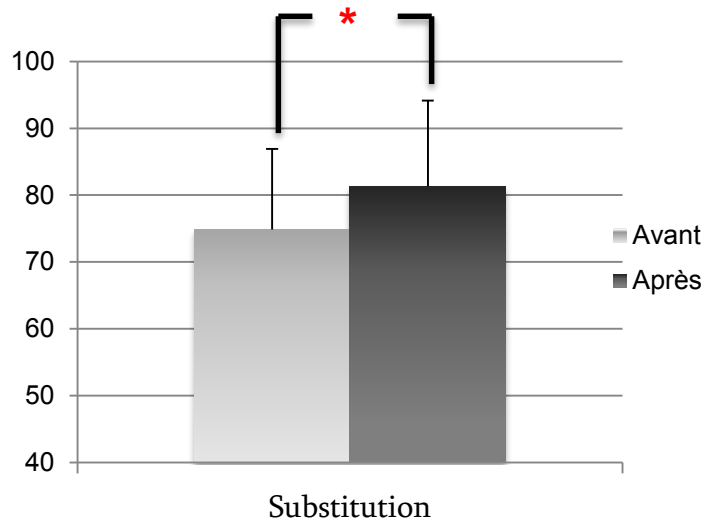
nt changes with p-value p<0,05

Résultats - Cognitif

- Exécutif



Stroop 3



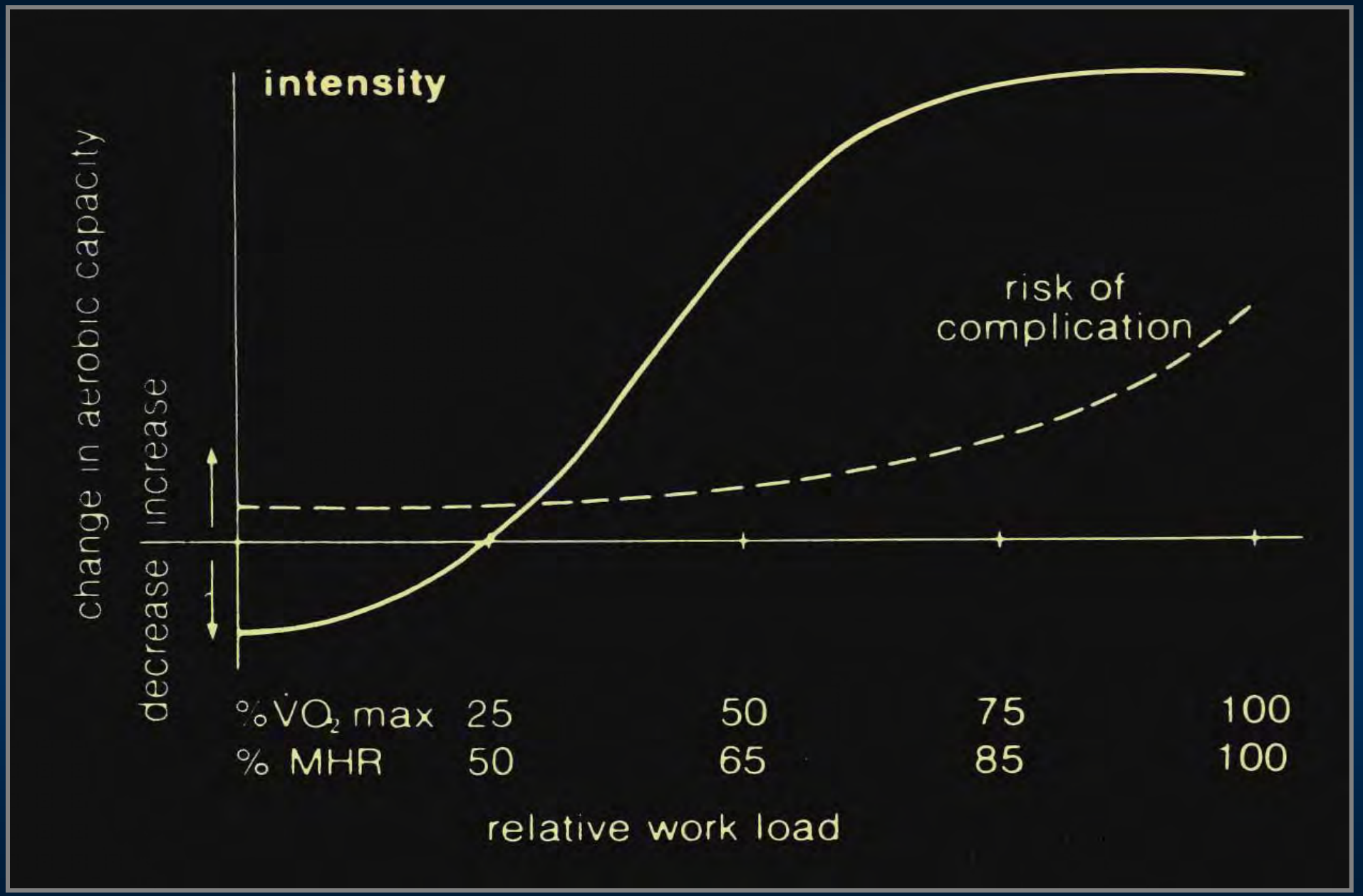
Substitution

- Corrélations

	R	P- value
Stroop – Tâche d'inhibition		
Perte de poids	**0,87**	**<0,05**
Diminution du tour de taille	**0,79**	**<0,05**
Gain en PMA	**-0,85**	**<0,05**
Empan de chiffre - Endroit		
Gain en PMA	**0,92**	**<0,05**

Prescription d'exercice

- Intensité
- Durée
- Fréquence
- Supervision
- Sécurité

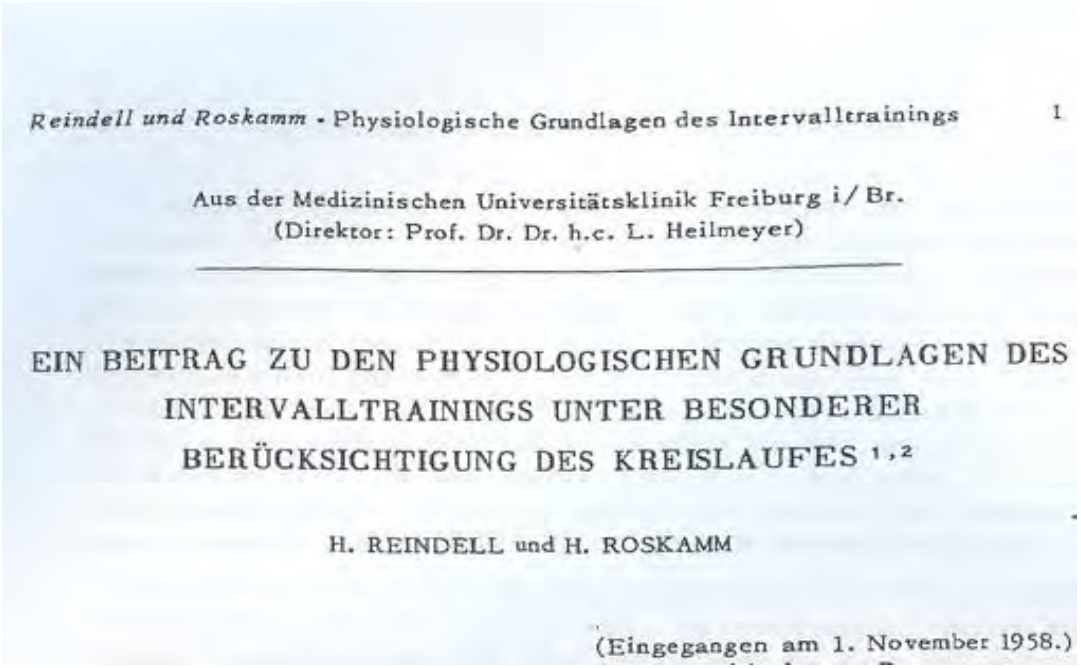

intensity
change in aerobic capacity
increase
decrease
risk of
complication
%VO2 max 25 50 75 100
% MHR 50 65 85 100
relative work load

ECHELLE DE BORG

Perception de la fatigue

	6
TRES TRES FACILE	7
	8
TRES FACILE	9
	10
ASSEZ FACILE	11
	12
UN PEU DIFFICILE	13
	14
DIFFICILE	15
	16
TRES DIFFICILE	17
	18
TRES TRES DIFFICILE	19
	20

EXERCICE INTERMITTENT : HISTORIQUE



Reindell und Roskamm - Physiologische Grundlagen des Intervalltrainings 1

Aus der Medizinischen Universitätsklinik Freiburg i/ Br.
(Direktor: Prof. Dr. Dr. h.c. L. Heilmeyer)

EIN BEITRAG ZU DEN PHYSIOLOGISCHEN GRUNDLAGEN DES INTERVALLTRAININGS UNTER BESONDERER BERÜCKSICHTIGUNG DES KREISLAUFES [1,2]

H. REINDELL und H. ROSKAMM

(Eingegangen am 1. November 1958.)

Reindell (1950's)

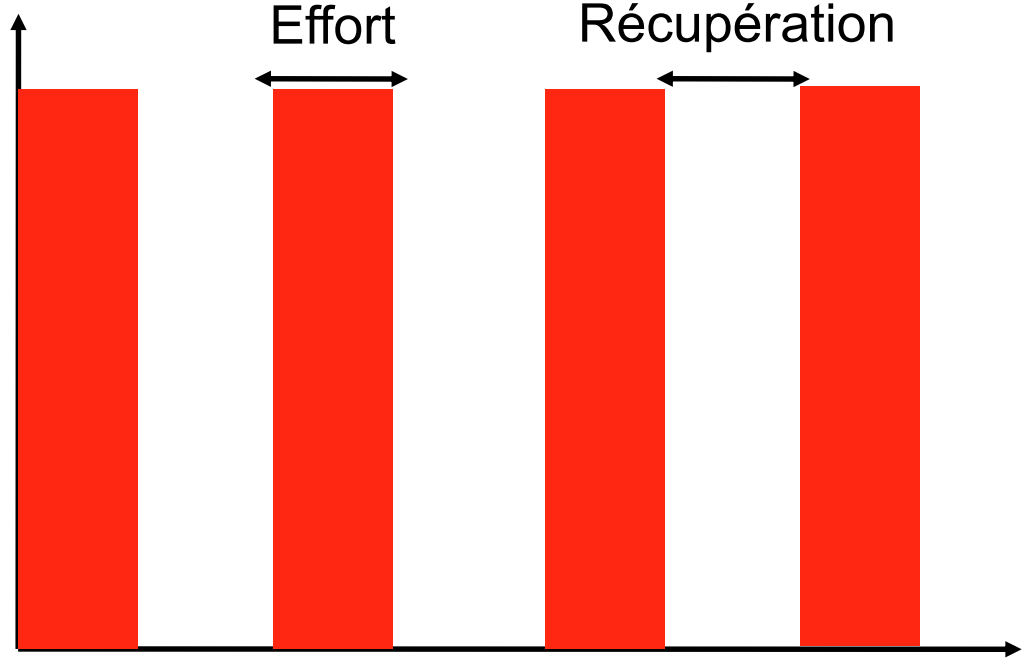
Emile Zatopek (1952)

Astrand et coll.

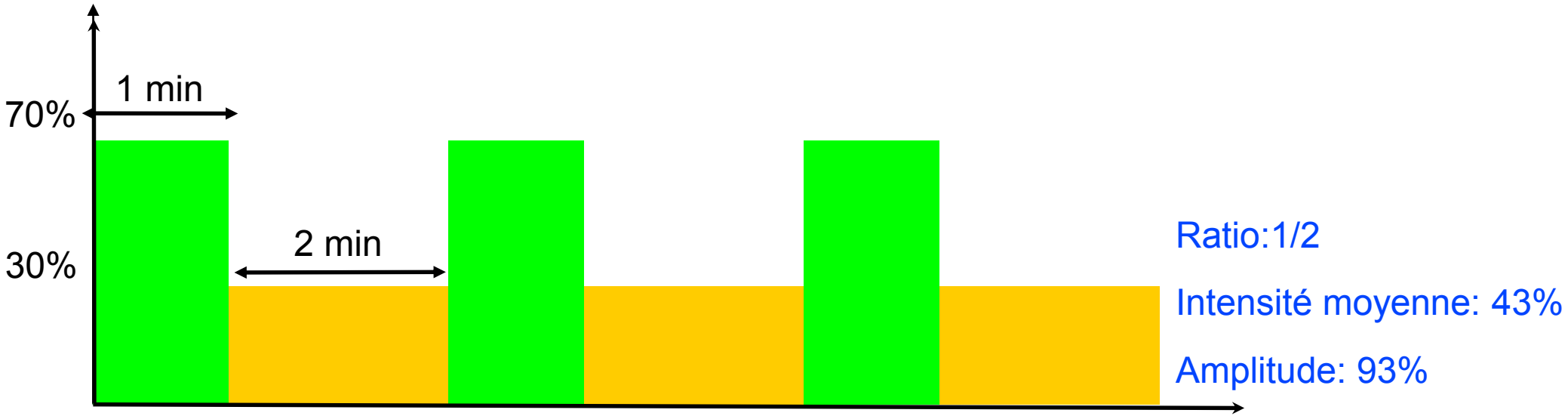
Intermittent muscular work.

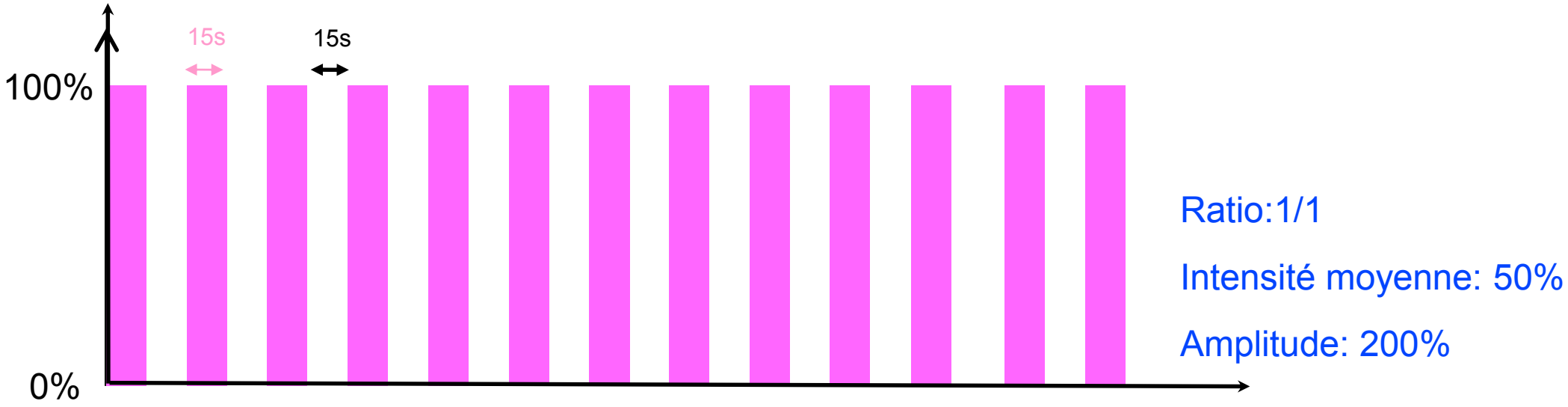
Acta Physiol Scand 1960 ; 48 : 448-453

Continu



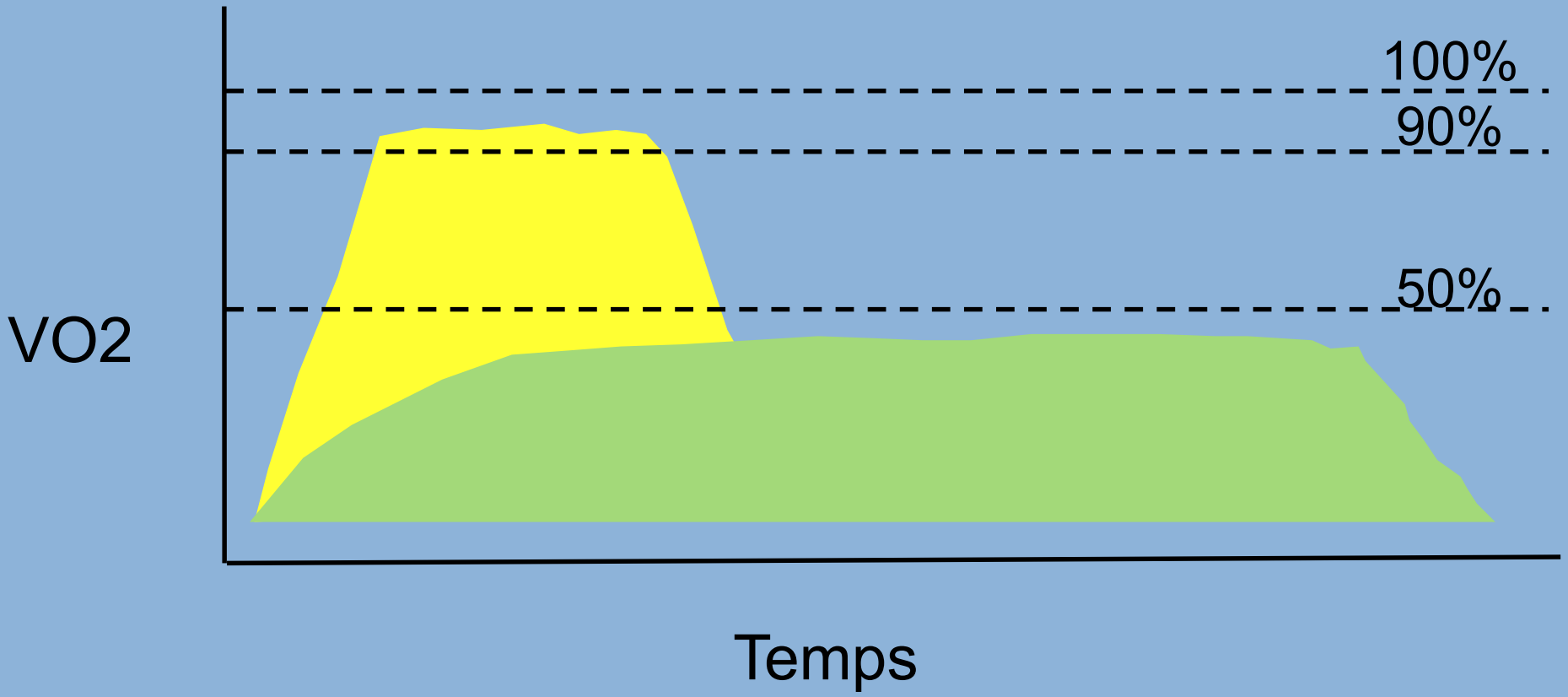
Intermittent





Saltin et al. 1960

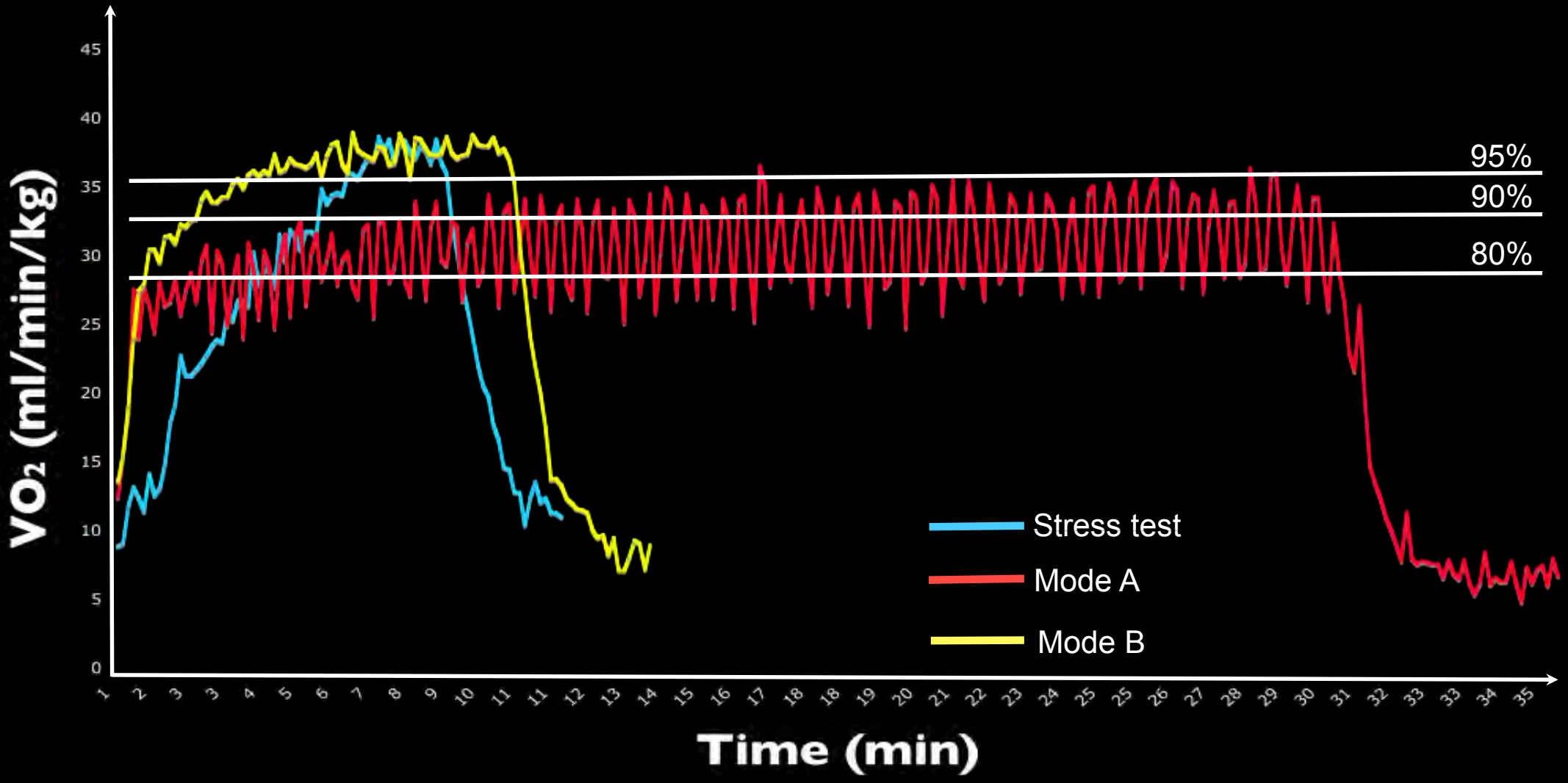
- **Pour ↑ VO_2max, il faut stimuler VO_2max, donc s'entraîner à des intensités proches du VO2 max**



INSTITUT DE CARDIOLOGIE DE MONTRÉAL

Université de Montréal

Methods: time spent near VO_2max



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Core Components of Cardiac Rehabilitation/Secondary Prevention Programs: 2007 Update: A Scientific Statement From the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation

Gary J. Balady, Mark A. Williams, Philip A. Ades, Vera Bittner, Patricia Comoss, JoAnne M. Foody, Barry Franklin, Bonnie Sanderson and Douglas Southard

Circulation 2007;115;2675-2682; originally published online May 18, 2007;

- Develop an individualized exercise prescription for aerobic and resistance training that is based on evaluation findings, risk stratification, comorbidities (eg, peripheral arterial disease and musculoskeletal conditions), and patient and program goals. The exercise regimen should be reviewed by the program medical director or referring physician, modified if necessary, and approved. Exercise prescription should specify frequency (F), intensity (I), duration (D), modalities (M), and progression (P).
  - For aerobic exercise: F=3-5 days/wk; I=50-80% of exercise capacity; D=20-60 minutes; and M=walking, treadmill, cycling, rowing, stair climbing, arm/leg ergometry, and others using continuous or interval training as appropriate.
  - For resistance exercise: F=2-3 days/wk; I=10-15 repetitions per set to moderate fatigue; D=1-3 sets of 8-10 different upper and lower body exercises; and M=calisthenics, elastic bands, cuff/hand weights, dumbbells, free weights, wall pulleys, or weight machines.
- Include warm-up, cool-down, and flexibility exercises in each exercise session.
- Provide progressive updates to the exercise prescription and modify further if clinical status changes.
- Supplement the formal exercise regimen with activity guidelines as outlined in the Physical Activity Counseling section of this table.

REVIEW ARTICLE

Sports Med 2012; 42 (7): 587-605
0112-1642/12/0007-0587/$49.95/0

High-Intensity Interval Training in Cardiac Rehabilitation

Thibaut Guiraud,[1,2,3] *Anil Nigam*,[1] *Vincent Gremeaux*,[1,4,5] *Philippe Meyer*,[1,6] *Martin Juneau*[1,7] and *Laurent Bosquet*[7,8]

1 Montreal Heart Institute, Cardiovascular Prevention Centre (centre ÉPIC), Université de Montréal, Montréal, Québec, Canada
2 Clinique de Rééducation Cardiovasculaire et Pulmonaire de Saint Orens, Saint Orens, France
3 Institut National de la Santé et de la Recherche Médicale, Institut des maladies métaboliques et cardiovasculaires, Toulouse, France
4 Pôle Rééducation-Rehabilitation, Dijon, France
5 Institut National de la Santé et de la Recherche Médicale, U1093 Cognition, Action, et Plasticité Sensorimotrice, Dijon, France
6 Cardiology Service, University Hospital of Geneva, Geneva, Switzerland
7 Department of Kinesiology, Université de Montréal, Montréal, Canada
8 Faculty of Sports Sciences and MOVE Laboratory (EA 6314), Université de Poitiers, Poitiers, France

MJ

ELSEVIER

Canadian Journal of Cardiology ■ (2016) 1–10

Review

Comparison of Different Forms of Exercise Training in Patients With Cardiac Disease: Where Does High-Intensity Interval Training Fit?

Mathieu Gayda, PhD,[a,b,c] Paula A.B. Ribeiro, PhD,[a,b,c] Martin Juneau, MD,[a,b,c] and Anil Nigam, MD[a,b,c]

[a] *Cardiovascular Prevention and Rehabilitation Center (ÉPIC), Montreal Heart Institute and University of Montréal, Québec, Canada*

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[c] *Department of Medicine, University of Montréal, Montréal, Québec, Canada*

Canadian Journal of Cardiology ■ (2014) 1–9

Review

Provocative Issues in Heart Disease Prevention

Martin Juneau, MD,[a,b,c] Douglas Hayami, MD,[a,b,c] Mathieu Gayda, PhD,[a,b,c] Sébastien Lacroix, PhD,[a,d] and Anil Nigam, MD[a,b,c]

[a] *Cardiovascular Prevention and Rehabilitation Centre (ÉPIC), Montreal Heart Institute and University of Montreal, Montreal, Quebec, Canada*

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ABSTRACT

RÉSUMÉ

Curr Heart Fail Rep
DOI 10.1007/s11897-013-0130-3

PATHOPHYSIOLOGY: NEUROENDOCRINE, VASCULAR, AND METABOLIC FACTORS (S.D. KATZ, SECTION EDITOR)

High-Intensity Aerobic Interval Exercise in Chronic Heart Failure

Philippe Meyer · Mathieu Gayda · Martin Juneau · Anil Nigam

Abstract Aerobic exercise training is strongly recommended in patients with heart failure (HF) and reduced

Introduction and Historical Perspective

Journal of the American College of Cardiology
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http://dx.doi.org/10.1016/j.jacc.2013.02.074

FOCUS ISSUE: CARDIOMETABOLIC RISK

Simvastatin Impairs Exercise Training Adaptations

Catherine R. Mikus, PhD,* Leryn J. Boyle, MSc,† Sarah J. Borengasser, PhD,‡
Douglas J. Oberlin, MSc,† Scott P. Naples, MSc,† Justin Fletcher, MSc,†
Grace M. Meers, BSc,§ Meghan Ruebel, MA,‖ M. Harold Laughlin, PhD,¶
Kevin C. Dellsperger, MD, PhD,§ Paul J. Fadel, PhD,# John P. Thyfault, PhD†‡**
Durham, North Carolina; Columbia, Missouri; and Little Rock, Arkansas

Objectives This study sought to determine if simvastatin impairs exercise training adaptations.

Background Statins are commonly prescribed in combination with therapeutic lifestyle changes, including exercise, to reduce cardiovascular disease risk in patients with metabolic syndrome. Statin use has been linked to skeletal muscle myopathy and impaired mitochondrial function, but it is unclear whether statin use alters adaptations to exercise training.

Methods This study examined the effects of simvastatin on changes in cardiorespiratory fitness and skeletal muscle mitochondrial content in response to aerobic exercise training. Sedentary overweight or obese adults with at least 2 metabolic syndrome risk factors (defined according to National Cholesterol Education Panel Adult Treatment Panel III criteria) were randomized to 12 weeks of aerobic exercise training or to exercise in combination with simvastatin (40 mg/day). The primary outcomes were cardiorespiratory fitness and skeletal muscle (vastus lateralis) mitochondrial content (citrate synthase enzyme activity).

Results Thirty-seven participants (exercise plus statins: $n = 18$; exercise only: $n = 19$) completed the study. Cardiorespiratory fitness increased by 10% ($p < 0.05$) in response to exercise training alone, but was blunted by the addition of simvastatin resulting in only a 1.5% increase ($p < 0.005$ for group by time interaction). Similarly, skeletal muscle citrate synthase activity increased by 13% in the exercise-only group ($p < 0.05$), but decreased by 4.5% in the simvastatin-plus-exercise group ($p < 0.05$ for group-by-time interaction).

Conclusions Simvastatin attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients at risk of the metabolic syndrome. (Exercise, Statins, and the Metabolic Syndrome; NCT01700530) (J Am Coll Cardiol 2013;62:709–14) © 2013 by the American College of Cardiology Foundation

JACC Vol. 62, No. 8, 2013
August 20, 2013:709–14

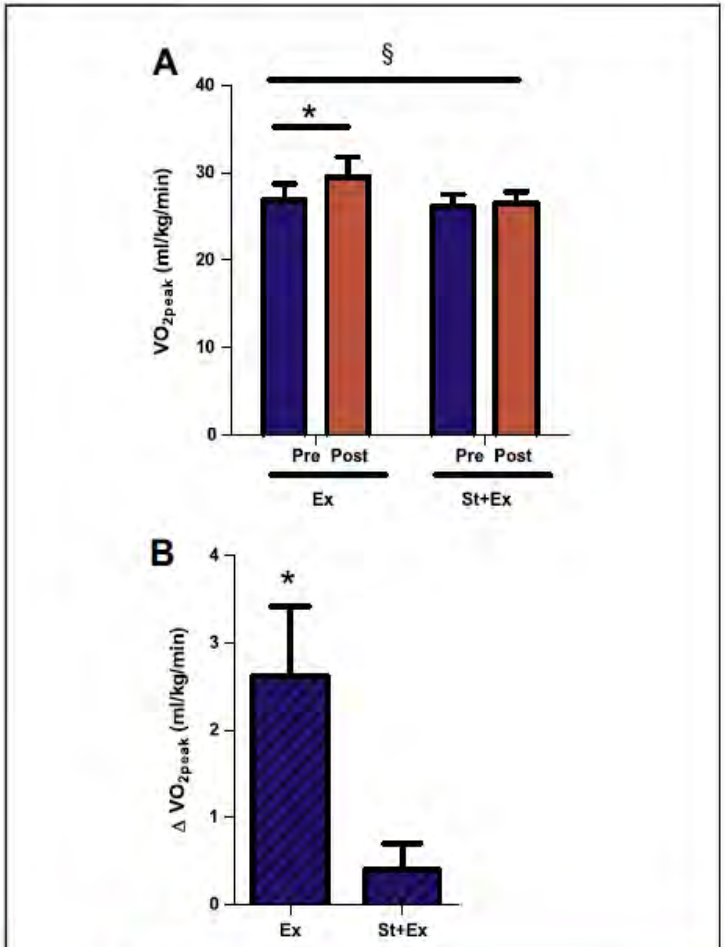


Figure 1 Cardiorespiratory Fitness

(A) Peak oxygen consumption (Vo_2peak) before (Pre) and after (Post) 12 weeks of supervised aerobic exercise training (Ex) or combination exercise-plus-statin therapy (St+Ex). **(B)** Vo_2peak presented as within-group change (Δ) from baseline. Data are expressed as mean ± SE. *$p < 0.005$ for within-group change from baseline. §$p < 0.005$ for between-group difference in change from baseline.

JACC Vol. 62, No. 8, 2013
August 20, 2013:709–14

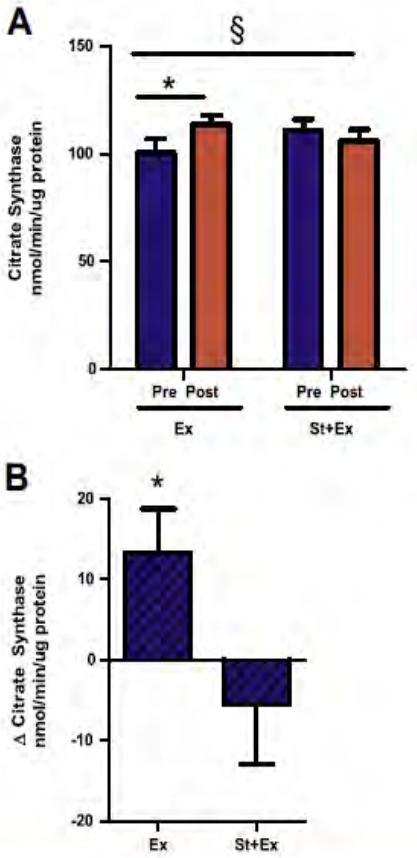


Figure 2 **Citrate Synthase Activity, a Marker of Skeletal Muscle Mitochondrial Content**

(A) Citrate synthase activity before and after 12 weeks of supervised aerobic exercise training or combination exercise-plus-statin therapy. **(B)** Citrate synthase activity presented as within-group change from baseline. Data are expressed as mean ± SE. *$p < 0.05$ for within-group change from baseline. §$p < 0.05$ for between-group difference in change from baseline. Abbreviations as in Figure 1.

MJ

MJ

Run for your life … at a comfortable speed and not too far

James H O'Keefe,[1,2] Carl J Lavie[3,4]

During the Greco-Persian War in 490 BCE, Phidippides, a 40-year-old herald messenger (professional running-courier) ran the 26 miles from a battlefield near Marathon, Greece, into Athens carrying momentous news of Greek victory. Upon arriving at the Acropolis, he proclaimed: 'Joy, we have won!' and then immediately collapsed and died.[1] Fast-forward about 2500 years to an era when the baby-boomer's came of age and long-distance running boomed. The prevailing logic held that aerobic exercise is clearly good for one's health and that, if some is good, more must be better. In 1975, Dr Thomas

may not kill you, it may erase many of the health advantages of regular moderate exercise.

Indeed, regular vigorous exercise is probably the single best step a person can take to ensure robust CV health. In a study of 416 000 adults followed for a mean of 8 years, 40–50 min per day of vigorous exercise reduced risk of death by about 40% (figure 1).[7] In that study, at about 45 min, a point of diminishing returns is reached whereby longer exercise efforts do not appear to translate into lower death risk. Light to moderate physical activity reduced death rates too, albeit not as

morbidity and mortality (figure 2).[8] However, fitness levels above 12 metabolic equivalents do not seem to translate into additional gains in CV health and longevity. Thus, if one is training to be able to run at speeds above 7.5 miles per hour, this is being done for some reason other than further improvements in life expectancy.

CV DAMAGE FROM EXCESSIVE EXERCISE

High-intensity exercise sessions lasting beyond 1–2 h cause acute volume overload of the atria and right ventricle (RV), which can bring about overstretching and micro-tears in the myocardium, as evidenced by a transient rise in cardiac biomarkers, including troponin and B-natriuretic peptide and a fall in the RV ejection fraction.[9] Although within 1 week, these transitory abnormalities

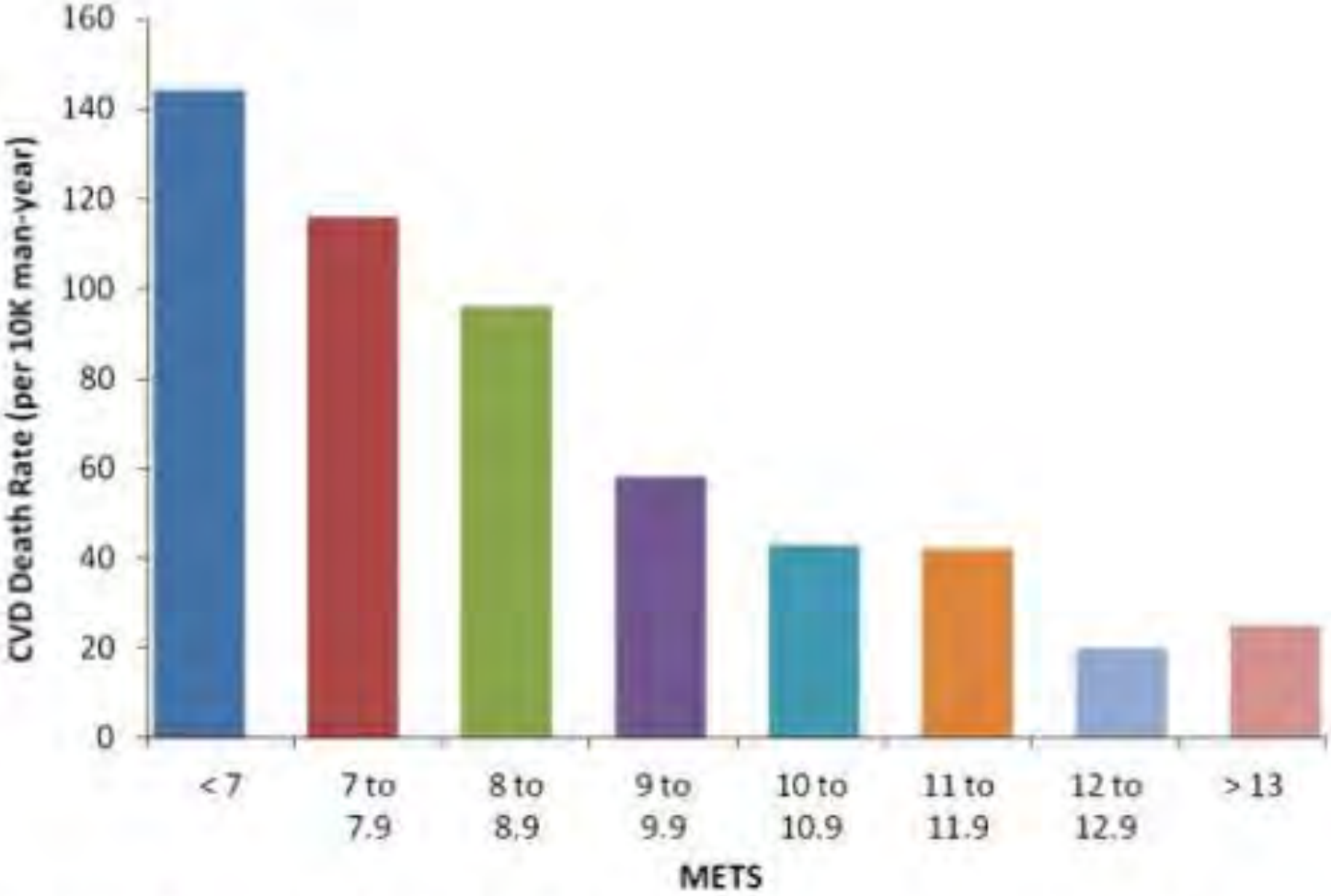


Figure 2 Death rates as a function of cardiovascular fitness as measured by metabolic equivalents achieved on maximal exercise treadmill testing.[8] CVD, cardiovascular disease.

European Heart Journal Advance Access published December 6, 2011

European Heart Journal
doi:10.1093/eurheartj/ehr397

CLINICAL RESEARCH

Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes

André La Gerche[1,2]*, Andrew T. Burns[3], Don J. Mooney[3], Warrick J. Inder[1], Andrew J. Taylor[4], Jan Bogaert[5], Andrew I. MacIsaac[3], Hein Heidbüchel[2], and David L. Prior[1,3]

[1]University of Melbourne Department of Medicine, St Vincent's Hospital, 29 Regent Street, Fitzroy VIC 3065, Australia; [2]Department of Cardiovascular Medicine, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; [3]Cardiology Department, St Vincent's Hospital, 41 Victoria Parade, Fitzroy VIC 3065, Australia; [4]Alfred Hospital and Baker IDI Heart and Diabetes Institute, Commercial Road, Melbourne VIC 3004, Australia; and [5]Radiology Department, Medical Imaging Research Center, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

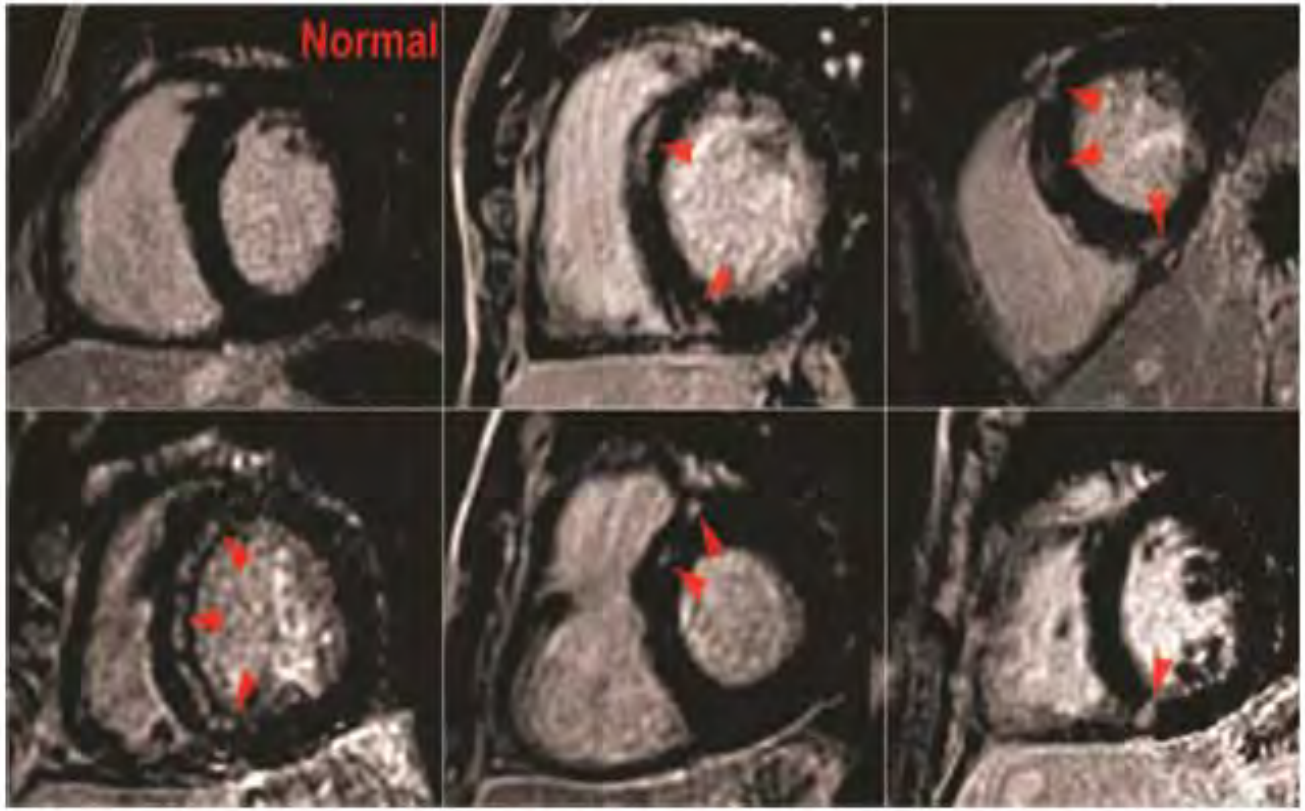


Figure 3 Delayed gadolinium enhancement in five athletes. Images of five athletes in whom focal delayed gadolinium enhancement (DGE) was identified in the interventricular septum (indicated with arrows) when compared with an athlete with a normal study (top left).

Cardiac Arrhythmogenic Remodeling in a Rat Model of Long-Term Intensive Exercise Training

Begoña Benito, MD*; Gemma Gay-Jordi, PhD*; Anna Serrano-Mollar, PhD; Eduard Guasch, MD; Yanfen Shi, MD; Jean-Claude Tardif, MD; Josep Brugada, MD, PhD; Stanley Nattel, MD†; Lluis Mont, MD, PhD†

Background—Recent clinical studies suggest that endurance sports may promote cardiac arrhythmias. The aim of this study was to use an animal model to evaluate whether sustained intensive exercise training induces potentially adverse myocardial remodeling and thus creates a potential substrate for arrhythmias.

Methods and Results—Male Wistar rats were conditioned to run vigorously for 4, 8, and 16 weeks; time-matched sedentary rats served as controls. Serial echocardiograms and in vivo electrophysiological studies at 16 weeks were obtained in both groups. After euthanasia, ventricular collagen deposition was quantified by histological and biochemical studies, and messenger RNA and protein expression of transforming growth factor-β1, fibronectin-1, matrix metalloproteinase-2, tissue inhibitor of metalloproteinase-1, procollagen-I, and procollagen-III was evaluated in all 4 cardiac chambers. At 16 weeks, exercise rats developed eccentric hypertrophy and diastolic dysfunction, together with atrial dilation. In addition, collagen deposition in the right ventricle and messenger RNA and protein expression

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal
doi:10.1093/eurheartj/eht188

CLINICAL RESEARCH

Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study

Kasper Andersen[1]*, Bahman Farahmand[2,3], Anders Ahlbom[2], Claes Held[1], Sverker Ljunghall[1], Karl Michaëlsson[4], and Johan Sundström[1]

[1]Department of Medical Sciences, Uppsala University Hospital, Entrance 40, 5th floor, SE-751 85 Uppsala, Sweden; [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Alzheimer Disease Research Center (KI-ADRC), Stockholm, Sweden; and [4]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Received 11 October 2012; revised 9 April 2013; accepted 14 May 2013

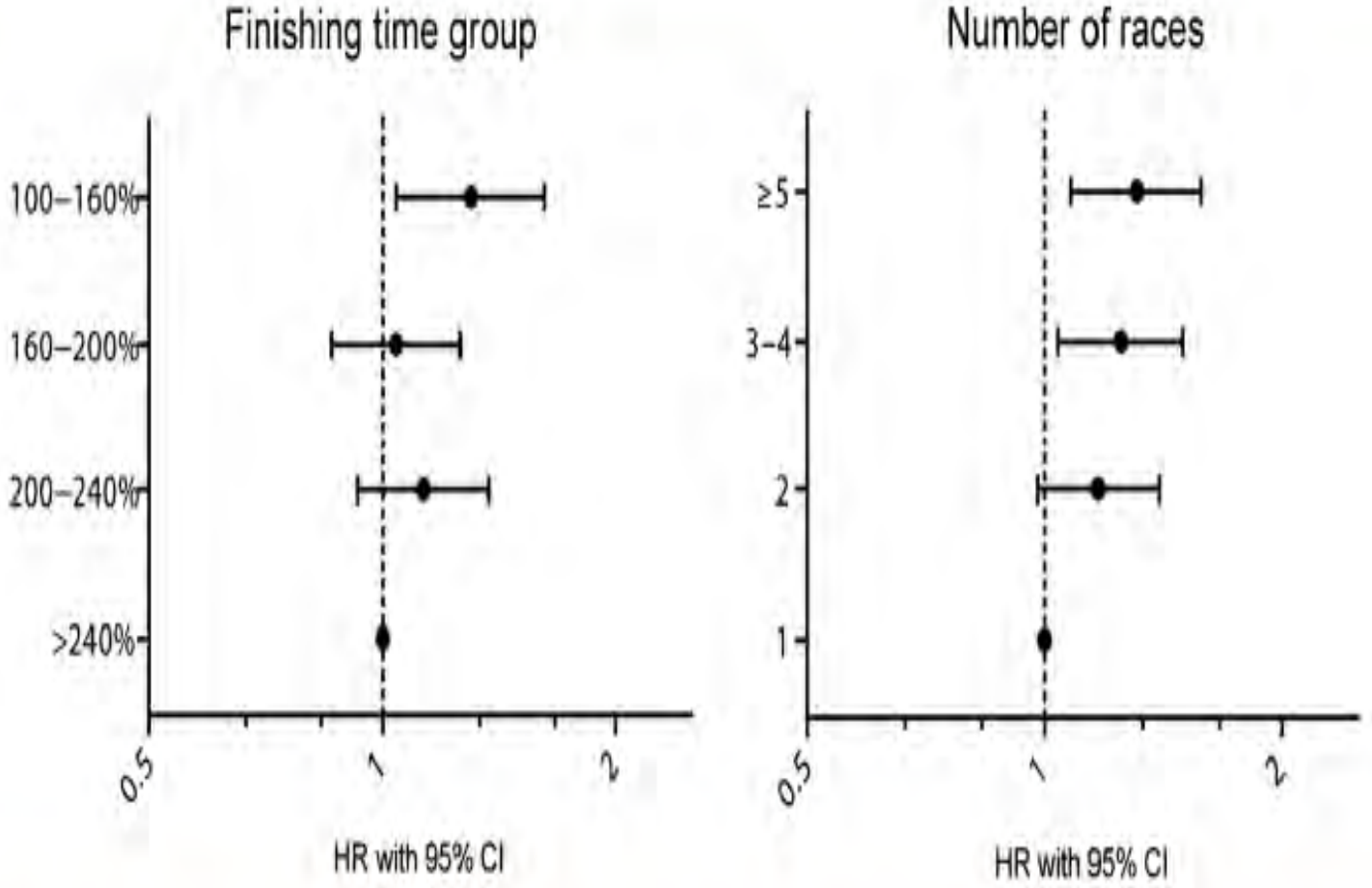
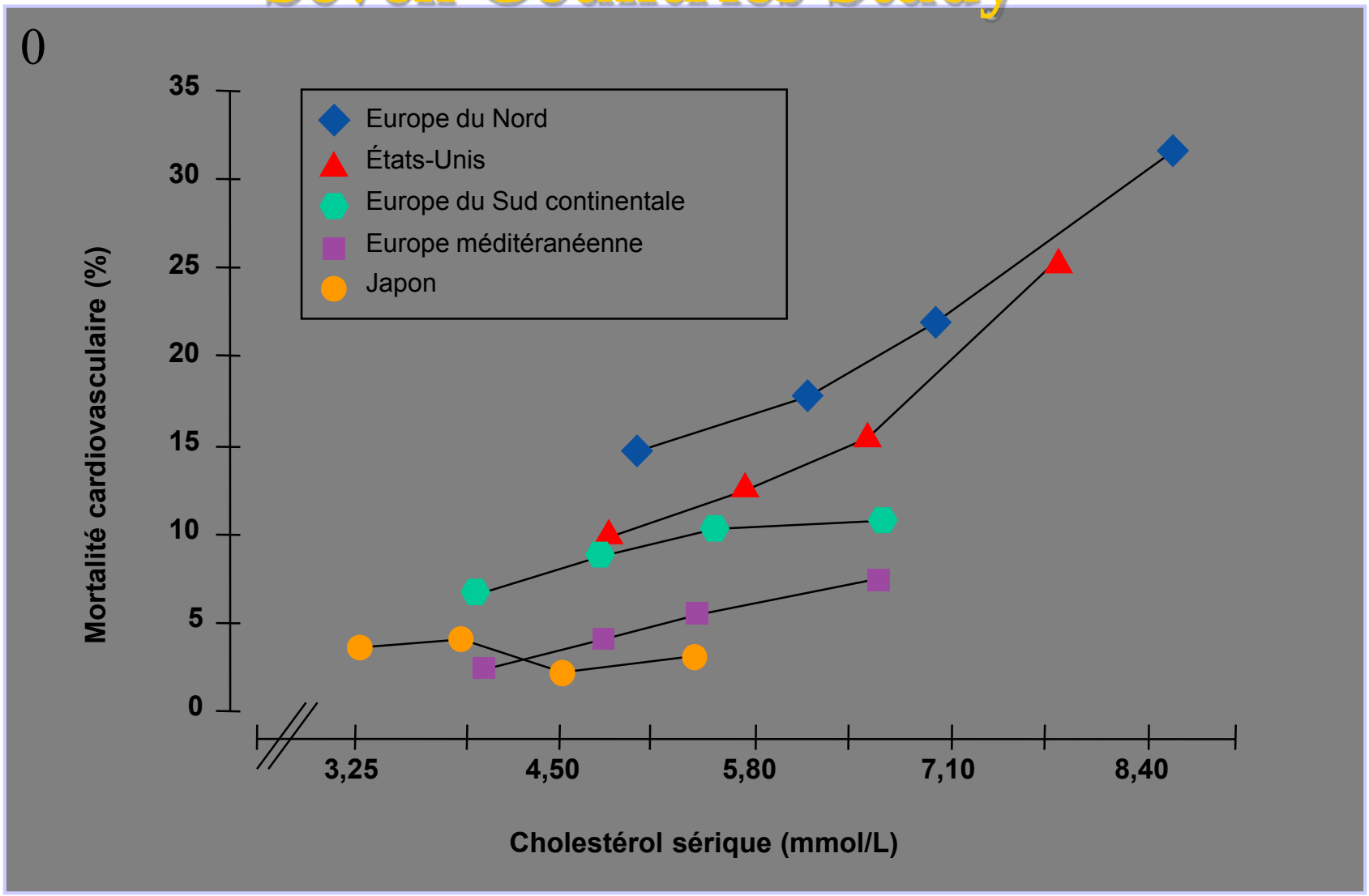


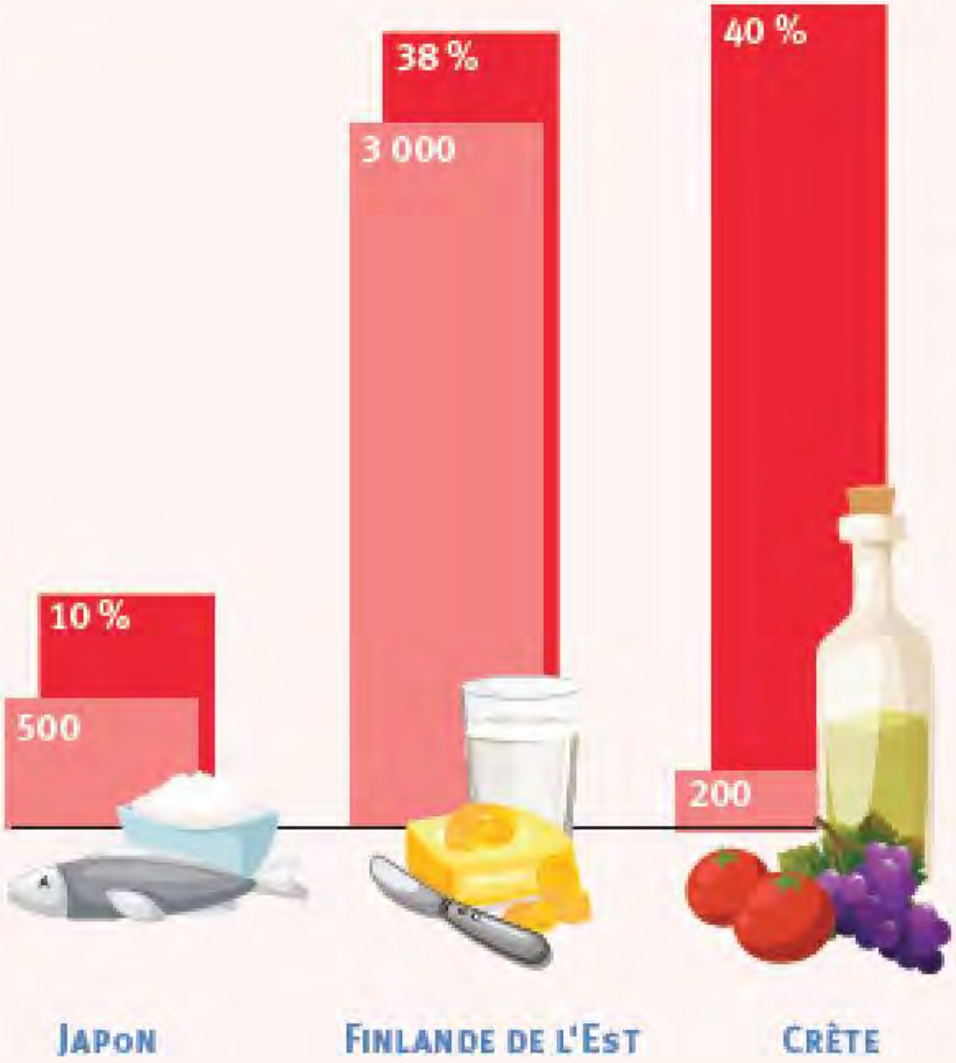
Figure 2 Hazard ratios of any arrhythmia with 95% confidence intervals (log scale) by finishing time group in per cent of winning time and number of previous races. Model adjusted for age, occupation, and education level.

Mortalité cardiovasculaire sur 25 ans

Seven Countries Study



BIEN CHOISIR SES GRAS POUR PRÉVENIR LES MALADIES CARDIOVASCULAIRES



Même si 6 % des gras de l'alimentation des Finlandais et des Crétois est similaire, c'est la qualité des gras (huile d'olive, noix, etc.) qui explique la faible incidence de maladies cardiovasculaires en Crète.

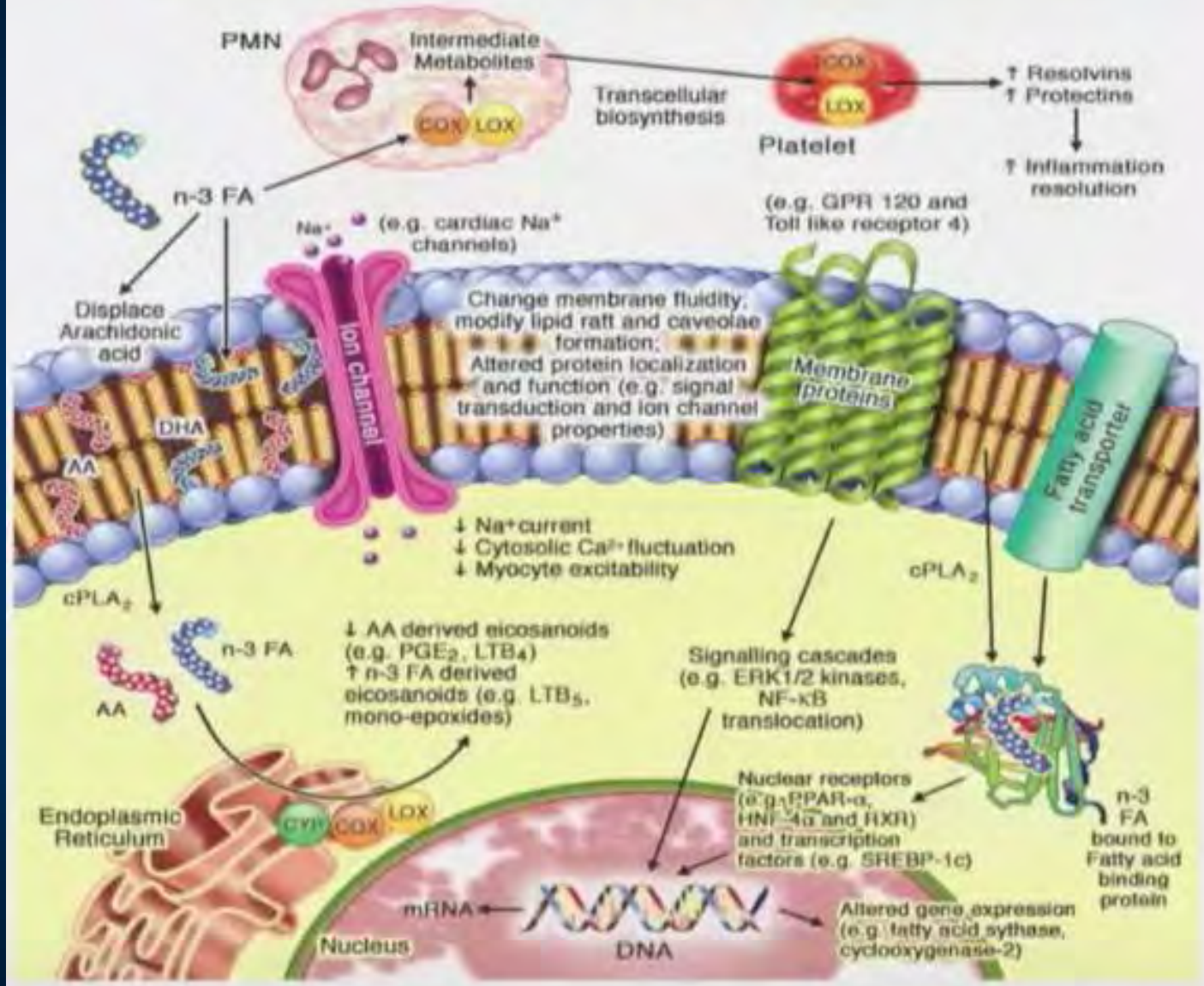
Pourcentage de calories provenant des gras

Incidence de maladie coronarienne dans une population de 10 000 hommes sur une période de 10 ans

FIGURE 29

D'après Stampfer et Willett (2006)

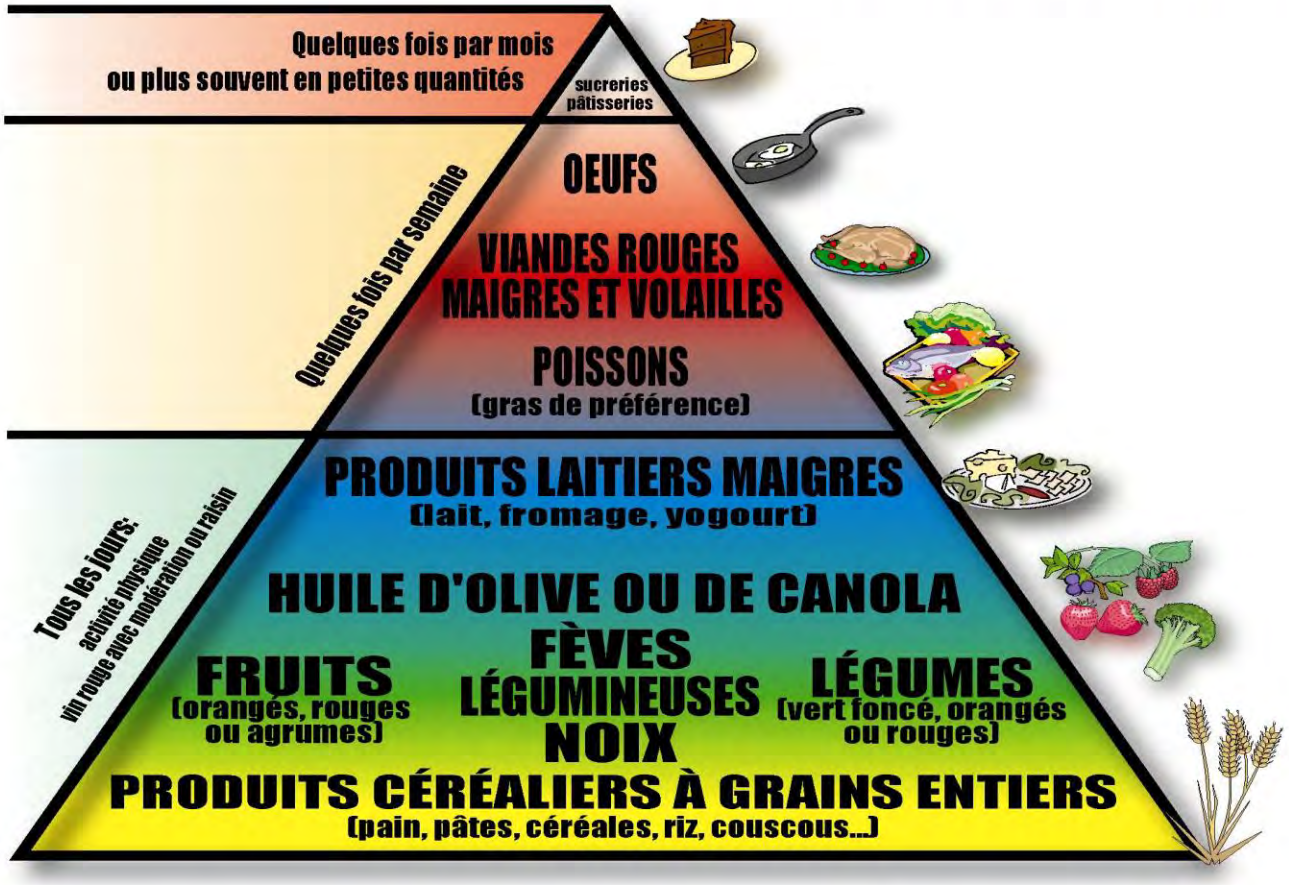
Dietary Fats: Highly Bioactive



Mozaffarian & Wu, JACC 2011

Alimentation Méditerranéenne Modifiée

ÉPIC

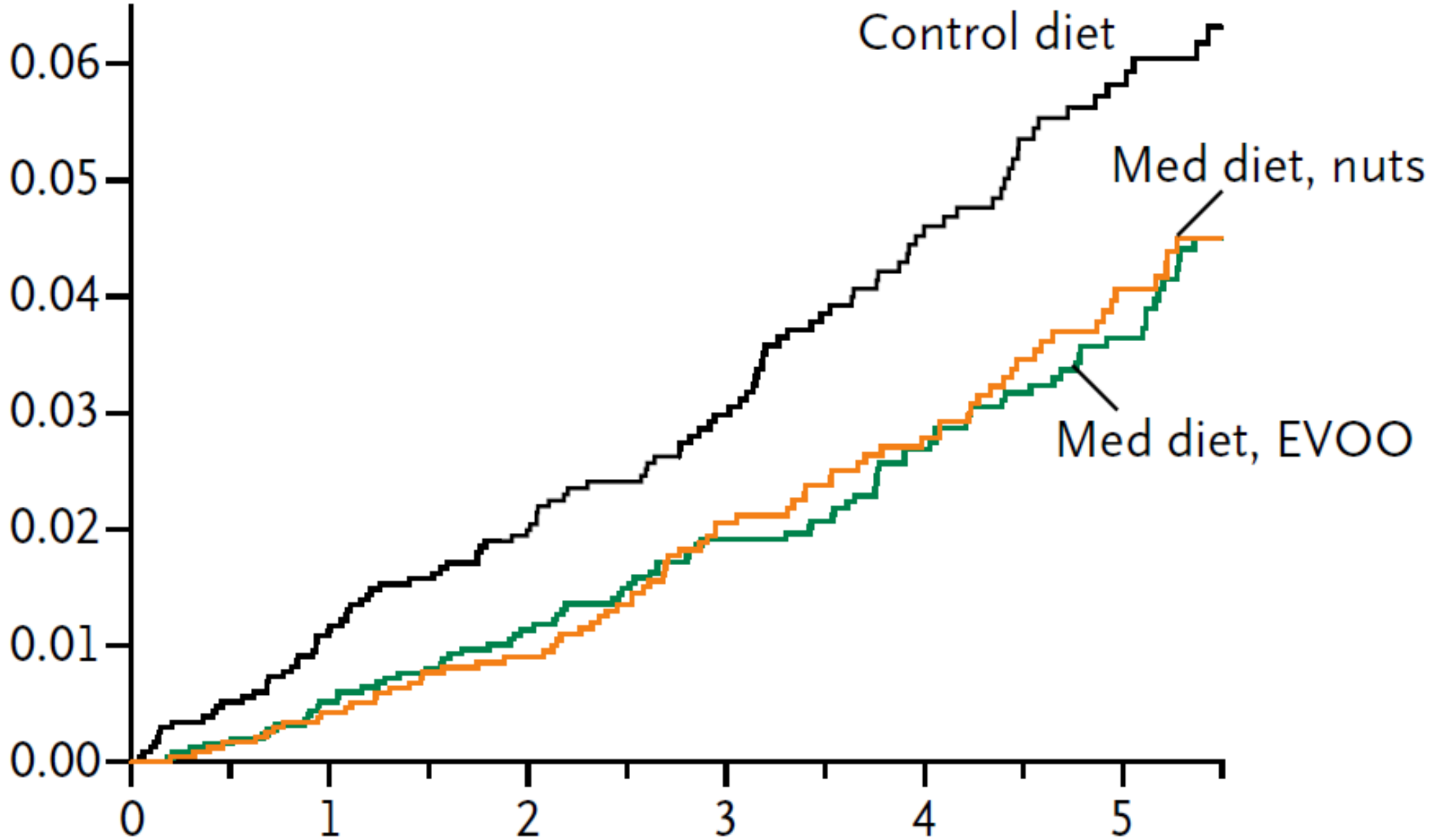


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*


Control diet
Med diet, nuts
Med diet, EVOO
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
1
2
3
4
5

Pyramide de la Diète Méditerranéenne: un style de vie actuel

Guide pour la population adulte

Les rations basées sur la frugalité
et les habitudes locales

Édition 2010

r = Ration

Fundación
Dieta Mediterránea

ICAF
International Commission on the
Anthropology of Food and Nutrition

FORUM ON MEDITERRANEAN FOOD CULTURES

Predimed

Ciiscam

H.H.F. HELLENIC HEALTH FOUNDATION

IUNS

CIHEAM

fens

Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction

Final Report of the Lyon Diet Heart Study

Michel de Lorgeril, MD; Patricia Salen, BSc; Jean-Louis Martin, PhD; Isabelle Monjaud, BSc; Jacques Delaye, MD; Nicole Mamelle, PhD

Background—The Lyon Diet Heart Study is a randomized secondary prevention trial aimed at testing whether a Mediterranean-type diet may reduce the rate of recurrence after a first myocardial infarction. An intermediate analysis showed a striking protective effect after 27 months of follow-up. This report presents results of an extended follow-up (with a mean of 46 months per patient) and deals with the relationships of dietary patterns and traditional risk factors with recurrence.

Methods and Results—Three composite outcomes (COs) combining either cardiac death and nonfatal myocardial infarction (CO 1), or the preceding plus major secondary end points (unstable angina, stroke, heart failure, pulmonary or peripheral embolism) (CO 2), or the preceding plus minor events requiring hospital admission (CO 3) were studied. In the Mediterranean diet group, CO 1 was reduced (14 events versus 44 in the prudent Western-type diet group, $P=0.0001$), as were CO 2 (27 events versus 90, $P=0.0001$) and CO 3 (95 events versus 180, $P=0.0002$). Adjusted risk ratios ranged from 0.28 to 0.53. Among the traditional risk factors, total cholesterol (1 mmol/L being associated with an increased risk of 18% to 28%), systolic blood pressure (1 mm Hg being associated with an increased risk of 1% to 2%), leukocyte count (adjusted risk ratios ranging from 1.64 to 2.86 with count $>9\times10^9$/L), female sex (adjusted risk ratios, 0.27 to 0.46), and aspirin use (adjusted risk ratios, 0.59 to 0.82) were each significantly and independently associated with recurrence.

Conclusions—The protective effect of the Mediterranean dietary pattern was maintained up to 4 years after the first infarction, confirming previous intermediate analyses. Major traditional risk factors, such as high blood cholesterol and blood pressure, were shown to be independent and joint predictors of recurrence, indicating that the Mediterranean dietary pattern did not alter, at least qualitatively, the usual relationships between major risk factors and recurrence. Thus, a comprehensive strategy to decrease cardiovascular morbidity and mortality should include primarily a cardioprotective diet. It should be associated with other (pharmacological?) means aimed at reducing modifiable risk factors. Further trials combining the 2 approaches are warranted. **(*Circulation*. 1999;99:779-785.)**

Key Words: diet ■ trials ■ coronary disease ■ myocardial infarction

TABLE 1. End Points in the 2 Groups and Risk Ratios for the 3 Composite Outcomes Calculated With the Cox Proportional-Hazards Model

	Control		Experimental			
	Number	Rate*	Number	Rate	Risk Ratio† (95% CI)	*P*
Major primary end points						
Cardiac deaths	19	1.37	6	0.41	0.35 (0.15–0.83)	0.01
Nonfatal AMI	25	2.70	8	0.83		
Total primary end points (composite outcome 1)	44	4.07	14	1.24	0.28 (0.15–0.53)	0.0001
Noncardiac deaths	5	0.36	8	0.54		
All-cause deaths	24	1.74	14	0.95	0.44 (0.21–0.94)	0.03
Major secondary end points						
Periprocedural infarction	2		0			
Unstable angina	24		6			
Heart failure	11		6			
Stroke	4		0			
Pulmonary embolism	3		0			
Peripheral embolism	2		1			
Total secondary end points	46	4.96	13	1.35		
Total primary+secondary end points (composite outcome 2)	90	9.03	27	2.59	0.33 (0.21–0.52)	0.0001
Minor secondary end points						
Stable angina	29		21			
Elective myocardial revascularization	45		37			
Post-PTCA restenosis	15		9			
Thrombophlebitis	1		2			
Total minor end points	90	9.71	68	7.04		
Total major and minor end points (composite outcome 3)	180	18.74	95	9.63	0.53 (0.38–0.74)	0.0002

AMI indicates acute myocardial infarction.

*The rates are given per 100 patients per year of follow-up; they were calculated from a follow-up of 1383 and 1467 person-years for mortality in the control and experimental groups, respectively, and 927 and 966 person-years for nonfatal events.

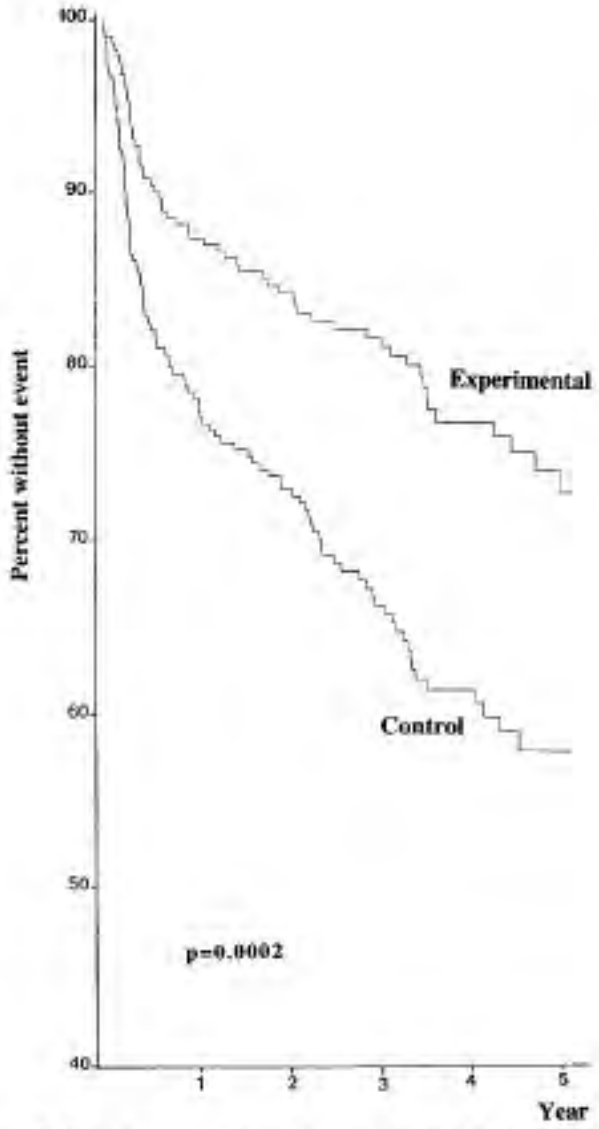


Figure 3. Cumulative survival without nonfatal infarction, without major secondary end points, and without minor secondary end points (CO 3).

TABLE 2. Main Risk Factors and Selected Biological Parameters Recorded on the Final Visit

	Control (n=204)	Experimental (n=219)
Body mass index, kg/m²	26.9 (3.4)	26.3 (3.7)
Systolic blood pressure, mm Hg	128 (16)	128 (17)
Diastolic blood pressure, mm Hg	79 (10)	78 (11)
Total cholesterol, mmol/L	6.18 (1.04)	6.20 (1.06)
Triglycerides, mmol/L	1.75 (0.83)	1.94 (0.85)
HDL-cholesterol, mmol/L	1.28 (0.34)	1.29 (0.34)
LDL-cholesterol, mmol/L	4.23 (0.98)	4.17 (0.93)
Lipoprotein (a), g/L	0.35 (0.49)	0.33 (0.35)
Albumin, g/L	47.10 (2.88)	47.28 (3.07)
Glycated hemoglobin, %	4.61 (1.23)	4.66 (1.52)
Creatinine, μmol/L	116 (20)	115 (21)
Uric acid, μmol/L	348 (81)	338 (87)
Leukocyte count, $\times 10^9$/L	6.00 (1.69)	5.99 (1.68)
Current smokers, %	17.9	18.3
Medication, %		
Anticoagulant agents	16.1	11.4
Antiplatelet agents	69.7	75.8
β-Blocking agents	47.3	47.5
Calcium channel blockers	28.4	25.6
ACE inhibitors	17.4	18.3
Lipid-lowering drugs	34.0	26.5

Values are mean (SD).

cholesterol, blood pressure, leukocyte count, and aspirin use). With regard to the effect of 18:3(ω-3) on CO 2 and CO 3, the associations were borderline nonsignificant ($P=0.08$ and $P=0.12$).

Évènements Étude de Lyon

- Mortalité CV:
- 19/204 = 9.3% 6/219=2.7% Diff absolue 6.6%

- Infarctus non fatal:
- 25/204= 12.2 % 8/219= 3.6% Diff absolue 8.6%

- Mortalité toutes causes:
- 24/204= 11.7% 14/219= 6.4% Diff absolue 5.3%

- DIFFÉRENCES RELATIVES: 71%, 70%, 45%

TABLE 3. Daily Nutrient Intake Recorded on the Final Visit in 83 Control and 144 Experimental Nonselected Consecutive Patients

	Control	Experimental	*P*
Total calories	2088 (490)	1947 (468)	0.033
% calories			
Total lipids	33.6 (7.80)	30.4 (7.00)	0.002
Saturated fats	11.7 (3.90)	8.0 (3.70)	0.0001
Polyunsaturated fats	6.10 (2.90)	4.60 (1.70)	0.0001
18:1(ω-9) (oleic)	10.8 (4.10)	12.9 (3.20)	0.0001
18:2(ω-6) (linoleic)	5.30 (2.80)	3.60 (1.20)	0.0001
18:3(ω-3) (linolenic)	0.29 (0.19)	0.84 (0.46)	0.0001
Alcohol	5.98 (6.90)	5.83 (5.80)	0.80
Proteins, g	16.6 (3.80)	16.2 (3.10)	0.30
Fiber, g	15.5 (6.80)	18.6 (8.10)	0.004
Cholesterol, mg	312 (180)	203 (145)	0.0001

Values are mean (SD).

Original Investigation

Association of Specific Dietary Fats With Total and Cause-Specific Mortality

Dong D. Wang, MD, MSc; Yanping Li, PhD; Stephanie E. Chiuve, ScD; Meir J. Stampfer, MD, DrPH; JoAnn E. Manson, MD, DrPH; Eric B. Rimm, ScD; Walter C. Willett, MD, DrPH; Frank B. Hu, MD, PhD

IMPORTANCE Previous studies have shown distinct associations between specific dietary fat and cardiovascular disease. However, evidence on specific dietary fat and mortality remains limited and inconsistent.

OBJECTIVE To examine the associations of specific dietary fats with total and cause-specific mortality in 2 large ongoing cohort studies.

DESIGN, SETTING, AND PARTICIPANTS This cohort study investigated 83 349 women from the Nurses' Health Study (July 1, 1980, to June 30, 2012) and 42 884 men from the Health Professionals Follow-up Study (February 1, 1986, to January 31, 2012) who were free of cardiovascular disease, cancer, and types 1 and 2 diabetes at baseline. Dietary fat intake was assessed at baseline and updated every 2 to 4 years. Information on mortality was obtained from systematic searches of the vital records of states and the National Death Index, supplemented by reports from family members or postal authorities. Data were analyzed from September 18, 2014, to March 27, 2016.

MAIN OUTCOMES AND MEASURES Total and cause-specific mortality.

RESULTS During 3 439 954 person-years of follow-up, 33 304 deaths were documented. After adjustment for known and suspected risk factors, dietary total fat compared with total carbohydrates was inversely associated with total mortality (hazard ratio [HR] comparing extreme quintiles, 0.84; 95% CI, 0.81-0.88; $P < .001$ for trend). The HRs of total mortality comparing extreme quintiles of specific dietary fats were 1.08 (95% CI, 1.03-1.14) for saturated fat, 0.81 (95% CI, 0.78-0.84) for polyunsaturated fatty acid (PUFA), 0.89 (95% CI, 0.84-0.94) for monounsaturated fatty acid (MUFA), and 1.13 (95% CI, 1.07-1.18) for *trans*-fat ($P < .001$ for trend for all). Replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% (HR, 0.73; 95% CI, 0.70-0.77) and 13% (HR, 0.87; 95% CI, 0.82-0.93), respectively. The HR for total mortality comparing extreme quintiles of ω-6 PUFA intake was 0.85 (95% CI, 0.81-0.89; $P < .001$ for trend). Intake of ω-6 PUFA, especially linoleic acid, was inversely associated with mortality owing to most major causes, whereas marine ω-3 PUFA intake was associated with a modestly lower total mortality (HR comparing extreme quintiles, 0.96; 95% CI, 0.93-1.00; $P = .002$ for trend).

CONCLUSIONS AND RELEVANCE Different types of dietary fats have divergent associations with total and cause-specific mortality. These findings support current dietary recommendations to replace saturated fat and *trans*-fat with unsaturated fats.

Related article

Supplemental content at jamainternalmedicine.com

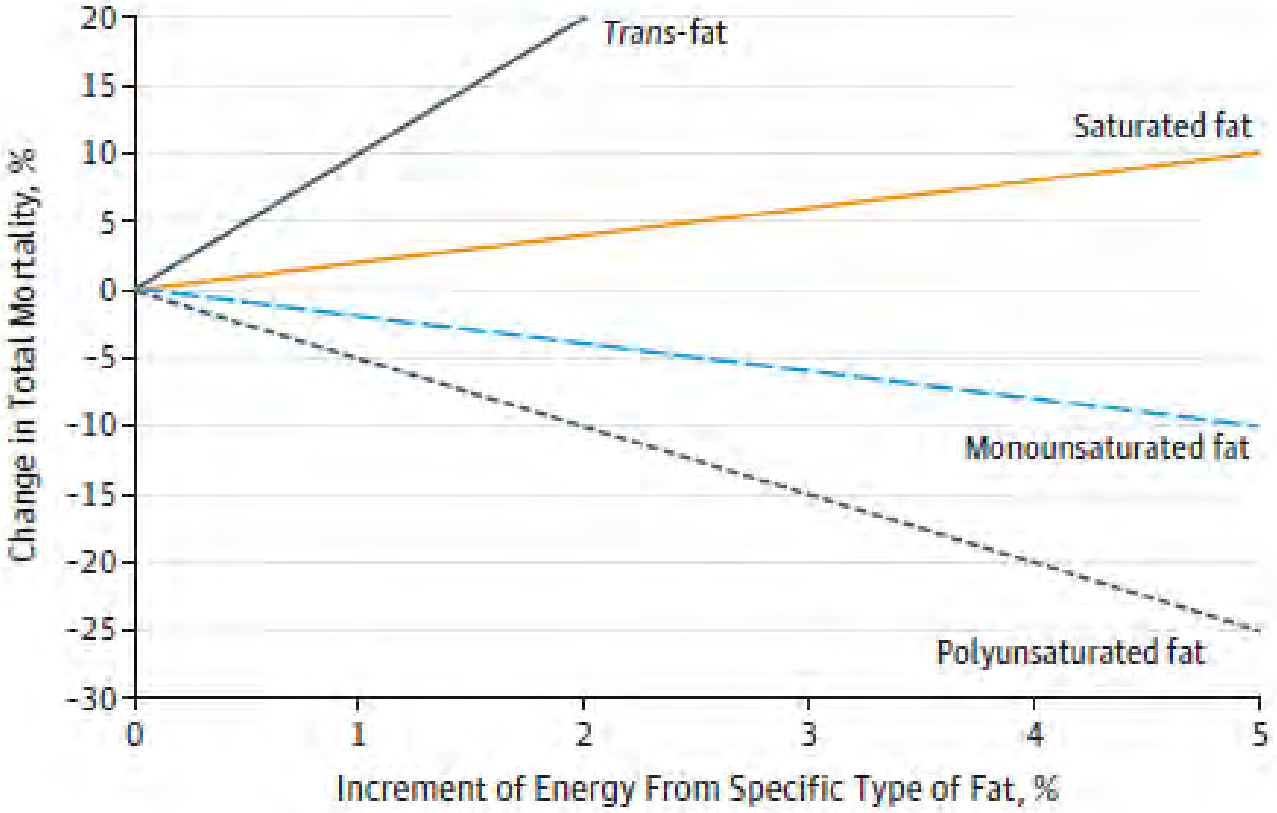
Author Affiliations: Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Wang, Li, Chiuve, Stampfer, Rimm, Willett, Hu); Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Chiuve, Stampfer, Manson); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Wang, Stampfer, Manson, Rimm, Willett, Hu); Channing Division for Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Stampfer, Manson, Rimm, Willett, Hu).

Corresponding Author: Frank B. Hu, MD, PhD, Department of Nutrition, Harvard T. H. Chan School of Public Health, 665 Huntington Ave, Boston, MA 02115 (nhbfh@channing.harvard.edu).

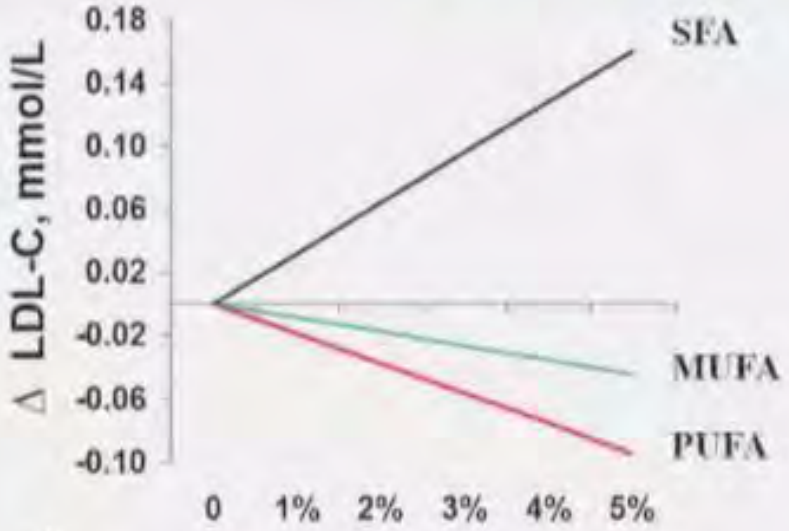
JAMA Intern Med. doi:10.1001/jamainternmed.2016.2417
Published online July 5, 2016.

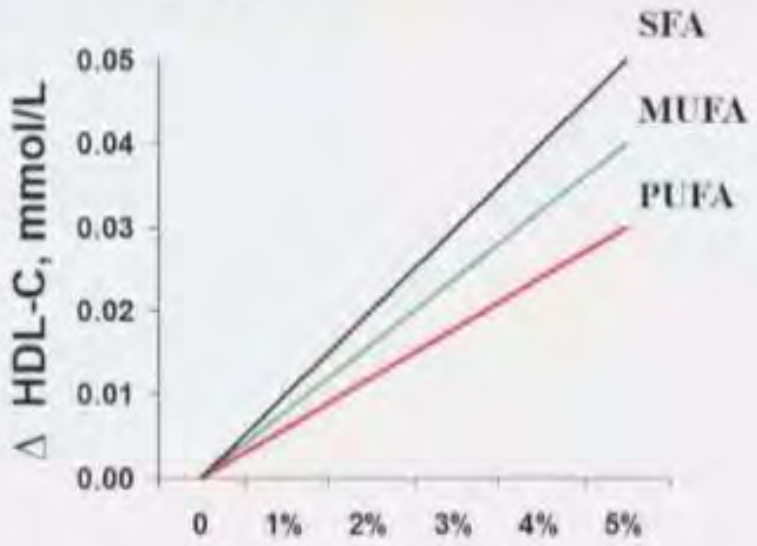
Association of Dietary Fats and Total and Cause-Specific Mortality

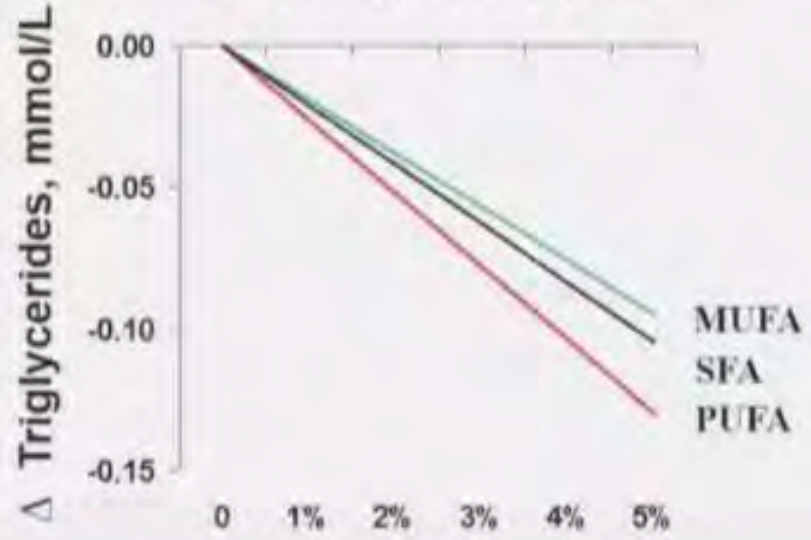
Figure 1. Change in Total Mortality Associated With Increases in the Percentage of Energy From Specific Types of Fat

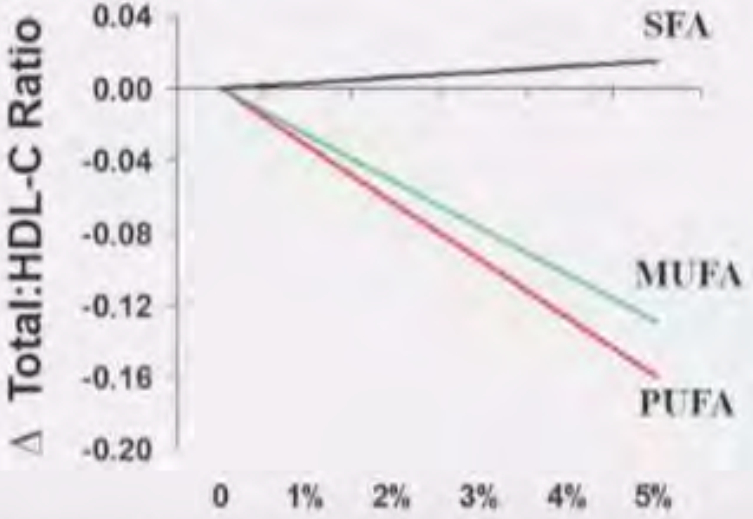


Dietary Fats & Blood Lipids









Tufts

Meta-analysis of 60 randomized feeding trials. Mensink & Katan, AJCN 2003

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SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

THE PRESENT AND FUTURE: COUNCIL PERSPECTIVES

Trending Cardiovascular Nutrition Controversies

Andrew M. Freeman, MD,[a] Pamela B. Morris, MD,[b] Neal Barnard, MD,[c] Caldwell B. Esselstyn, MD,[d] Emilio Ros, MD, PhD,[e] Arthur Agatston, MD,[f] Stephen Devries, MD,[g,h] James O'Keefe, MD,[i] Michael Miller, MD,[j] Dean Ornish, MD,[k] Kim Williams, MD,[l] Penny Kris-Etherton, PhD[m]

ABSTRACT

The potential cardiovascular benefits of several trending foods and dietary patterns are still incompletely understood, and nutritional science continues to evolve. However, in the meantime, a number of controversial dietary patterns, foods, and nutrients have received significant media exposure and are mired by hype. This review addresses some of the more popular foods and dietary patterns that are promoted for cardiovascular health to provide clinicians with accurate information for patient discussions in the clinical setting. (J Am Coll Cardiol 2017;69:1172–87)

NUTRITION AND CARDIOVASCULAR DISEASE

based dietary patterns with accompanying specific

CENTRAL ILLUSTRATION: Evidence for Cardiovascular Health Impact of Foods Reviewed

Summary of heart-harmful and heart-healthy foods/diets

Evidence of harm; limit or avoid

- **Coconut oil** and **palm oil** are high in saturated fatty acids and raise cholesterol
- **Eggs** have a serum cholesterol-raising effect
- **Juicing** of fruits/vegetables with pulp removal increases caloric concentration*
- **Southern diets** (added fats and oils, fried foods, eggs, organ and processed meats, sugar-sweetened drinks)

Inconclusive evidence; for harm or benefit

- **Virgin coconut oil**
- High-dose antioxidant **supplements**
- **Juicing** of fruits/vegetables without pulp removal*
- **Gluten-containing foods** (for people without gluten-related disease)

Evidence of benefit; recommended

- **Extra-virgin olive oil** reduces some CVD outcomes when consumed in moderate quantities
- **Blueberries** and **strawberries** (>3 servings/week) induce protective antioxidants
- 30 g serving of **nuts**/day. Portion control is necessary to avoid weight gain.†
- **Green leafy vegetables** have significant cardio-protective properties when consumed daily
- **Plant-based proteins** are significantly more heart-healthy compared to animal proteins

Freeman, A.M. et al. J Am Coll Cardiol. 2017;69(9):1172-87.

JAMA Internal Medicine | Original Investigation

Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality

Mingyang Song, MD, ScD; Teresa T. Fung, ScD; Frank B. Hu, MD, PhD; Walter C. Willett, MD, DrPH; Valter D. Longo, PhD; Andrew T. Chan, MD, MPH; Edward L. Giovannucci, MD, ScD

IMPORTANCE Defining what represents a macronutritionally balanced diet remains an open question and a high priority in nutrition research. Although the amount of protein may have specific effects, from a broader dietary perspective, the choice of protein sources will inevitably influence other components of diet and may be a critical determinant for the health outcome.

OBJECTIVE To examine the associations of animal and plant protein intake with the risk for mortality.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study of US health care professionals included 131 342 participants from the Nurses' Health Study (1980 to end of follow-up on June 1, 2012) and Health Professionals Follow-up Study (1986 to end of follow-up on January 31, 2012). Animal and plant protein intake was assessed by regularly updated validated food frequency questionnaires. Data were analyzed from June 20, 2014, to January 18, 2016.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for all-cause and cause-specific mortality.

RESULTS Of the 131 342 participants, 85 013 were women (64.7%) and 46 329 were men (35.3%) (mean [SD] age, 49 [9] years). The median protein intake, as assessed by percentage of energy, was 14% for animal protein (5th-95th percentile, 9%-22%) and 4% for plant protein (5th-95th percentile, 2%-6%). After adjusting for major lifestyle and dietary risk factors, animal protein intake was not associated with all-cause mortality (HR, 1.02 per 10% energy increment; 95% CI, 0.98-1.05; *P* for trend = .33) but was associated with higher cardiovascular mortality (HR, 1.08 per 10% energy increment; 95% CI, 1.01-1.16; *P* for trend = .04). Plant protein was associated with lower all-cause mortality (HR, 0.90 per 3% energy increment; 95% CI, 0.86-0.95; *P* for trend < .001) and cardiovascular mortality (HR, 0.88 per 3% energy increment; 95% CI, 0.80-0.97; *P* for trend = .007). These associations were confined to participants with at least 1 unhealthy lifestyle factor based on smoking, heavy alcohol intake, overweight or obesity, and physical inactivity, but not evident among those without any of these risk factors. Replacing animal protein of various origins with plant protein was associated with lower mortality. In particular, the HRs for all-cause mortality were 0.66 (95% CI, 0.59-0.75) when 3% of energy from plant protein was substituted for an equivalent amount of protein from processed red meat, 0.88 (95% CI, 0.84-0.92) from unprocessed red meat, and 0.81 (95% CI, 0.75-0.88) from egg.

CONCLUSIONS AND RELEVANCE High animal protein intake was positively associated with cardiovascular mortality and high plant protein intake was inversely associated with all-cause and cardiovascular mortality, especially among individuals with at least 1 lifestyle risk factor. Substitution of plant protein for animal protein, especially that from processed red meat, was associated with lower mortality, suggesting the importance of protein source.

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Supplemental content
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Author Affiliations: Author affiliations are listed at the end of this article.

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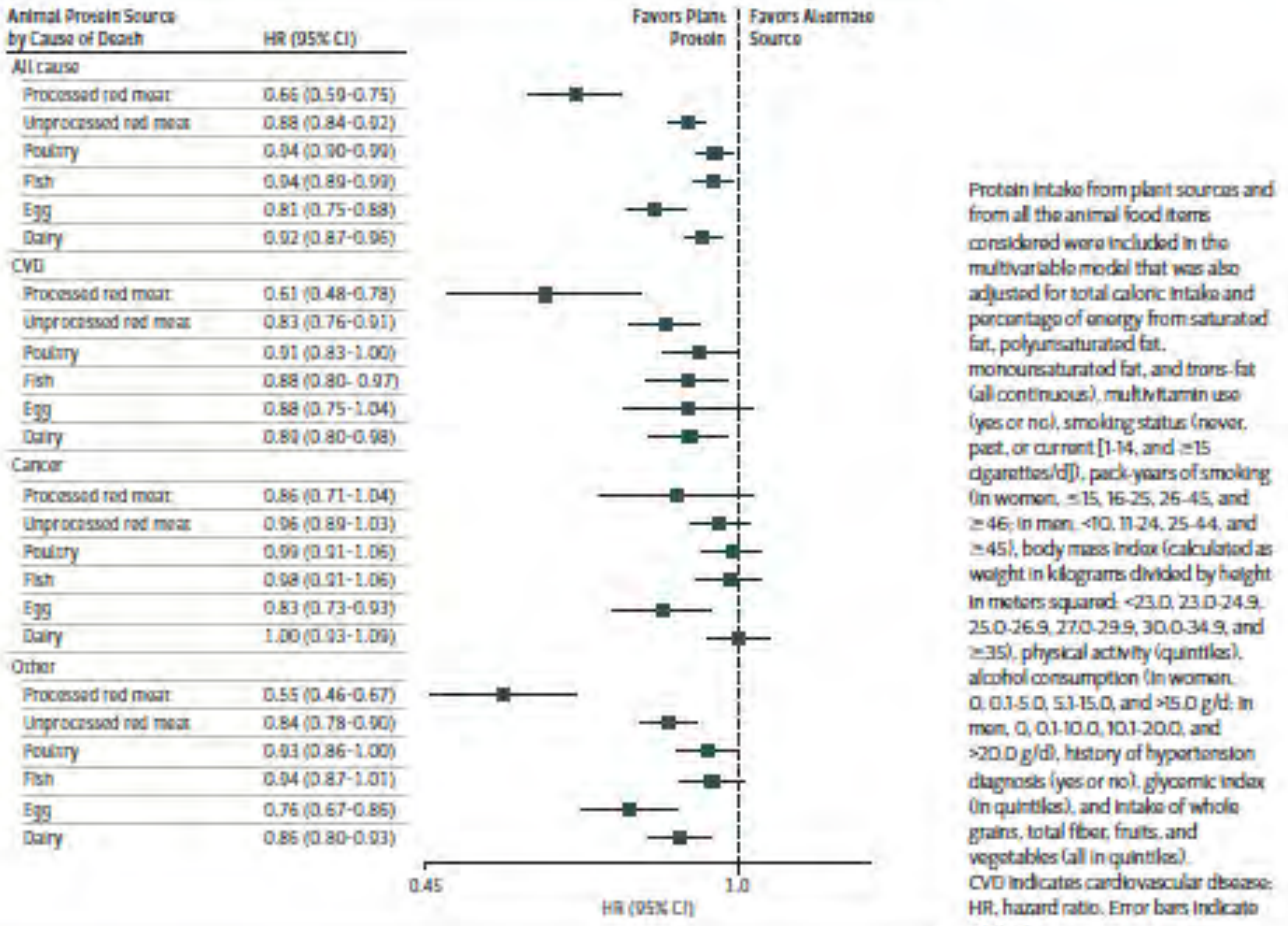
Figure. Risk for Mortality Associated With Replacement of 3% Energy From Various Animal Protein Sources With Plant Protein



Protein intake from plant sources and from all the animal food items considered were included in the multivariable model that was also adjusted for total caloric intake and percentage of energy from saturated fat, polyunsaturated fat, monounsaturated fat, and trans-fat (all continuous), multivitamin use (yes or no), smoking status (never, past, or current [1-14, and ≥15 cigarettes/d]), pack-years of smoking (in women, <15, 16-25, 26-45, and ≥46; in men, <10, 11-24, 25-44, and ≥45), body mass index (calculated as weight in kilograms divided by height in meters squared; <23.0, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-34.9, and ≥35), physical activity (quintiles), alcohol consumption (in women, 0, 0.1-5.0, 5.1-15.0, and >15.0 g/d; in men, 0, 0.1-10.0, 10.1-20.0, and >20.0 g/d), history of hypertension diagnosis (yes or no), glycemic index (in quintiles), and intake of whole grains, total fiber, fruits, and vegetables (all in quintiles). CVD indicates cardiovascular disease; HR, hazard ratio. Error bars indicate 95% CIs.

Gras et acides gras

Gras saturés
Gras animal, beurre, saindoux, huiles tropicales

Gras insaturés

Gras « trans »
Huiles hydrogénées shortening, margarines

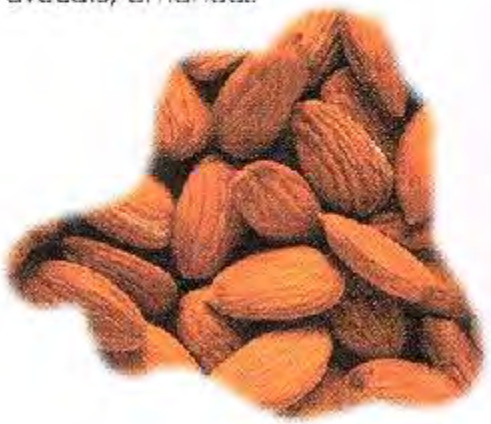
Gras polyinsaturés

Gras mono-insaturés

Acides gras oméga-6
Huiles végétales (maïs, tournesol...)
Pro-inflammatoires
Procancéreux

Acides gras oméga-3
Sardine, maquereau, saumon, graines de lin, soja, noix
Anti-inflammatoires
Anticancéreux

Acides gras oméga-9
Huiles d'olive, de canola, avocats, amandes



Original Investigation

Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial
A Randomized Clinical Trial

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IMPORTANCE Breast cancer is the leading cause of female cancer burden, and its incidence has increased by more than 20% worldwide since 2008. Some observational studies have suggested that the Mediterranean diet may reduce the risk of breast cancer.

OBJECTIVE To evaluate the effect of 2 interventions with Mediterranean diet vs the advice to follow a low-fat diet (control) on breast cancer incidence.

DESIGN, SETTING, AND PARTICIPANTS The PREDIMED study is a 1:1:1 randomized, single-blind, controlled field trial conducted at primary health care centers in Spain. From 2003 to 2009, 4282 women aged 60 to 80 years and at high cardiovascular disease risk were recruited after invitation by their primary care physicians.

INTERVENTIONS Participants were randomly allocated to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat).

MAIN OUTCOMES AND MEASURES Breast cancer incidence was a prespecified secondary outcome of the trial for women without a prior history of breast cancer (n = 4152).

RESULTS After a median follow-up of 4.8 years, we identified 35 confirmed incident cases of breast cancer. Observed rates (per 1000 person-years) were 1.1 for the Mediterranean diet with extra-virgin olive oil group, 1.8 for the Mediterranean diet with nuts group, and 2.9 for the control group. The multivariable-adjusted hazard ratios vs the control group were 0.32 (95% CI, 0.13-0.79) for the Mediterranean diet with extra-virgin olive oil group and 0.59 (95% CI, 0.26-1.35) for the Mediterranean diet with nuts group. In analyses with yearly cumulative updated dietary exposures, the hazard ratio for each additional 5% of calories from extra-virgin olive oil was 0.72 (95% CI, 0.57-0.90).

CONCLUSIONS AND RELEVANCE This is the first randomized trial finding an effect of a long-term dietary intervention on breast cancer incidence. Our results suggest a beneficial effect of a Mediterranean diet supplemented with extra-virgin olive oil in the primary prevention of breast cancer. These results come from a secondary analysis of a previous trial and are based on few incident cases and, therefore, need to be confirmed in longer-term and larger studies.

Editor's Note

Supplemental content at jamainternalmedicine.com

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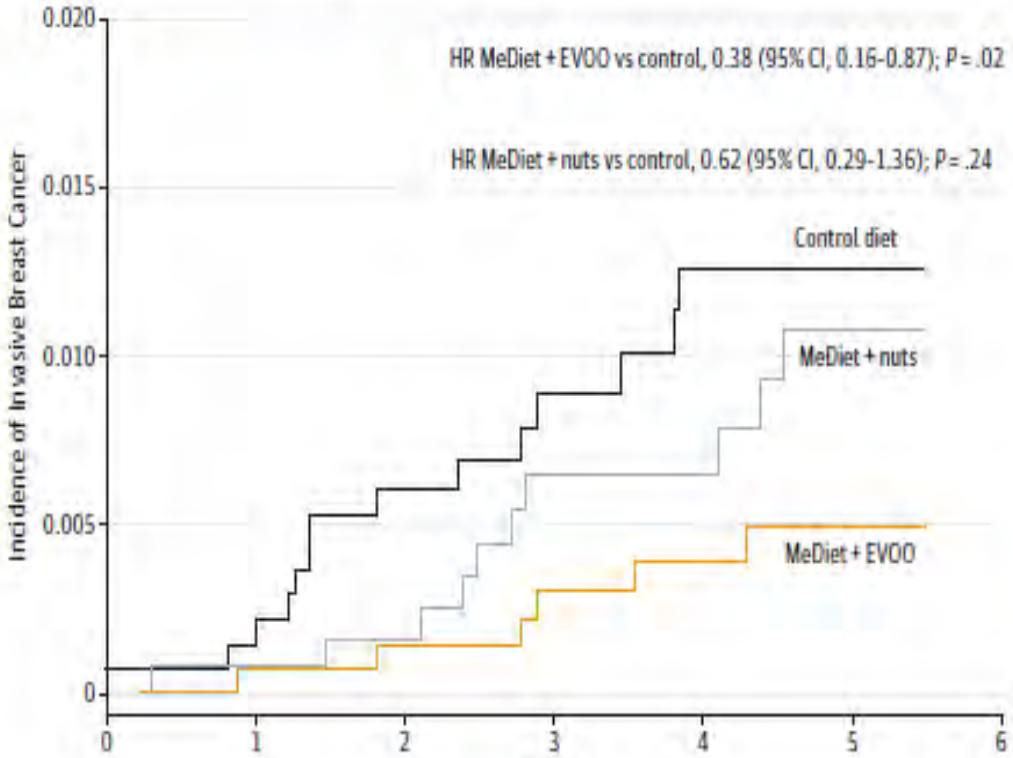
Group Information: The PREDIMED (Prevención con Dieta Mediterránea)

Figure 1. Incidence of Invasive Breast Cancer, According to the Intervention Group



No. at risk						
MeDiet + EVOO	1476	1463	1369	1184	1013	785
MeDiet + nuts	1285	1271	1117	879	741	532
Control diet	1391	1353	1209	940	759	573

Hazard ratios were obtained from Cox regression models.
EVOO indicates extra-virgin olive oil;
HR, hazard ratio;
MeDiet, Mediterranean diet.

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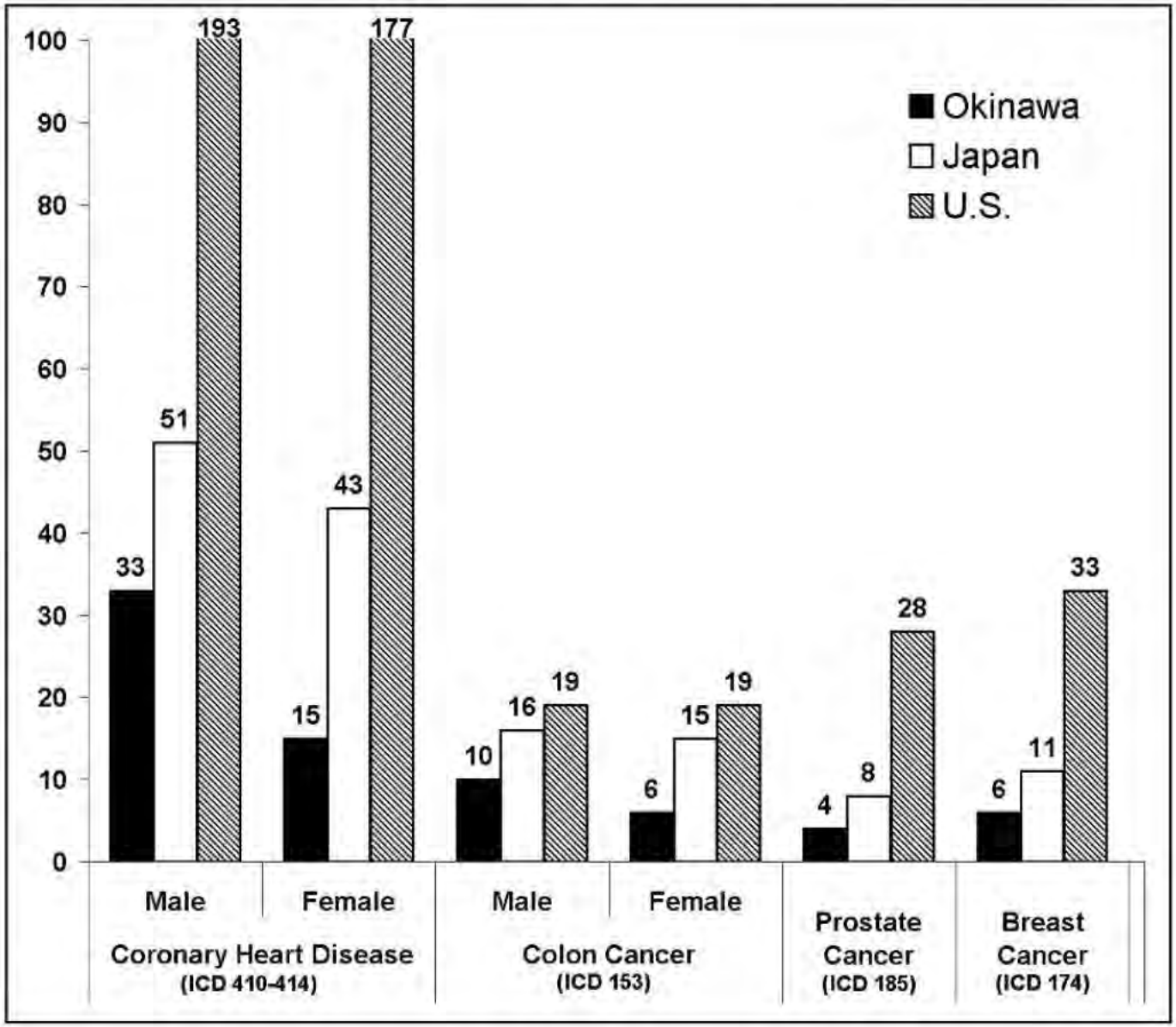
The Okinawan Diet: Health Implications of a Low-Calorie, Nutrient-Dense, Antioxidant-Rich Dietary Pattern Low in Glycemic Load

D. Craig Willcox PhD, Bradley J. Willcox MD, Hidemi Todoriki PhD & Makoto Suzuki MD, PhD



Mortality rates from coronary heart disease and cancers in Okinawans, Japanese, and Americans [1].

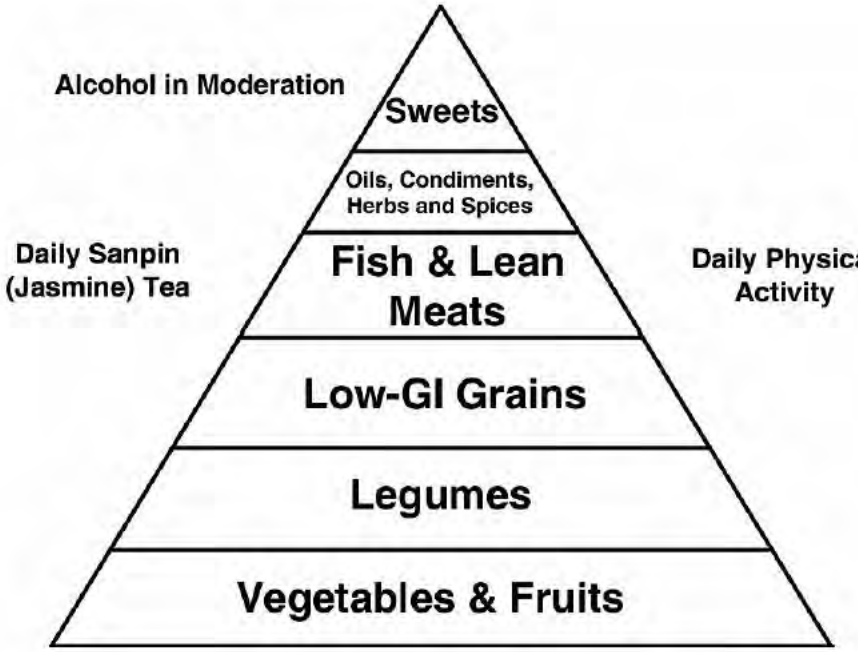


Fig. 2. Traditional Okinawan diet food pyramid.

3) Moderate consumption of fish products (especially in coastal areas),
4) Low consumption of meat and meat products,
5) Low consumption of dairy products,
6) Moderate alcohol consumption,
7) Low caloric intake,
8) Rich in omega-3 fats,
9) High monounsaturated-to-saturated-fat ratio, and
10) Emphasis on low-GI carbohydrates.

Articles

Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study

Kay-Tee Khaw, Sheila Bingham, Ailsa Welch, Robert Luben, Nicholas Wareham, Suzy Oakes, Nicholas Day

Summary

Background Ascorbic acid (vitamin C) might be protective for several chronic diseases. However, findings from prospective studies that relate ascorbic acid to cardiovascular disease or cancer are not consistent. We aimed to assess the relation between plasma ascorbic acid and subsequent mortality due to all causes, cardiovascular disease, ischaemic heart disease, and cancer.

Methods We prospectively examined for 4 years the relation between plasma ascorbic acid concentrations and mortality due to all causes, and to cardiovascular disease, ischaemic heart disease, and cancer in 19 496 men and women aged 45–79 years. We recruited individuals by post using age-sex registers of general practices. Participants completed a health and lifestyle questionnaire and were examined at a clinic visit. They were followed-up for causes of death for about 4 years. Individuals were divided into sex-specific quintiles of plasma ascorbic acid. We used the Cox proportional hazard model to determine the effect of ascorbic acid and other risk factors on mortality.

Findings Plasma ascorbic acid concentration was inversely related to mortality from all-causes, and from cardiovascular disease, and ischaemic heart disease in men and women. Risk of mortality in the top ascorbic acid quintile was about half the risk in the lowest quintile ($p<0·0001$). The relation with mortality was continuous through the whole distribution of ascorbic acid concentrations. 20 μmol/L rise in plasma ascorbic acid concentration, equivalent to about 50 g per day increase in fruit and vegetable intake, was associated with about a 20% reduction in risk of all-cause mortality ($p<0·0001$), independent of age, systolic blood pressure, blood cholesterol, cigarette smoking habit, diabetes, and supplement use. Ascorbic acid was inversely related to cancer mortality in men but not women.

Interpretation Small increases in fruit and vegetable intake of about one serving daily has encouraging prospects for possible prevention of disease.

Lancet 2001; **357:** 657–63

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Introduction

The role of antioxidants in chronic diseases such as cardiovascular disease and cancer is controversial. Evidence from prospective studies suggests that a high dietary intake of antioxidants is protective for cardiovascular disease and cancer, although findings have not been consistent and trial data have not been conclusive.[1–3] Ascorbic acid (vitamin C) plays a part in many biological processes, including free radical scavenging, collagen and hormone synthesis, haemostasis, and protection of lipid membranes which might affect chronic disease risk.[4–13] Investigators in some prospective studies have shown a significant inverse relation between ascorbic acid and cancer or cardiovascular disease, but the protective concentration and the potential size of the relation have varied between these studies. Results of some studies show only increased risk of mortality or cardiovascular disease at very low concentrations,[12] but no effect within the usual population range; conversely, those of others indicate only reduced risk in individuals with high concentrations or those who take supplements.[12] Findings from trials on the effect of supplementation have shown no change in mortality, but these trials have been generally small and of short duration.[14,15] Most studies have been in men or with data for men and women pooled. Data for women alone are more inconsistent than data on men.[13]

We present data from a prospective population study examining the relation between plasma ascorbic acid and subsequent mortality due to all causes, cardiovascular disease, ischaemic heart disease, and cancer in men and women.

Methods

Participants

The individuals in this analysis were part of EPIC-Norfolk, a prospective population study of 30 466 men and women aged between 45 and 79 years, resident in Norfolk, UK, who completed a baseline questionnaire survey, and of whom 25 663 attended a clinic visit.[16] They were recruited from age-sex registers of general practices in Norfolk as part of a nine-country collaborative study (EPIC, European Prospective Investigation into Cancer and Nutrition) designed to investigate dietary and other determinants of cancer. We obtained additional data for the EPIC-Norfolk cohort to enable the assessment of chronic disease determinants. Eligible participants were recruited by post. Because we requested individuals to provide detailed dietary, biological and other health data, and to be followed up over a few years, we had about a 45% response rate, so participants were not a random population sample. Nevertheless, they were closely similar to UK population samples with respect to many characteristics, including anthropometry, blood pressure, and lipids, but with a lower proportion of smokers.[16]

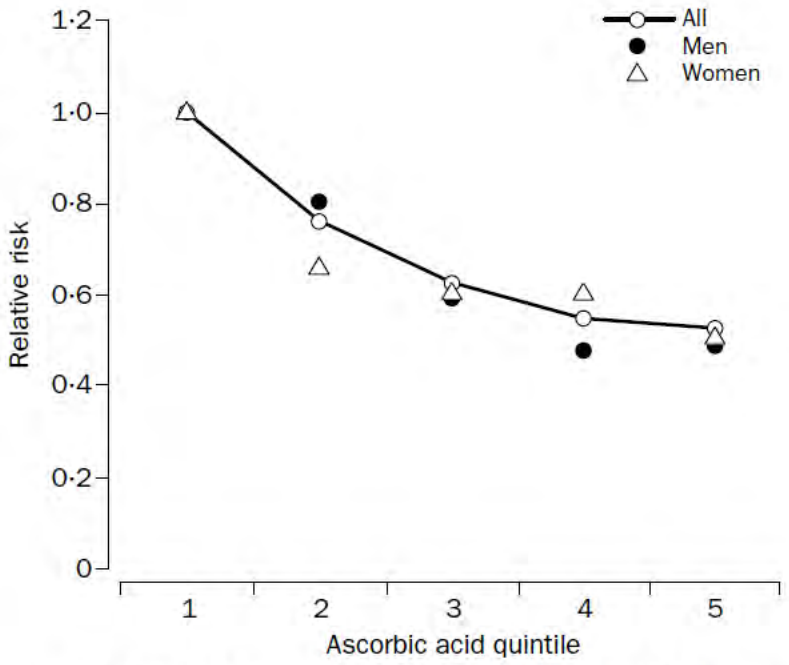

Figure 1: **Relative risk of total mortality by quintile of plasma ascorbic acid**
Age-adjusted and sex adjusted Cox regression model for relative risk, including a quadratic term for ascorbic-acid.

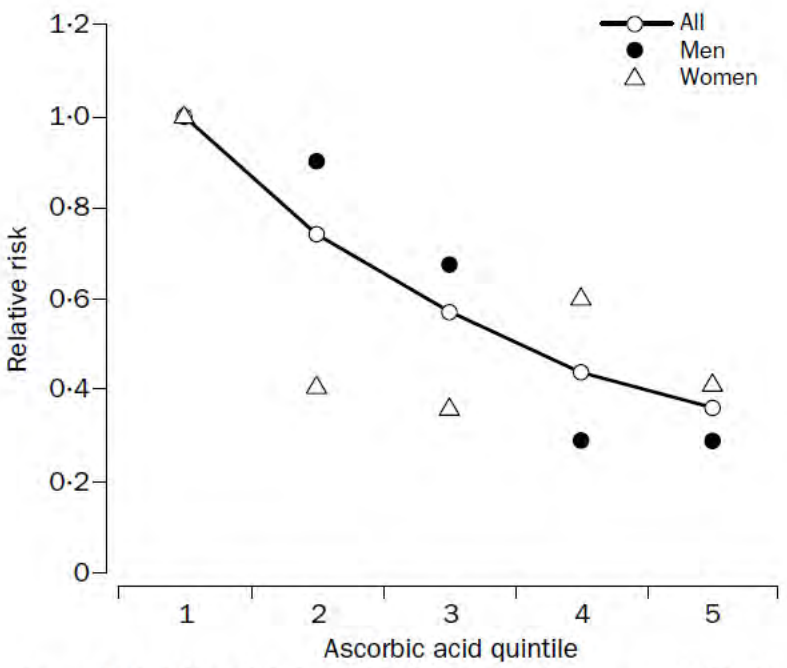

Figure 2: **Relative risk for cardiovascular disease mortality by quintile of plasma ascorbic acid**
Age-adjusted and sex-adjusted Cox regression model for relative risk, including a quadratic term for ascorbic acid.

MJ

Ten Years of Life

Is It a Matter of Choice?

Gary E. Fraser, MB, ChB, PhD; David J. Shavlik, MSPH

Background: Relative risk estimates suggest that effective implementation of behaviors commonly advocated in preventive medicine should increase life expectancy, although there is little direct evidence.

Objective: To test the hypothesis that choices regarding diet, exercise, and smoking influence life expectancy.

Methods: A total of 34 192 California Seventh-Day Adventists (75% of those eligible) were enrolled in a cohort and followed up from 1976 to 1988. A mailed questionnaire provided dietary and other exposure information at study baseline. Mortality for all subjects was ascertained by matching to state death tapes and the National Death Index.

Results: California Adventists have higher life expectancies at the age of 30 years than other white Californians by 7.28 years (95% confidence interval, 6.59-7.97 years) in men and by 4.42 years (95% confidence interval, 3.96-4.88 years) in women, giving them perhaps the highest life expectancy of any formally described population. Commonly observed combinations of diet, exercise, body mass index, past smoking habits, and hormone replacement therapy (in women) can account for differences of up to 10 years of life expectancy among Adventists. A comparison of life expectancy when these factors take high-risk compared with low-risk values shows independent effects that vary between 1.06 and 2.74 years for different variables. The effect of each variable is assessed with all others at either medium- or high-risk levels.

Conclusions: Choices regarding diet, exercise, cigarette smoking, body weight, and hormone replacement therapy, in combination, appear to change life expectancy by many years. The longevity experience of Adventists probably demonstrates the beneficial effects of more optimal behaviors.

Arch Intern Med. 2001;161:1645-1652

Table 5. Expected Length of Life at Birth and at the Age of 65 Years: California Adventists Compared With International Populations

	Length of Life, y			
	Men		Women	
Country (Year)	At Birth	At Age 65 y	At Birth	At Age 65 y
Australia (1990)	73.9	15.2	80.0	19.0
Canada (1985-1987)	73.0	14.9	79.7	19.1
Denmark (1989-1990)	72.0	14.1	77.7	17.9
Finland (1989)	70.9	13.8	78.9	17.7
Iceland (1989-1990)	75.7	16.1	80.3	19.3
Japan (1990)	75.9	16.2	81.8	19.9
New Zealand (1987-1989)	71.6	14.1	77.6	17.8
Norway (1990)	73.4	14.6	79.8	18.6
United Kingdom (1985-1987)	71.9	13.4	77.6	17.3
United States (1990)	73.0	14.9	79.7	19.1
California Adventists (1980-1988)*	78.5	19.1	82.3	21.6
Vegetarians	80.2	20.3	84.8	22.6

*Hazards for those aged 0 to 29 years are those from California State data, as data for these ages are not available for Adventists. Non-Adventist data are taken from international longevity comparisons (1992).[22]

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Usefulness of Vegetarian and Vegan Diets for Treating Type 2 Diabetes

Caroline B. Trapp · Neal D. Barnard

Published online: 9 March 2010

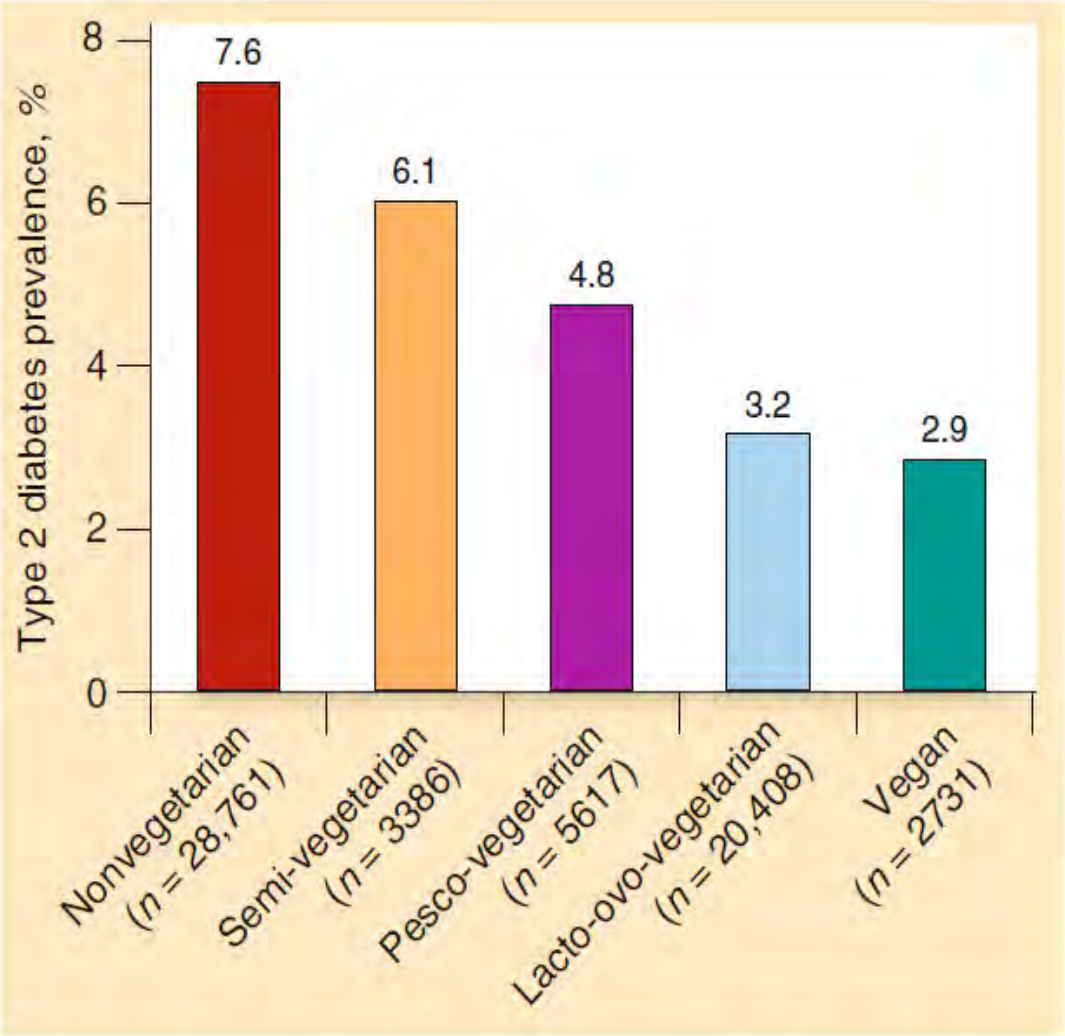

Fig. 1 The Adventist Health Study-2, with 60,903 participants, ≥30 years of age, enrolled from 2002 to 2006. (*Adapted from* Tonstad et al. [18••].)

Table 1 Components of a low-fat, plant-based diet

Ad libitum[a] foods from four food groups: whole grains, legumes (beans, peas, and lentils), vegetables, and fruits
Limit or avoid added vegetable oils and other high-fat foods for weight and glycemic control. Use nuts and seeds sparingly (to top a salad or oatmeal; not as a snack)
Unprocessed and minimally processed foods are best
Choosing low glycemic index foods (eg, old-fashioned oatmeal, sweet potatoes, pasta, grains, most fruits and vegetables) may have an additional benefit
≥40 g of fiber from whole foods per day is recommended
Avoid all animal products
B12 supplementation of 5 μg/d (eg, a common multivitamin) is recommended for anyone avoiding animal products and all people over 50 years of age
A macronutrient profile of ~75% to 80% of energy from carbohydrate, 10% to 15% from protein, and 10% from fat is recommended

[a] Those individuals who adjust insulin based on carbohydrate intake will still need to count carbohydrates; Insulin requirements may change, requiring dose adjustment

Non-Profit Produces First-Ever Agreement on Overall Principles of Healthy Eating

PR Newswire – BOSTON, MA (November 19, 2015)

agreement. Scientific co-chairs Dr. Walter Willett, Nutrition Chair of the Harvard School of Public Health and Dr. David Katz, Founding Director of the Yale Prevention Research Center, led the group in a two-day debate dissecting scientific studies and comparing diets to arrive at a clear outline of what healthy eating entails, agreeing on standards and sources of evidence, and the need to base judgments on the weight of evidence.

"The foods that define a healthy diet include abundant fruits, vegetables, nuts, whole grains, legumes and minimal amounts of refined starch, sugar and red meat, especially keeping processed red meat intake low. When you put it all together, that's a lot of common ground."

EN RÉSUMÉ

EAT FOOD,
MOSTLY PLANTS,
NOT TOO MUCH.

M Pollan

MEDICAL SCIENCE

Can lifestyle changes reverse coronary heart disease?

The Lifestyle Heart Trial

DEAN ORNISH SHIRLEY E. BROWN LARRY W. SCHERWITZ
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RICHARD J. BRAND K. LANCE GOULD

In a prospective, randomised, controlled trial to determine whether comprehensive lifestyle changes affect coronary atherosclerosis after 1 year, 28 patients were assigned to an experimental group (low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise) and 20 to a usual-care control group. 195 coronary artery lesions were analysed by quantitative coronary angiography. The average percentage diameter stenosis regressed from 40·0 (SD 16·9)% to 37·8 (16·5)% in the experimental group yet progressed from 42·7 (15·5)% to 46·1 (18·5)% in the control group. When only lesions greater than 50% stenosed were analysed, the average percentage diameter stenosis regressed from 61·1 (8·8)% to 55·8 (11·0)% in the experimental group and progressed from 61·7 (9·5)% to 64·4 (16·3)% in the control group. Overall, 82% of experimental-group patients had an average change towards regression. Comprehensive lifestyle changes may be able to bring about regression of even severe coronary atherosclerosis after only 1 year, without use of lipid-lowering drugs.

Lancet 1990; **336**: 129-33.

Introduction

The Lifestyle Heart Trial is the first randomised, controlled clinical trial to determine whether patients outside hospital can be motivated to make and sustain comprehensive lifestyle changes and, if so, whether regression of coronary atherosclerosis can occur as a result of lifestyle changes alone. Over twenty clinical trials are being carried out to determine whether the progression of coronary atherosclerosis can be modified; in all of these, cholesterol-lowering drugs, plasmapheresis, or partial ileal bypass surgery are the primary interventions.[1]

We carried out trials in 1977 and 1980 to assess the short-term effects of lifestyle changes on coronary heart disease with non-invasive endpoint measures (improvements in cardiac risk factors, functional status, myocardial perfusion,[2] and left ventricular function[3]). However, the subjects of those studies were not living in the community during the trial, and we did not use angiography to assess changes in coronary atherosclerosis.

Patients and methods

Patients with angiographically documented coronary artery disease were randomly assigned to an experimental group or to a usual-care control group. Experimental-group patients were prescribed a lifestyle programme that included a low-fat vegetarian diet, moderate aerobic exercise, stress management training, stopping smoking, and group support. Control-group patients were not asked to make lifestyle changes, although they were free to do so. Progression or regression of coronary artery lesions was assessed in both groups by quantitative coronary angiography at baseline and after about a year.

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Intensive Lifestyle Changes for Reversal of Coronary Heart Disease

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Context.—The Lifestyle Heart Trial demonstrated that intensive lifestyle changes may lead to regression of coronary atherosclerosis after 1 year.

Objectives.—To determine the feasibility of patients to sustain intensive lifestyle changes for a total of 5 years and the effects of these lifestyle changes (without lipid-lowering drugs) on coronary heart disease.

Design.—Randomized controlled trial conducted from 1986 to 1992 using a randomized invitational design.

Patients.—Forty-eight patients with moderate to severe coronary heart disease were randomized to an intensive lifestyle change group or to a usual-care control group, and 35 completed the 5-year follow-up quantitative coronary arteriography.

Setting.—Two tertiary care university medical centers.

Intervention.—Intensive lifestyle changes (10% fat whole foods vegetarian diet, aerobic exercise, stress management training, smoking cessation, group psychosocial support) for 5 years.

Main Outcome Measures.—Adherence to intensive lifestyle changes, changes in coronary artery percent diameter stenosis, and cardiac events.

Results.—Experimental group patients (20 [71%] of 28 patients completed 5-year follow-up) made and maintained comprehensive lifestyle changes for 5 years, whereas control group patients (15 [75%] of 20 patients completed 5-year follow-up) made more moderate changes. In the experimental group, the average percent diameter stenosis at baseline decreased 1.75 absolute percentage points after 1 year (a 4.5% relative improvement) and by 3.1 absolute percentage points after 5 years (a 7.9% relative improvement). In contrast, the average percent diameter stenosis in the control group increased by 2.3 percentage points after 1 year (a 5.4% relative worsening) and by 11.8 percentage points after 5 years (a 27.7% relative worsening) ($P = .001$ between groups. Twenty-five cardiac events occurred in 28 experimental group patients vs 45 events in 20 control group patients during the 5-year follow-up (risk ratio for any event for the control group, 2.47 [95% confidence interval, 1.48-4.20]).

Conclusions.—More regression of coronary atherosclerosis occurred after 5 years than after 1 year in the experimental group. In contrast, in the control group, coronary atherosclerosis continued to progress and more than twice as many cardiac events occurred.

JAMA. 1998;280:2001-2007

From the Department of Medicine (Dr Ornish), and the Division of Cardiology (Dr Armstrong), California Pacific Medical Center, San Francisco; the Department of Medicine (Dr Ornish), the Division of Cardiology, Cardiac Catheterization Laboratory, Cardiovascular Research Institute (Dr Ports), and the Division of Biostatistics (Drs Brand and Hogeboom), School of Medicine, University of California, San Francisco; the Division of Cardiology, University of Texas Medical School, Houston (Drs Gould and Kirkeeide); and the Preventive Medicine Research Institute, Sausalito, Calif (Drs Ornish, Scherwitz, and Billings, Mr Sparler, and Ms Merritt).

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THE LIFESTYLE Heart Trial was the first randomized clinical trial to investigate whether ambulatory patients could be motivated to make and sustain comprehensive lifestyle changes and, if so, whether the progression of coronary atherosclerosis could be stopped or reversed without using lipid-lowering drugs as measured by computer-assisted quantitative coronary arteriography. This study derived from earlier studies that used noninvasive measures.[1,2]

After 1 year, we found that experimental group participants were able to make and maintain intensive lifestyle changes and had a 37.2% reduction in low-density lipoprotein (LDL) cholesterol levels and a 91% reduction in the frequency of anginal episodes.[3] Average percent diameter stenosis regressed from 40.0% at baseline to 37.8% 1 year later, a change that was correlated with the degree of lifestyle change. In contrast, patients in the usual-care control group made more moderate changes in lifestyle, reduced LDL cholesterol levels by 6%, and had a 165% increase in the frequency of reported anginal episodes. Average percent diameter stenosis progressed from 42.7% to 46.1%.

Given these encouraging findings, we extended the study for an additional 4 years to determine (1) the feasibility of patients sustaining intensive changes in diet and lifestyle for a much longer time, and (2) the effects of these changes on risk factors, coronary atherosclerosis, myocardial perfusion, and cardiac events after 4 additional years.

METHODS

The design, recruitment, and study population were previously described.[3,4] In brief, we recruited men and women

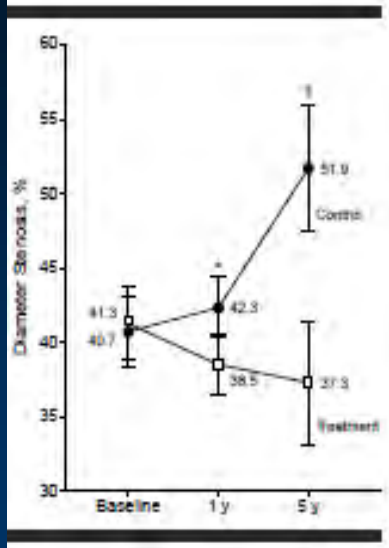

Figure 1.—Mean percentage diameter stenosis in treatment and control groups at baseline, 1 year, and 5 years. Error bars represent SEM; asterisk, $P = .02$ by between-group 2-tailed test; dagger, $P = .001$ by between-group 2-tailed test.

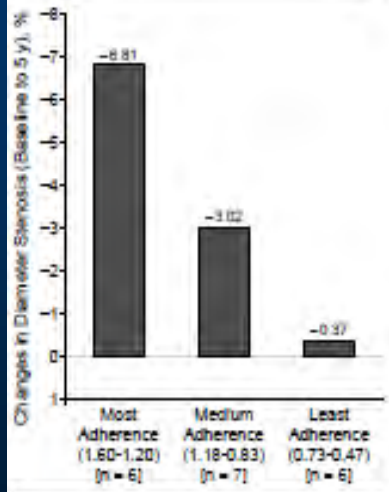

Figure 2.—Changes in percentage diameter stenosis by 5-year adherence tertiles for the experimental group.

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The authors reported no potential conflict of interest relevant to this article.

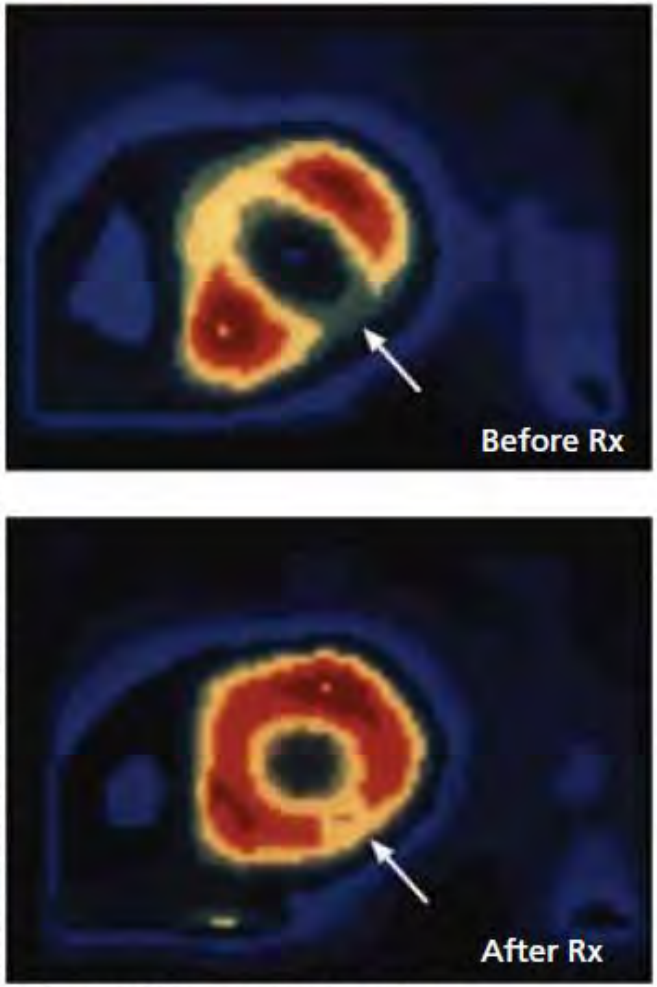
ORIGINAL RESEARCH

A way to reverse CAD?

Though current medical and surgical treatments manage coronary artery disease, they do little to prevent or stop it. Nutritional intervention, as shown in our study and others, has halted and even reversed CAD.

FIGURE 1

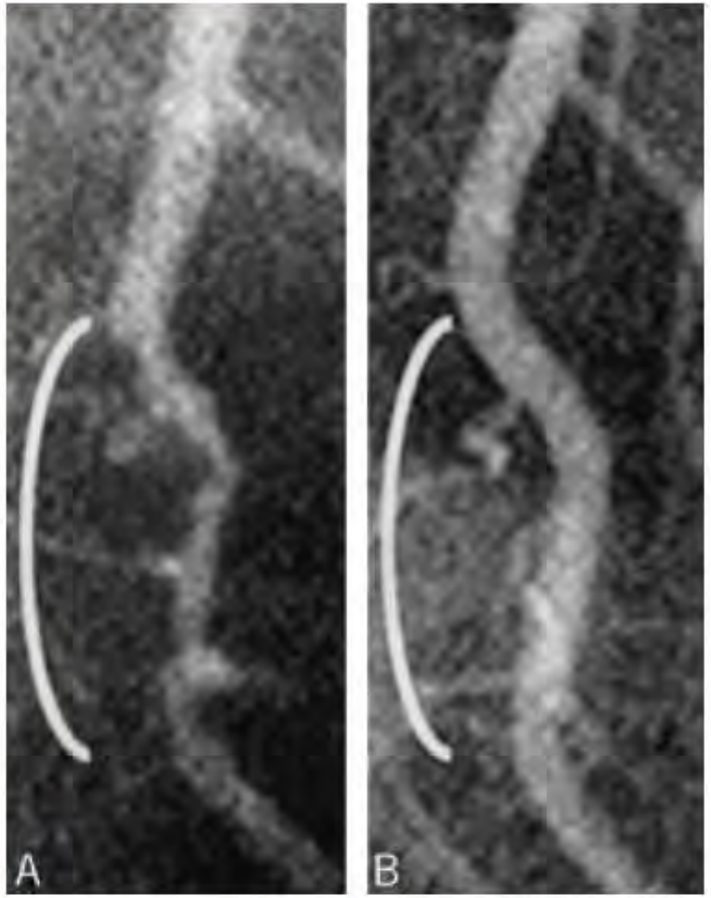
Restoration of myocardial perfusion[2]



Positron emission tomography performed on a patient with coronary artery disease shows an area of myocardium with insufficient blood flow (top). Following only 3 weeks of plant-based nutritional intervention, normal blood flow was restored (bottom).

FIGURE 2

Reversal of coronary artery disease[4]



Coronary angiography reveals a diseased distal left anterior descending artery (A). Following 32 months of a plant-based nutritional intervention without cholesterol-lowering medication, the artery regained its normal configuration (B).

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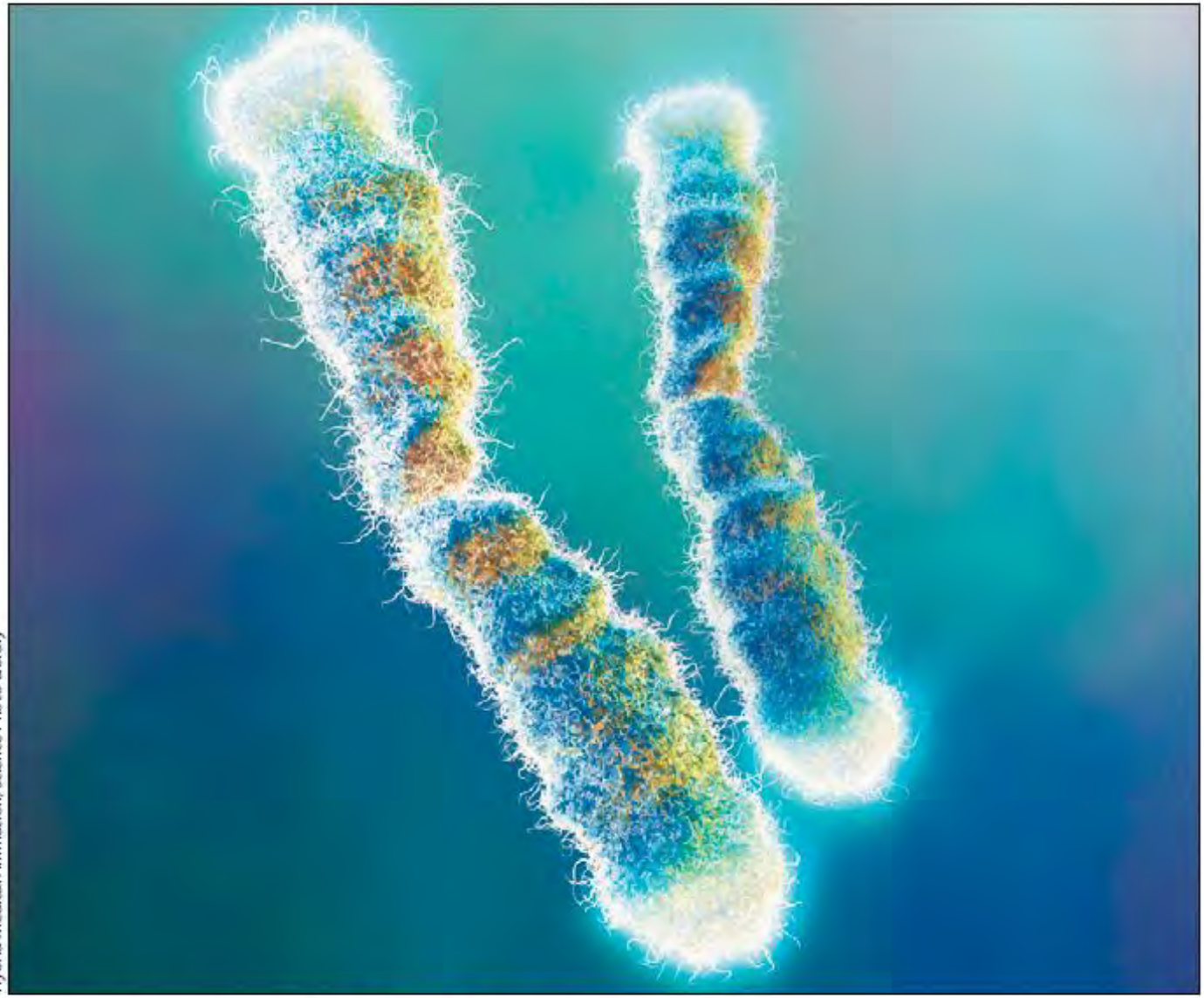

Telomeres help prevent the loss of genetic information

Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study

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Summary

Background Telomere shortness in human beings is a prognostic marker of ageing, disease, and premature morbidity. We previously found an association between 3 months of comprehensive lifestyle changes and increased telomerase activity in human immune-system cells. We followed up participants to investigate long-term effects.

Methods This follow-up study compared ten men and 25 external controls who had biopsy-proven low-risk prostate cancer and had chosen to undergo active surveillance. Eligible participants were enrolled between 2003 and 2007 from previous studies and selected according to the same criteria. Men in the intervention group followed a programme of comprehensive lifestyle changes (diet, activity, stress management, and social support), and the men in the control group underwent active surveillance alone. We took blood samples at 5 years and compared relative telomere length and telomerase enzymatic activity per viable cell with those at baseline, and assessed their relation to the degree of lifestyle changes.

Findings Relative telomere length increased from baseline by a median of 0·06 telomere to single-copy gene ratio (T/S) units (IQR −0·05 to 0·11) in the lifestyle intervention group, but decreased in the control group (−0·03 T/S units

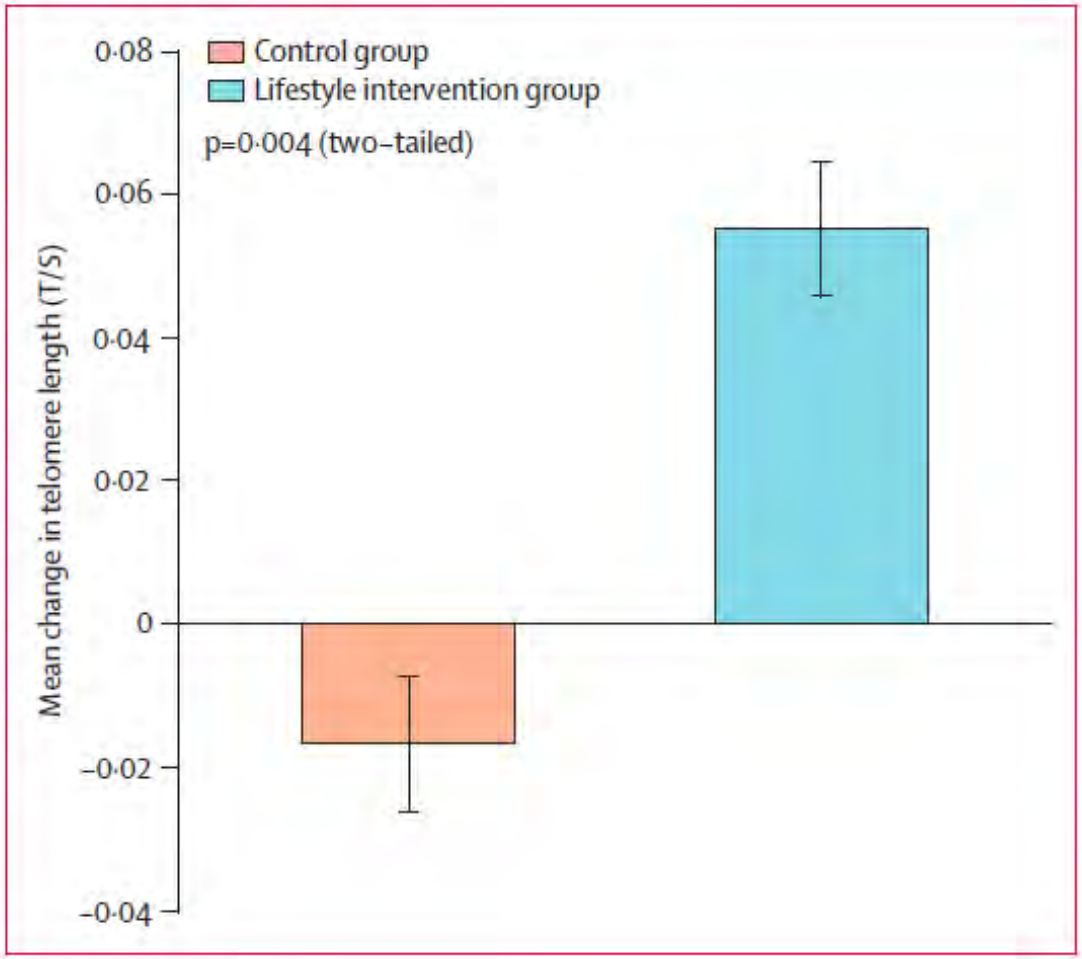

***Figure 1*: Mean change in relative telomere length over 5 years with lifestyle intervention compared with control**

Vertical lines represent 1 SEM. T/S=telomere to single-copy gene ratio units.

Genomics Data 4 (2015) 50–53

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Data in Brief

Gene expression profiling during intensive cardiovascular lifestyle modification: Relationships with vascular function and weight loss

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ipants and 63 matched controls to examine the impact of the lifestyle program on individual gene expression profiles and regulatory pathways important to cardiovascular health. Using ANOVA with FDR correction for multiple testing, we identified 143 genes that were differentially-expressed from baseline to 1 year in lifestyle participants but observed little change in gene expression among controls. Lifestyle modification reduced the expression of proinflammatory genes associated with neutrophil activation and molecular pathways that are important to vascular function [4].

Many genes with the largest fold-changes were significantly correlated with body mass index (BMI) throughout the lifestyle program;

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.

ABSTRACT

BACKGROUND

Both genetic and lifestyle factors contribute to individual-level risk of coronary artery disease. The extent to which increased genetic risk can be offset by a healthy lifestyle is unknown.

METHODS

Using a polygenic score of DNA sequence polymorphisms, we quantified genetic risk for coronary artery disease in three prospective cohorts — 7814 participants in the Atherosclerosis Risk in Communities (ARIC) study, 21,222 in the Women's Genome Health Study (WGHS), and 22,389 in the Malmö Diet and Cancer Study (MDCS) — and in 4260 participants in the cross-sectional BioImage Study for whom genotype and covariate data were available. We also determined adherence to a healthy lifestyle among the participants using a scoring system consisting of four factors: no current smoking, no obesity, regular physical activity, and a healthy diet.

RESULTS

The relative risk of incident coronary events was 91% higher among participants at high genetic risk (top quintile of polygenic scores) than among those at low genetic risk (bottom quintile of polygenic scores) (hazard ratio, 1.91; 95% confidence interval [CI], 1.75 to 2.09). A favorable lifestyle (defined as at least three of the four healthy lifestyle factors) was associated with a substantially lower risk of coronary events than an unfavorable lifestyle (defined as no or only one healthy lifestyle factor), regardless of the genetic risk category. Among participants at high genetic risk, a favorable lifestyle was associated with a 46% lower relative risk of coronary events than an unfavorable lifestyle (hazard ratio, 0.54; 95% CI, 0.47 to 0.63). This finding corresponded to a reduction in the standardized 10-year incidence of coronary events from 10.7% for an unfavorable lifestyle to 5.1% for a favorable lifestyle in ARIC, from 4.6% to 2.0% in WGHS, and from 8.2% to 5.3% in MDCS. In the BioImage Study, a favorable lifestyle was associated with significantly less coronary-artery calcification within each genetic risk category.

CONCLUSIONS

Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavorable lifestyle. (Funded by the National Institutes of Health and others.)

From the Center for Human Genetic Research and Cardiology Division, Massachusetts General Hospital (A.V.K., P.N., S.K.), and the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital (N.R.C., D.I.C., P.M.R.), Boston, and the Program in Medical and Population Genetics, Broad Institute, Cambridge (A.V.K., C.A.E., A.G.B., S.K.) — all in Massachusetts; the Department of Clinical Sciences, Lund University, Malmö, Sweden (I.D., O.M., M.O.-M.); the Cardiovascular Institute, Mount Sinai Medical Center, Icahn School of Medicine at Mount Sinai, New York (U.B., R.M., V.F.); Department of Genetics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (D.J.R.); and the University of Texas Health Science Center School of Public Health, Houston (E.B.). Address reprint requests to Dr. Kathiresan at the Center for Human Genetics Research, Massachusetts General Hospital, 185 Cambridge St., CPZN 5.252, Boston, MA 02114, or at skathiresan1@mgh.harvard.edu.

Drs. Khera and Emdin contributed equally to this article.

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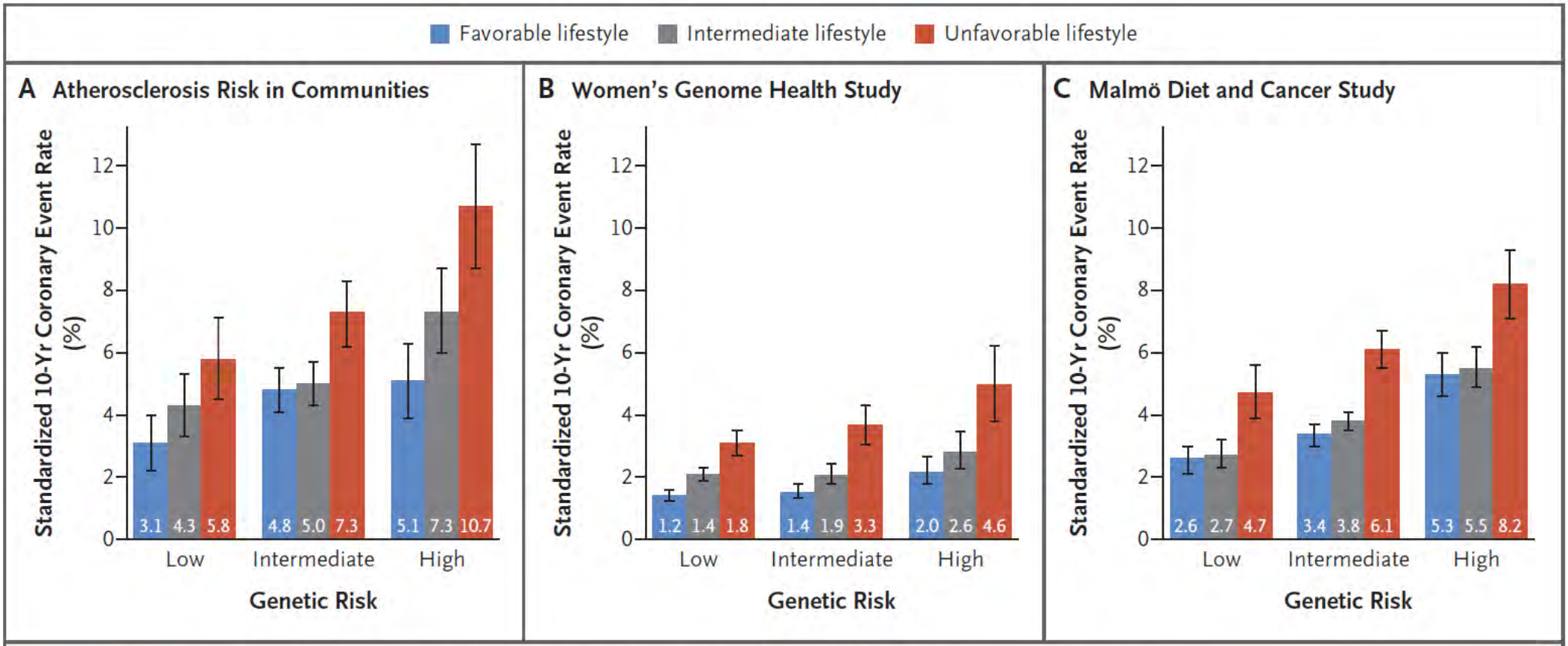

Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each covariate. The I bars represent 95% confidence intervals.

ORIGINAL INVESTIGATION

Meat Intake and Mortality

A Prospective Study of Over Half a Million People

Rashmi Sinha, PhD; Amanda J. Cross, PhD; Barry I. Graubard, PhD; Michael F. Leitzmann, MD, DrPH; Arthur Schatzkin, MD, DrPH

Background: High intakes of red or processed meat may increase the risk of mortality. Our objective was to determine the relations of red, white, and processed meat intakes to risk for total and cause-specific mortality.

Methods: The study population included the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study cohort of half a million people aged 50 to 71 years at baseline. Meat intake was estimated from a food frequency questionnaire administered at baseline. Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) within quintiles of meat intake. The covariates included in the models were age, education, marital status, family history of cancer (yes/no) (cancer mortality only), race, body

in the highest vs lowest quintile of red (HR, 1.31 [95% CI, 1.27-1.35], and HR, 1.36 [95% CI, 1.30-1.43], respectively) and processed meat (HR, 1.16 [95% CI, 1.12-1.20], and HR, 1.25 [95% CI, 1.20-1.31], respectively) intakes had elevated risks for overall mortality. Regarding cause-specific mortality, men and women had elevated risks for cancer mortality for red (HR, 1.22 [95% CI, 1.16-1.29], and HR, 1.20 [95% CI, 1.12-1.30], respectively) and processed meat (HR, 1.12 [95% CI, 1.06-1.19], and HR, 1.11 [95% CI 1.04-1.19], respectively) intakes. Furthermore, cardiovascular disease risk was elevated for men and women in the highest quintile of red (HR, 1.27 [95% CI, 1.20-1.35], and HR, 1.50 [95% CI, 1.37-1.65], respectively) and processed meat (HR, 1.09 [95% CI, 1.03-1.15], and HR, 1.38 [95% CI, 1.26-1.51], respectively) intakes. When comparing the highest with

Table 2. Multivariate Analysis for Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Men in the National Institutes of Health–AARP Diet and Health Study[a]

Mortality in Men (n=322 263)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
			Red Meat Intake[b]			
All mortality						
Deaths	6437	7835	9366	10 988	13 350	
Basic model[c]	1 [Reference]	1.07 (1.03-1.10)	1.17 (1.13-1.21)	1.27 (1.23-1.31)	1.48 (1.43-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.06 (1.03-1.10)	1.14 (1.10-1.18)	1.21 (1.17-1.25)	1.31 (1.27-1.35)	<.001
Cancer mortality						
Deaths	2136	2701	3309	3839	4448	
Basic model[c]	1 [Reference]	1.10 (1.04-1.17)	1.23 (1.16-1.29)	1.31 (1.24-1.39)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.05 (0.99-1.11)	1.13 (1.07-1.20)	1.18 (1.12-1.25)	1.22 (1.16-1.29)	<.001
CVD mortality						
Deaths	1997	2304	2703	3256	3961	
Basic model[c]	1 [Reference]	1.02 (0.96-1.08)	1.10 (1.04-1.17)	1.24 (1.17-1.31)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	0.99 (0.96-1.09)	1.08 (1.02-1.15)	1.18 (1.12-1.26)	1.27 (1.20-1.35)	<.001
Mortality from injuries and sudden deaths						
Deaths	184	216	228	280	343	
Basic model[c]	1 [Reference]	1.02 (0.84-1.24)	0.97 (0.80-1.18)	1.09 (0.90-1.31)	1.24 (1.03-1.49)	.01
Adjusted model[d]	1 [Reference]	1.06 (0.86-1.29)	1.01 (0.83-1.24)	1.14 (0.94-1.39)	1.26 (1.04-1.54)	.008
All other deaths						
Deaths	1268	1636	1971	2239	2962	
Basic model[c]	1 [Reference]	1.13 (1.05-1.22)	1.25 (1.17-1.35)	1.33 (1.24-1.42)	1.68 (1.57-1.80)	<.001
Adjusted model[d]	1 [Reference]	1.17 (1.09-1.26)	1.28 (1.19-1.38)	1.34 (1.25-1.44)	1.58 (1.47-1.70)	<.001

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http://www.biomedcentral.com/1741-7015/11/63

Metabolism, diet and disease

BMC Medicine

RESEARCH ARTICLE Open Access

Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition

Sabine Rohrmann[1,2*], Kim Overvad[3], H Bas Bueno-de-Mesquita[4,5], Marianne U Jakobsen[3], Rikke Egeberg[6], Anne Tjønneland[6], Laura Nailler[7,8], Marie-Christine Boutron-Ruault[7,8], Françoise Clavel-Chapelon[7,8], Vittorio Krogh[9], Domenico Palli[10], Salvatore Panico[11], Rosario Tumino[12], Fulvio Ricceri[13], Manuela M Bergmann[14], Heiner Boeing[14], Kuanrong Li[2], Rudolf Kaaks[2], Kay-Tee Khaw[15], Nicholas J Wareham[16], Francesca L Crowe[17], Timothy J Key[17], Androniki Naska[18], Antonia Trichopoulou[18,19], Dimitrios Trichopoulos[19,20,21], Max Leenders[5], Petra HM Peeters[22,23], Dagrun Engeset[24], Christine L Parr[25], Guri Skeie[24], Paula Jakszyn[26], María-José Sánchez[27,28], José M Huerta[27,29], M Luisa Redondo[30], Aurelio Barricarte[28,31], Pilar Amiano[28,32], Isabel Drake[33], Emily Sonestedt[33], Göran Hallmans[34], Ingegerd Johansson[35], Veronika Fedirko[36], Isabelle Romieux[36], Pietro Ferrari[36], Teresa Norat[23], Anne C Vergnaud[23], Elio Riboli[23] and and Jakob Linseisen[2,37]

Abstract

Background: Recently, some US cohorts have shown a moderate association between red and processed meat consumption and mortality supporting the results of previous studies among vegetarians. The aim of this study was to examine the association of red meat, processed meat, and poultry consumption with the risk of early death in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Methods: Included in the analysis were 448,568 men and women without prevalent cancer, stroke, or myocardial infarction, and with complete information on diet, smoking, physical activity and body mass index, who were between 35 and 69 years old at baseline. Cox proportional hazards regression was used to examine the association of meat consumption with all-cause and cause-specific mortality.

Results: As of June 2009, 26,344 deaths were observed. After multivariate adjustment, a high consumption of red meat was related to higher all-cause mortality (hazard ratio (HR) = 1.14, 95% confidence interval (CI) 1.01 to 1.28, 160+ versus 10 to 19.9 g/day), and the association was stronger for processed meat (HR = 1.44, 95% CI 1.24 to 1.66, 160+ versus 10 to 19.9 g/day). After correction for measurement error, higher all-cause mortality remained significant only for processed meat (HR = 1.18, 95% CI 1.11 to 1.25, per 50 g/d). We estimated that 3.3% (95% CI 1.5% to 5.0%) of deaths could be prevented if all participants had a processed meat consumption of less than

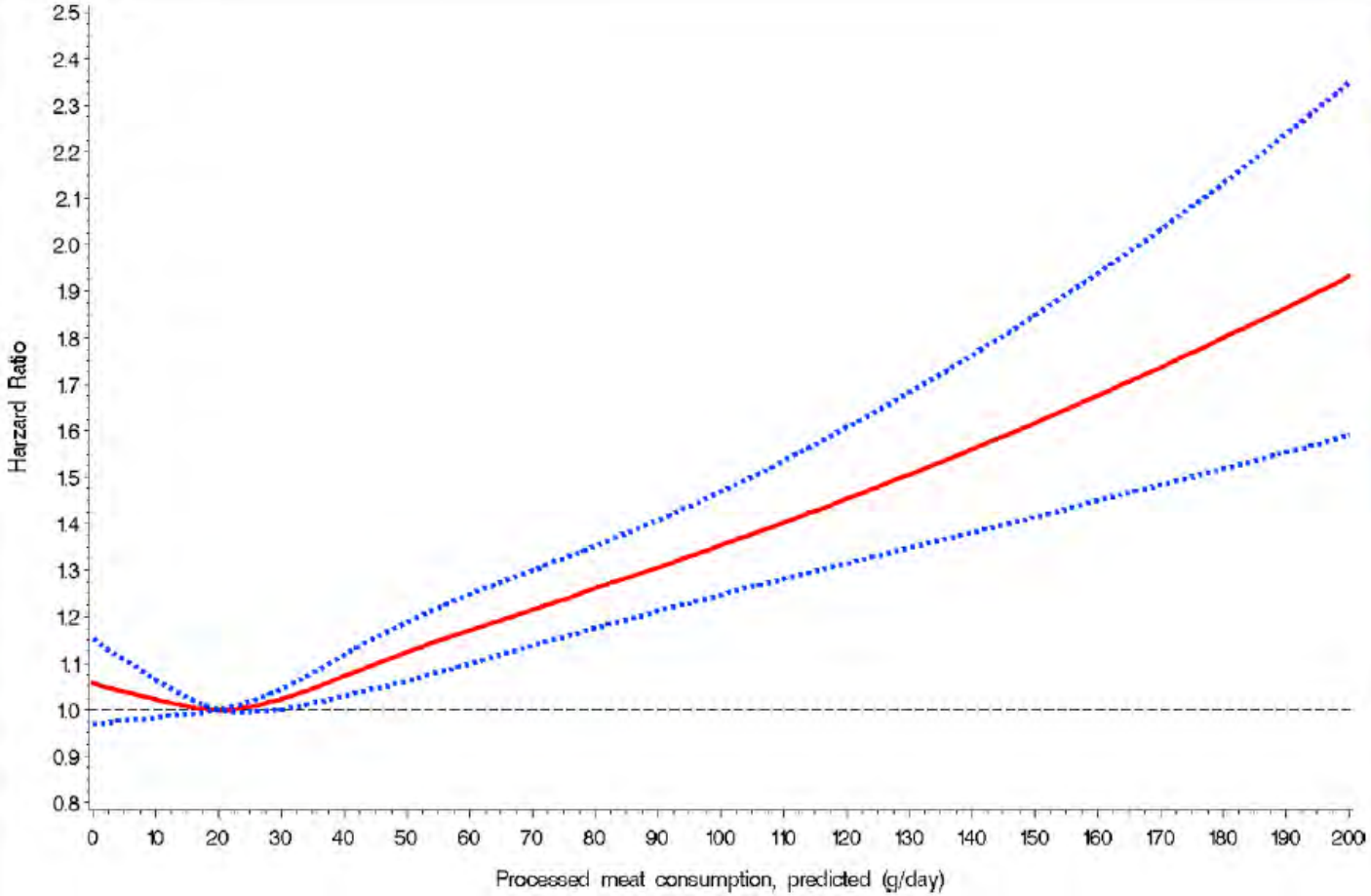

Figure 1 Nonparametric regression curve for the relation of processed meat intake at recruitment with all-cause mortality, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992-2009. Solid line, effect estimate; dotted lines, 95 percent confidence interval.

nature medicine

Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis

Robert A Koeth[1,2], Zeneng Wang[1,2], Bruce S Levison[1,2], Jennifer A Buffa[1,2], Elin Org[3], Brendan T Sheehy[1], Earl B Britt[1,2], Xiaoming Fu[1,2], Yuping Wu[4], Lin Li[1,2], Jonathan D Smith[1,2,5], Joseph A DiDonato[1,2], Jun Chen[6], Hongzhe Li[6], Gary D Wu[7], James D Lewis[6,8], Manya Warrier[9], J Mark Brown[9], Ronald M Krauss[10], W H Wilson Tang[1,2,5], Frederic D Bushman[5], Aldons J Lusis[3] & Stanley L Hazen[1,2,5]

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Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.

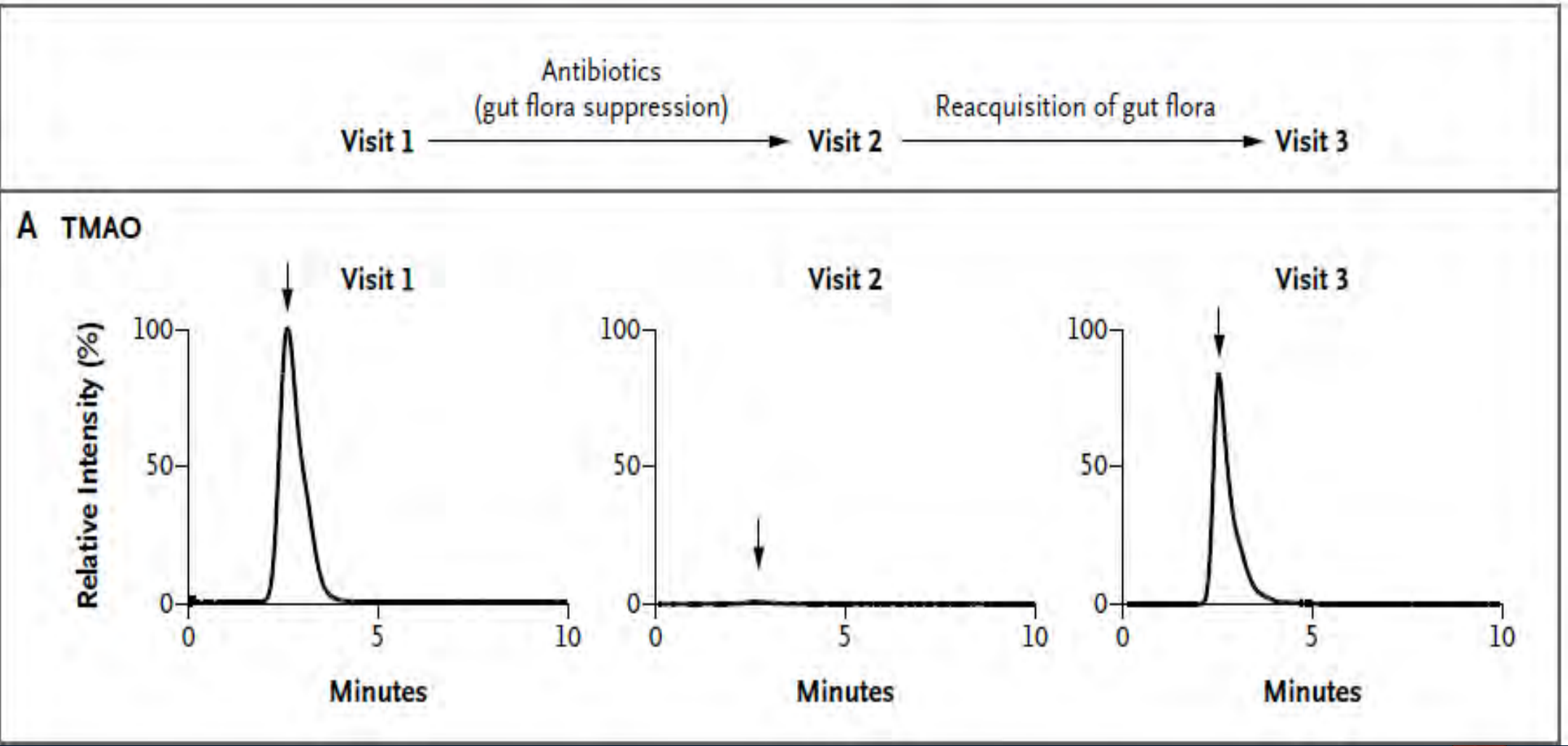

Antibiotics
(gut flora suppression)
Visit 1
Visit 2
Reacquisition of gut flora
Visit 3
A TMAO
Visit 1
Visit 2
Visit 3
Relative Intensity (%)
100
50
0
0
5
10
Minutes

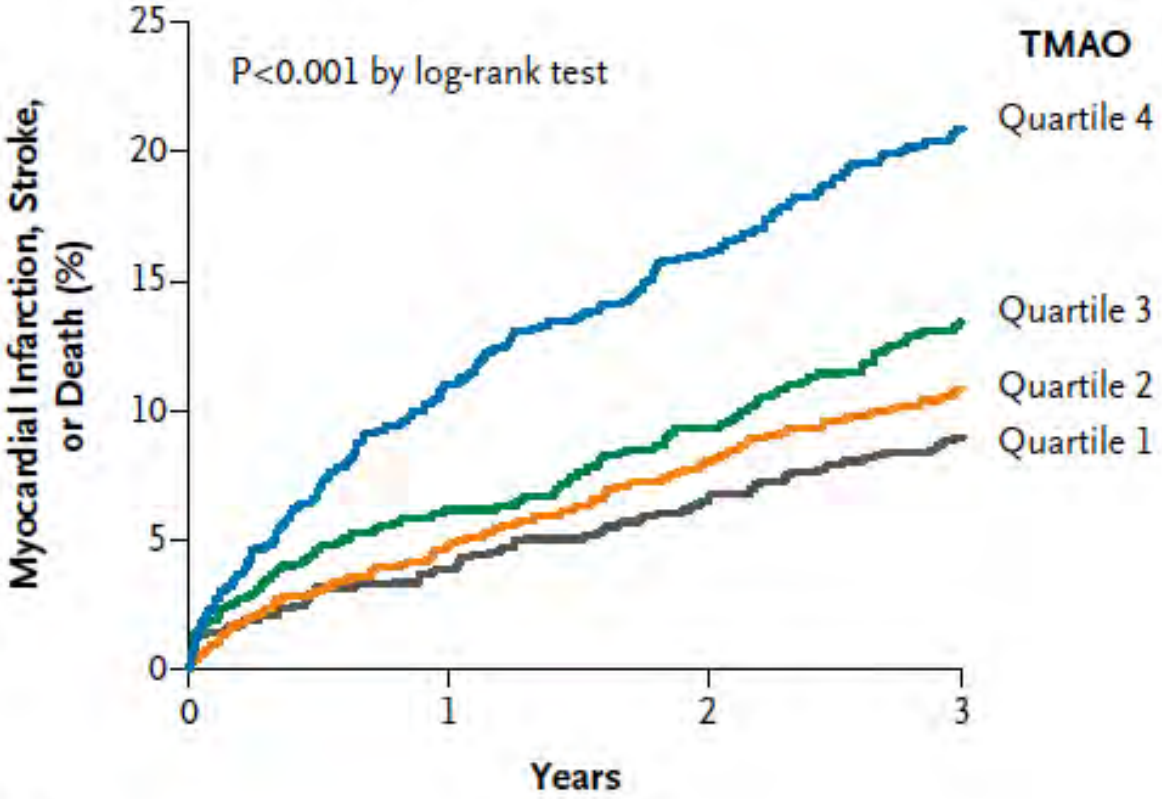
Table 2. Risk of a Major Adverse Cardiovascular Event at 3 Years, According to Quartile of TMAO Level.*

Risk of Event	TMAO Level					
	Quartile 1	Quartile 2		Quartile 3		Quartile 4	
	reference	hazard ratio (95% CI)	P value	hazard ratio (95% CI)	P value	hazard ratio (95% CI)	P value
Unadjusted hazard ratio	1.00	1.24 (0.93–1.66)	0.15	1.53 (1.16–2.02)	0.003	2.54 (1.96–3.28)	<0.001
Adjusted hazard ratio							
Model 1†	1.00	1.14 (0.86–1.53)	0.37	1.29 (0.98–1.71)	0.07	1.88 (1.44–2.44)	<0.001
Model 2‡	1.00	1.08 (0.79–1.48)	0.61	1.15 (0.85–1.56)	0.36	1.49 (1.10–2.03)	0.01
Model 3§	1.00	1.06 (0.77–1.45)	0.72	1.11 (0.82–1.51)	0.50	1.43 (1.05–1.94)	0.02

* A major adverse cardiovascular event was defined as death, myocardial infarction, or stroke. The quartiles of TMAO levels are as follows: quartile 1, less than 2.43 μM; quartile 2 2.43 to 3.66 μM; quartile 3, 3.67 to 6.18 μM; and quartile 4, more than 6.18 μM. Hazard ratios and P values are for the comparison with quartile 1.

† In model 1, hazard ratios were adjusted for traditional risk factors (age, sex, smoking status, systolic blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, and status with respect to diabetes mellitus), plus log-transformed high-sensitivity C-reactive protein level.

‡ In model 2, hazard ratios were adjusted for all factors in model 1, plus myeloperoxidase level, log-transformed estimated glomerular filtration rate, total white-cell count, body-mass index, and status with respect to receipt of certain medications



No. at Risk

Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Figure 2. Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level.

MJ

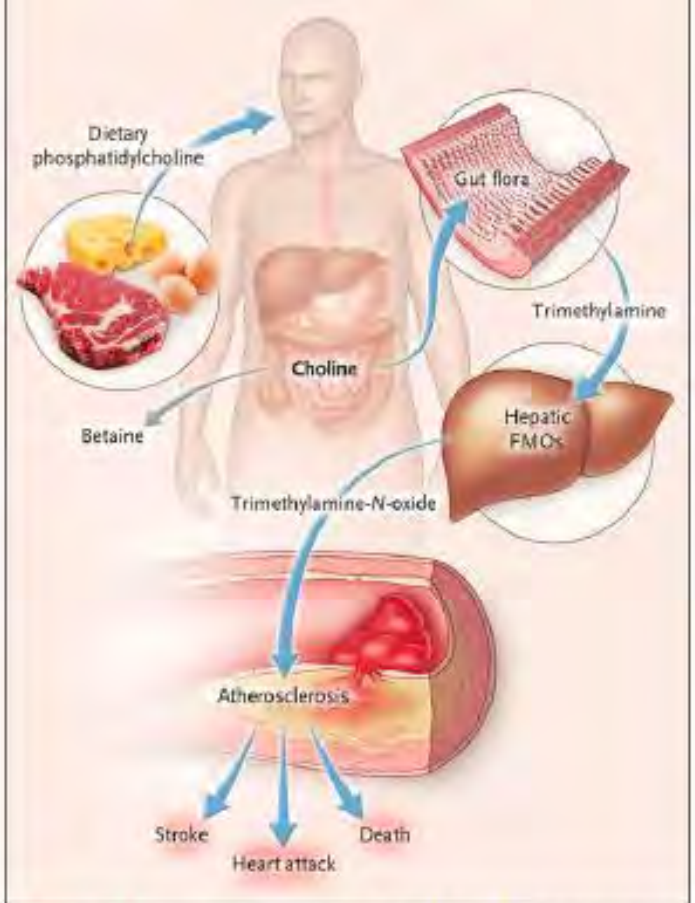


Figure 3. Pathways Linking Dietary Phosphatidylcholine, Intestinal Microbiota, and Incident Adverse Cardiovascular Events.

Ingested phosphatidylcholine (lecithin), the major dietary source of total choline, is acted on by intestinal lipases to form a variety of metabolic products, including the choline-containing nutrients glycerophosphocholine, phosphocholine, and choline. Choline-containing nutrients that reach the cecum and large bowel may serve as fuel for intestinal microbiota (gut flora), producing trimethylamine (TMA). TMA is rapidly further oxidized to trimethylamine-*N*-oxide (TMAO) by hepatic flavin-containing monooxygenases (FMOs). TMAO enhances the accumulation of cholesterol in macrophages, the accumulation of foam cells in artery walls, and atherosclerosis,[7] all factors that are associated with an increased risk of heart attack, stroke, and death. Choline can also be oxidized to betaine in both the liver and kidneys.[20] Dietary betaine can serve as a substrate for bacteria to form TMA[21] and presumably TMAO.

EUROPEAN SOCIETY OF CARDIOLOGY®

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REVIEW

Nutrition in cardiovascular disease

The gut microbiome as novel cardio-metabolic target: the time has come!

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Energy and Health 5

Food, livestock production, energy, climate change, and health

Anthony J McMichael, John W Powles, Colin D Butler, Ricardo Uauy

Food provides energy and nutrients, but its acquisition requires energy expenditure. In post-hunter-gatherer societies, extra-somatic energy has greatly expanded and intensified the catching, gathering, and production of food. Modern relations between energy, food, and health are very complex, raising serious, high-level policy challenges. Together with persistent widespread under-nutrition, over-nutrition (and sedentarism) is causing obesity and associated serious health consequences. Worldwide, agricultural activity, especially livestock production, accounts for about a fifth of total greenhouse-gas emissions, thus contributing to climate change and its adverse health consequences, including the threat to food yields in many regions. Particular policy attention should be paid to the health risks posed by the rapid worldwide growth in meat consumption, both by exacerbating climate change and by directly contributing to certain diseases. To prevent increased greenhouse-gas emissions from this production sector, both the average worldwide consumption level of animal products and the intensity of emissions from livestock production must be reduced. An international contraction and convergence strategy offers a feasible route to such a goal. The current global average meat consumption is 100 g per person per day, with about a ten-fold variation between high-consuming and low-consuming populations. 90 g per day is proposed as a working global target, shared more evenly, with not more than 50 g per day coming from red meat from ruminants (ie, cattle, sheep, goats, and other digastric grazers).

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This is the fifth in a **Series** of six papers about energy and health

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L'ombre portée
de l'élevage
impacts environnementaux et
options pour leur atténuation
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