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Introduction



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In 1976, the general practitioner Leopold Bischof wrote an article in *Methods of Information in Medicine* entitled

"Die Datenverarbeitung für die Gesundheitsvorsorge in Vorarlberg".

In this work, Bischof laid the visionary foundation of a system of population-based, data-driven health examinations in Vorarlberg, the westernmost province of Austria.

The 'Arbeitskreis für Vorsorge- und Sozialmedizin' (*aks*) in Bregenz began to routinely document health examinations, from 1985 onwards with an IT system that functions to this day.

In the beginning, contrarily to Bischof's intent, the data-recording was mainly used for accounting purposes.

It was only in 2003, that the data started to be re-used for epidemiological research under the name of "Vorarlberg Health Monitoring & Promotion Programme" (VHM&PP).

vhmpp, aks

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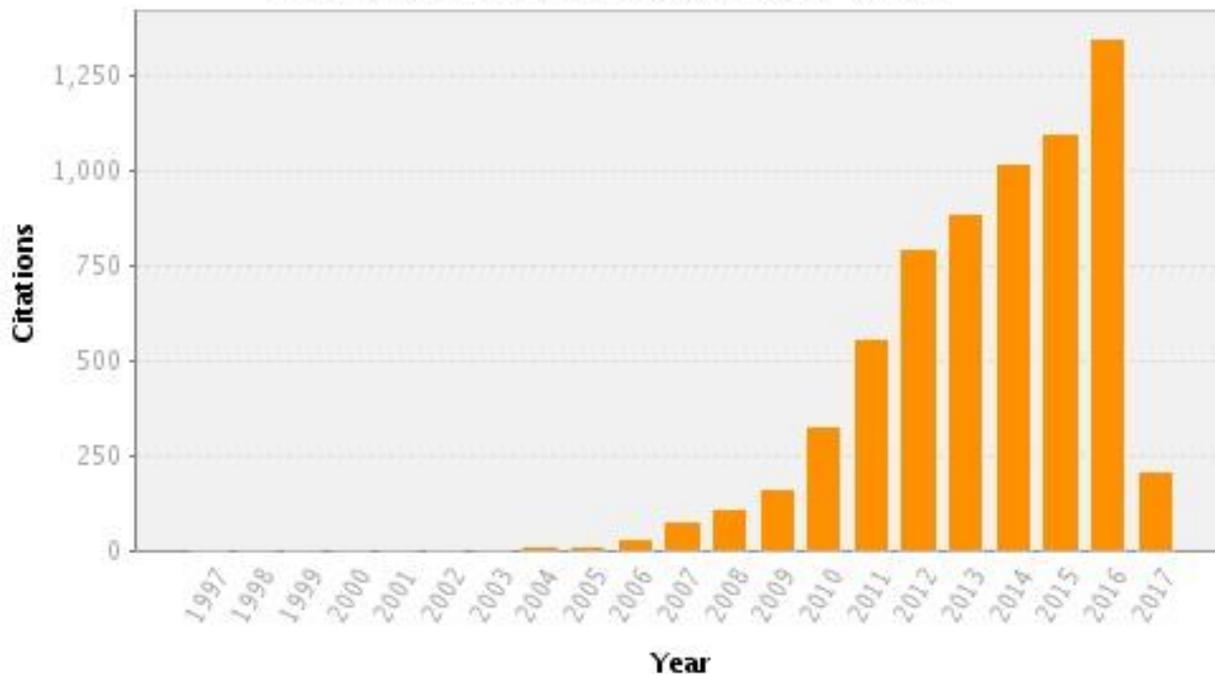
URL: <http://www.researcherid.com/rid/F-9756-2012>

Primary Institution: **Agency for Social- and Preventive Medicine**

Subject: **Public, Environmental & Occupational Health**

Sub-org/Dept:

Citation Distribution by year



Total Articles in Publication List: 120
Articles With Citation Data: 116
Sum of the Times Cited: 6865
Average Citations per Article: 59.18
h-index: 36
Last Updated: 04/03/2017 13:25 GMT

Milestones on the way to the use of the database



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- Hans Concini took responsibility for the Wissenschaft
- Cecily Kelleher, epidemiologist and public health expert from University of Dublin. She was the first to recognize in 2001 the full potential of the database
- The first peer-reviewed publication:
Ulmer H, Kelleher C, Diem G, Concini H. Tracking of Cardiovascular Risk Factors: the Vorarlberg Health Monitoring & Promotion Programme. European Heart Journal 2003.
- Statistical and methodological discussions with Prof. Larry Brant, chief statistician of the Baltimore Longitudinal Study of Aging (BLSA)
- The involvement of epidemiologists from nearby located University of Ulm: Prof. Stefan Weiland, Killian Rapp, Jochen Klenk and Gabriele Nagel
- Highly motivated scientists: Alexander Strasak, Wegene Borena, Susanne Strohmaier, Michael Edlinger, Josef Fritz and Phd students from Ulm

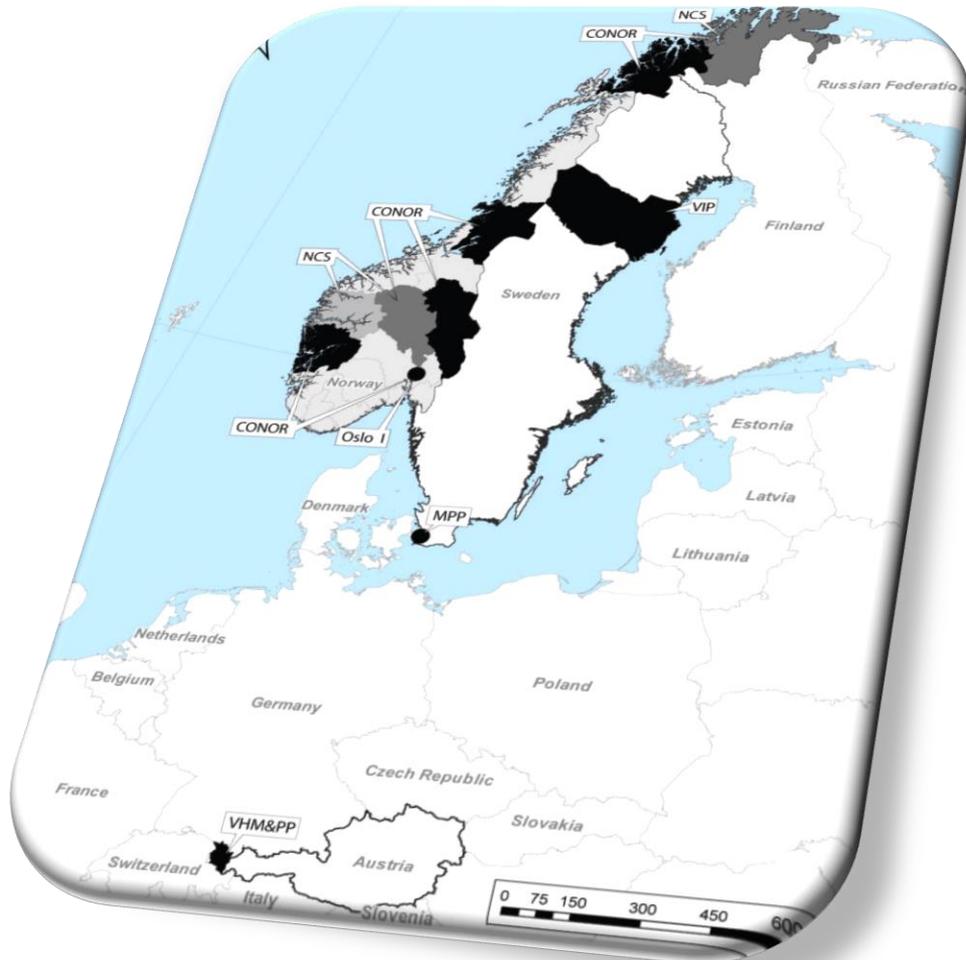
Milestones on the way to the use of the database



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- Invitation to collaborate in the Metabolic Syndrome and Cancer (Me-Can) and in the ESCAPE projects
- Cooperations with
 - the Emerging Risk Factor Collaboration (ERFC) - University of Cambridge,
 - the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration – Harvard University,
 - and the NCDRisC Factor Collaboration – Imperial College London

Me-Can project



In 2006, the **Metabolic syndrome and Cancer project (Me-Can)** was initiated in order to create a large pooled cohort **to investigate factors of the metabolic syndrome on the association with cancer risk.**

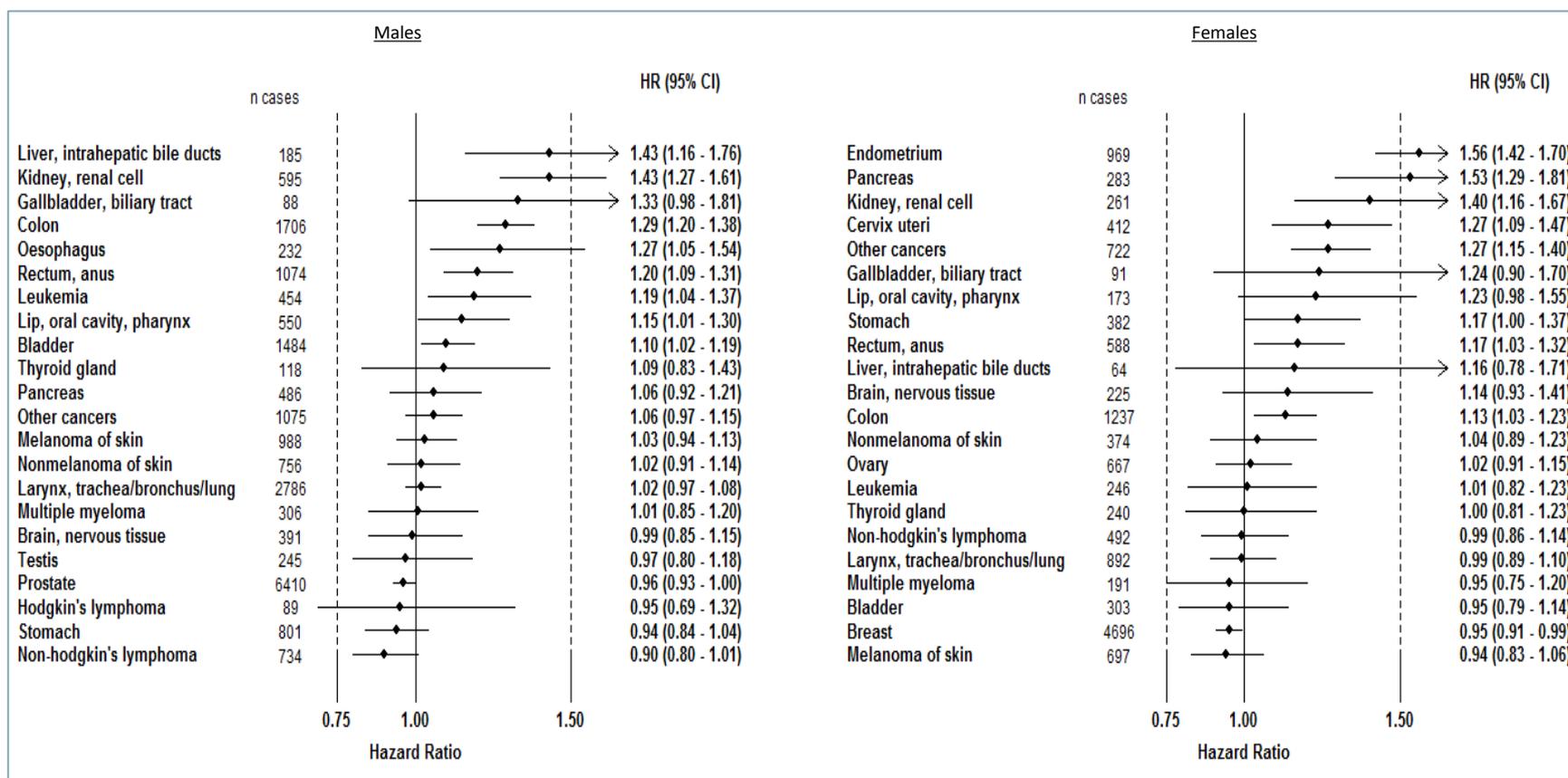
Existing cohorts in Norway, Austria and Sweden were included in the project. The cohorts were: in Norway, the Oslo study I (Oslo), the Norwegian Counties Study (NCS), the Cohort of Norway (CONOR) and the Age 40 programme (40-years); in Austria, the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP); and in Sweden, the Vasterbotten Intervention Project (VIP) and the Malmo Preventive Project (MPP).

Me-Can project



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Sex-specific risk estimates of incident cancer by site per unit MetS score (standardised sum of the five separate z-scores)



Emerging Risk Factors Collaboration (ERFC) – University of Cambridge



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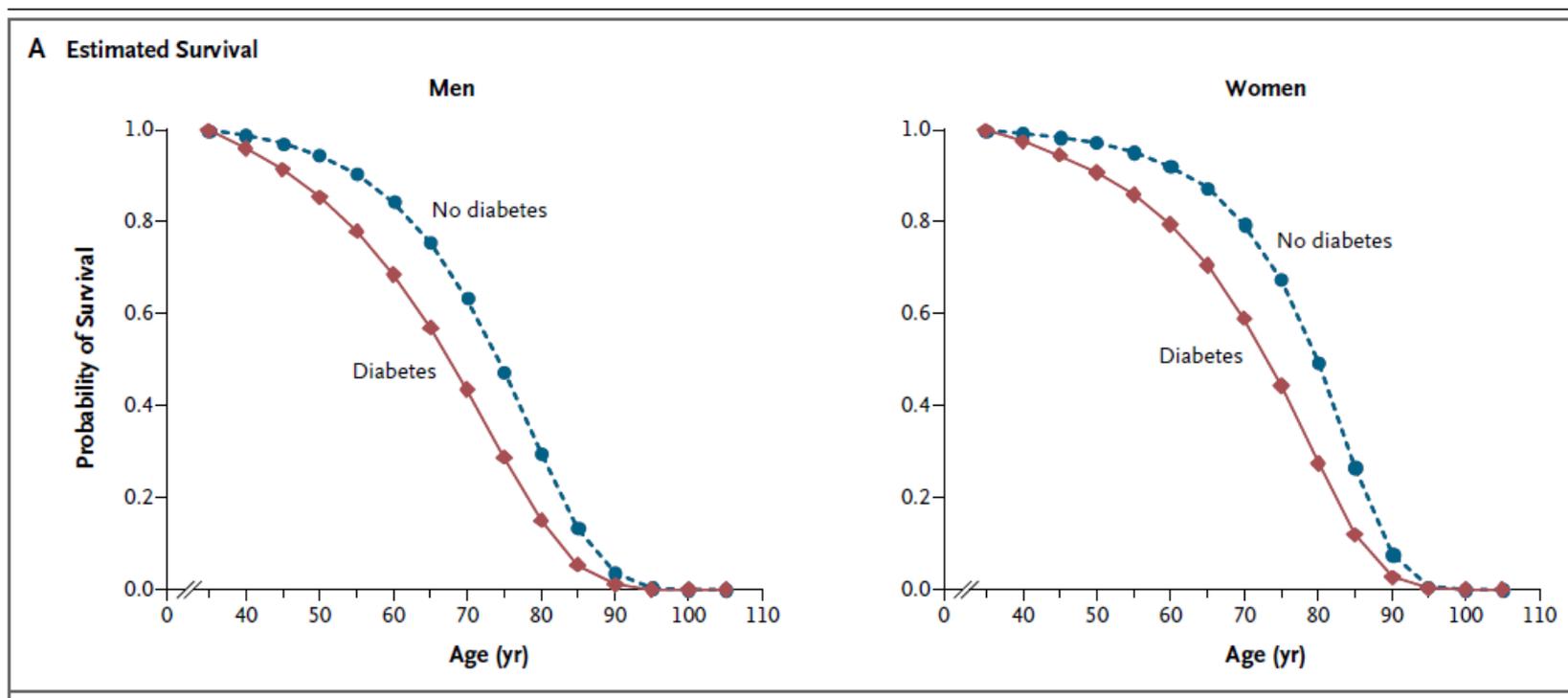
The Emerging Risk Factors Collaboration (ERFC) has established a central database on over 1.2 million participants from >100 prospective population-based studies, in which subsets have information on lipid and inflammatory markers, other established risk factors and characteristics, as well as major cardiovascular morbidity and cause-specific mortality.

Information on repeated measurements on relevant characteristics has been collected in over 300,000 participants to enable estimation of and adjustment for within-person variability. Re-analysis of individual data will yield up to approximately 70,000 incident fatal or first ever major cardiovascular outcomes recorded during about 12 million person years at risk.

Mainly focussing on cardiovascular disease, however there are now already two papers with cancer mortality as an outcome

Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

*The Emerging Risk Factors Collaboration**



ORIGINAL ARTICLE

Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration*

B Noncancer, Nonvascular Death

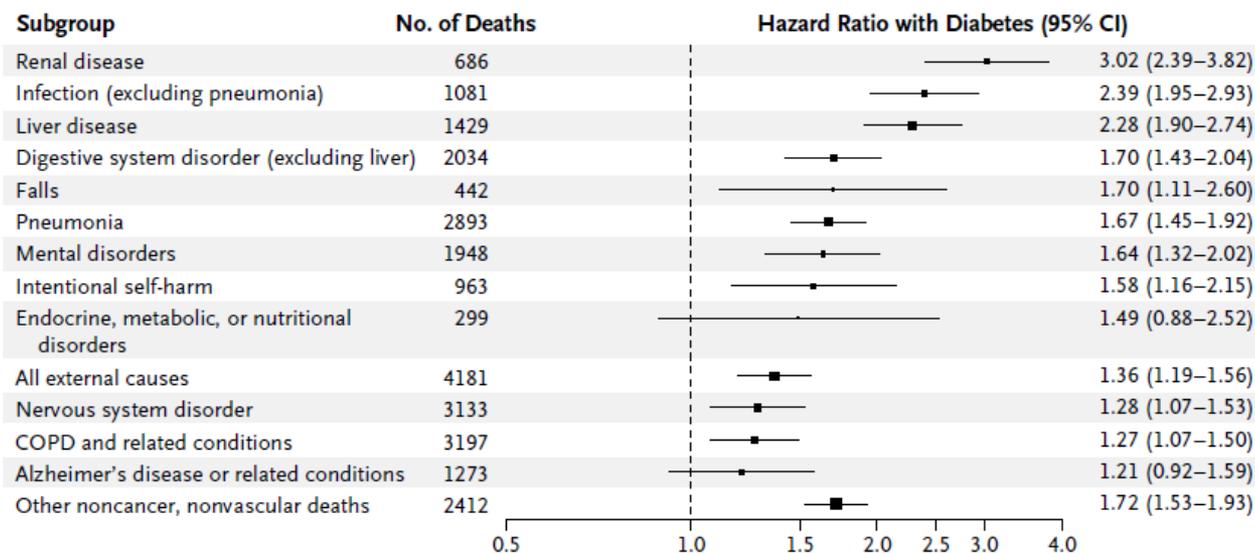


Figure 1. Hazard Ratios for Death from Cancer and from Noncancer, Nonvascular Causes among Participants with Diabetes as Compared with Those without Diabetes at Baseline.

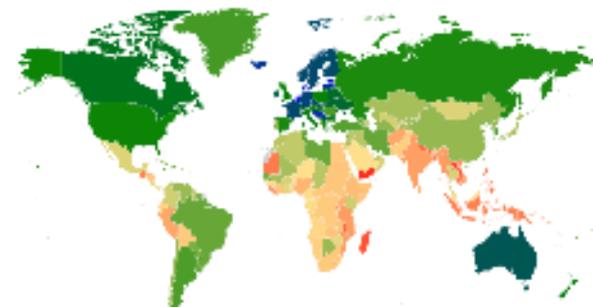
Obesity
(BMI ≥ 30 kg/m²)



Diabetes



Raised BP
(SBP ≥ 140 mmHg
or DBP ≥ 90 mmHg)



Austria:

Agency for Preventive and Social Medicine, Bregenz, Austria

Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University

Department of General Internal Medicine, Section Oncology, Innsbruck Medical University

Department of Cardiac Surgery, Innsbruck Medical University, Innsbruck

Cancer Registry of Tyrol, Department of Clinical Epidemiology of the Tyrolean State Hospitals, Innsbruck

Department of Social Medicine, Medical University of Vienna

Department of Pathology, Academic Teaching Hospital, Feldkirch

Denmark:

Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen

Germany:

Institute of Epidemiology and Medical Biometry, Ulm University

Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg

England:

Department of Public Health and Primary Care, University of Cambridge

Ireland:

School of Public Health and Population Sciences, University College Dublin, Dublin

Italy:

Department of Experimental Pathology & BMIE, University of Pisa Medical School

Norway:

Department of Public Health and Primary Health Care, University of Bergen, Bergen

Norwegian Institute of Public Health, Oslo/Bergen

Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, Oslo

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Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå

Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University

Department of Radiation Sciences, Oncology, Umeå University, Umeå

Department of Surgery, Malmö University Hospital, Lund University, Malmö

Department of Internal Medicine, Division of Gastroenterology, Sahlgrenska University Hospital, Gothenburg

U.S.A:

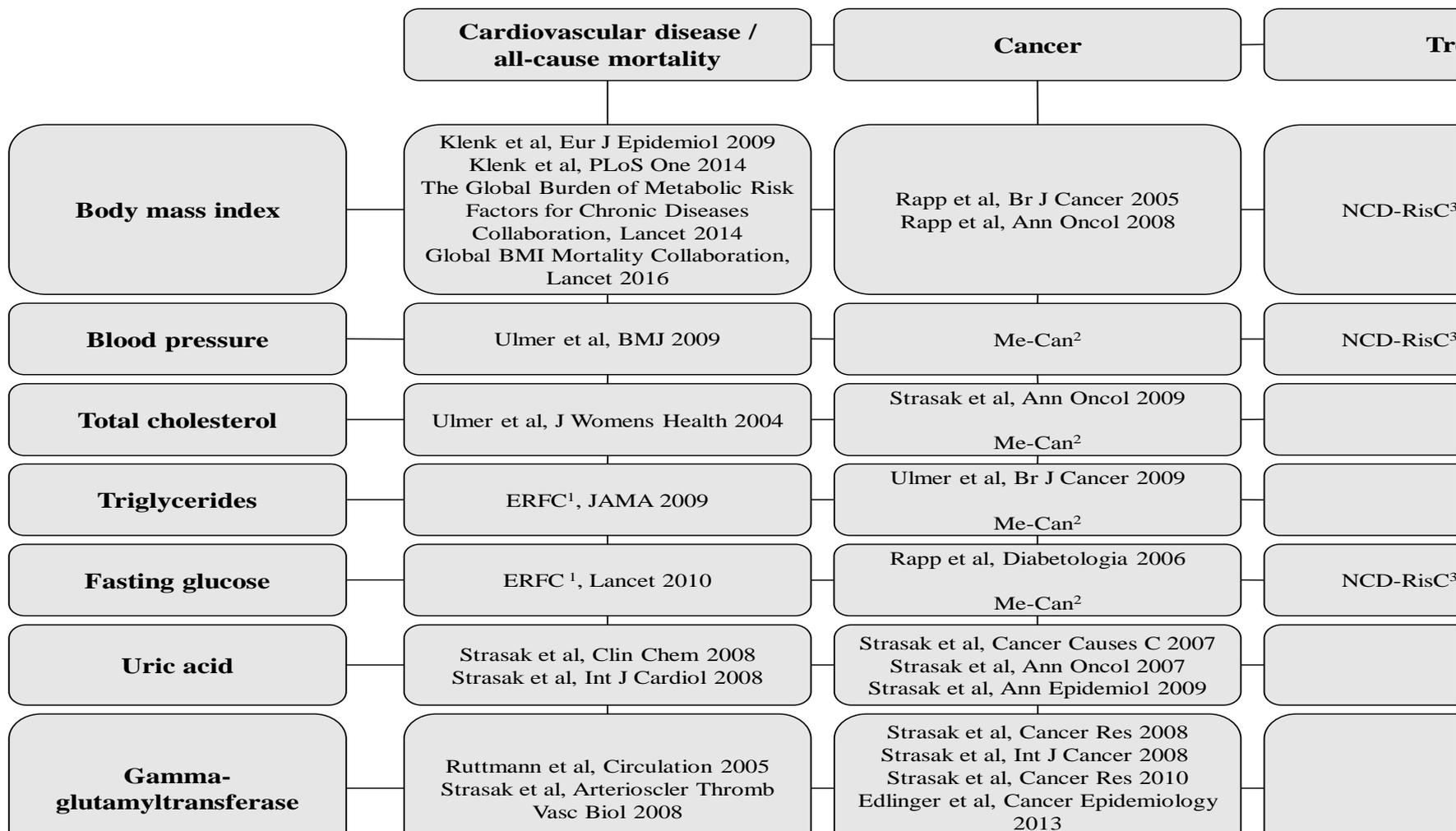
Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland

Gerontology Research Center, National Institute on Aging, Baltimore, Maryland

Publications



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Studies in Cardiovascular Epidemiology

*The Vorarlberg Health Monitoring
& Promotion Programme
(VHM&PP)*

Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme

Ulmer H, Kelleher C, Diem G, Concin H (2003)

Tracking of cardiovascular risk factors is most pronounced for body-mass index.

To document tracking patterns, if any, over time, of classical cardiovascular risk factors in men and women participants in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)

67 413 men and 82 237 women underwent a total of 454 448 standardised examinations in the 15 year period 1985–1999. Measures included were systolic and diastolic blood pressure, height, weight and fasting sample for total cholesterol, triglycerides, gamma-gt and blood glucose. Tracking coefficients were calculated by multivariable regression models using the GEE estimation method. All variables showed evidence of significant tracking over time, whether estimated in 10-year age bands or among individuals categorized as being at high risk using cut-points proposed by international guidelines. Effects were most marked for body mass index (0.87, SE 0.005 in men and 0.89, SE 0.003 in women), and were also associated with increasing age. Women who died during follow-up showed stronger tracking patterns for triglycerides and gamma-gt and weaker effects for blood pressure, but there was no effect on patterns according to survival in men. Tracking coefficients were weaker among initially high-risk individuals.

This is the largest study yet of adults to demonstrate significant tracking effects of cardiovascular risk factors over time. The strength of this effect should be considered in assessing effectiveness of risk factor modification programmes. The study is novel too in highlighting more fully differences according to gender and social circumstances and in taking account of the impact on long-term survival.

Estimation of seasonal variations in risk factor profiles and mortality from coronary heart disease

Ulmer H, Kelleher C, Diem G, Concin H, Ruttman E

Total cholesterol, blood pressure and body mass index showed pronounced seasonal variations with average levels significantly higher during the winter months.

Seasonal variations in coronary heart disease (CHD) and related risk factors have been reported previously. However, no studies to date quantify the contribution of seasonal variations in risk factors to actual mortality in both men and women using a single database of sufficient size and follow-up.

We investigated the database from the Western Austrian Vorarlberg Health Monitoring and Promotion Programme (VHM&PP) including over 450.000 repeated measurements of 149.650 individuals between 1985 and 1999. Results: Of a total of 1266 deaths from CHD (ICD-9 410–414), 353 deaths occurred between December and February (27.9%), in contrast to 275 (21.7%) between June and August. While the frequency of deaths through acute myocardial infarction (ICD-9 410) was similar over the seasons, chronic forms of CHD (ICD-9 414) occurred significantly ($p < 0.001$) more frequently in winter. Total cholesterol, blood pressure and body mass index showed pronounced seasonal variations with average levels significantly higher during the winter months in all age groups and both sexes, giving an estimated increase in SCORE risk of 6.8% in men and 3.6% in women. However by contrast, use of single time point risk factor data tended to over-estimate subsequent 10 year mortality if measured in winter and the converse in summer.

For the first time, this study quantifies the contribution of seasonal risk factor variation to CHD mortality. The consistent effect across demographic groups suggests that this is a real physiological phenomenon and not an artefact of living conditions. Interpretation of standard risk scores should take account of this seasonal fluctuation in subsequent investigation and follow-up.

Why eve is not adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality

Ulmer H, Kelleher C, Diem G, Concin H

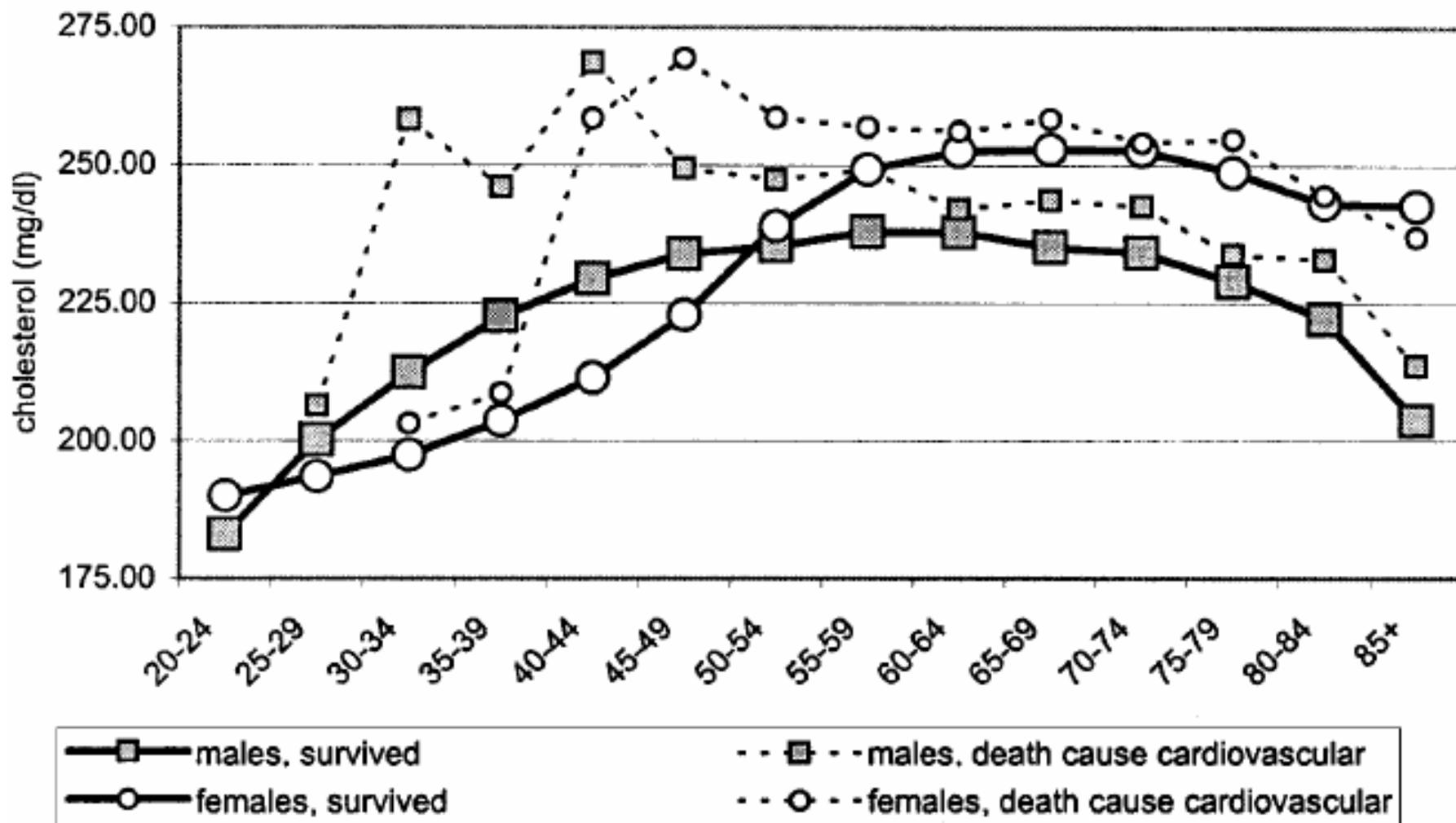
Cholesterol shows pronounced sex-specific differences

To assess the impact of sex-specific patterns in cholesterol levels on all-cause and cardiovascular mortality in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)

In this study, 67,413 men and 82,237 women (aged 20–95 years) underwent 454,448 standardized examinations, which included measures of blood pressure, height, weight, and fasting samples for cholesterol, triglycerides, gamma-glutamyl transferase (GGT), and glucose in the 15-year period 1985–1999. Relations between these variables and risk of death were analyzed using two approaches of multivariate analyses (Cox proportional hazard and GEE models).

Patterns of cholesterol levels showed marked differences between men and women in relation to age and cause of death. The role of high cholesterol in predicting death from coronary heart disease could be confirmed in men of all ages and in women under the age of 50. In men, across the entire age range, although of borderline significance under the age of 50, and in women from the age of 50 onward only, low cholesterol was significantly associated with all-cause mortality, showing significant associations with death through cancer, liver diseases, and mental diseases. Triglycerides greater 200 mg/dl had an effect in women 65 years and older but not in men

This large-scale population-based study clearly demonstrates the contrasting patterns of cholesterol level in relation to risk, particularly among those less well studied previously, that is, women of all ages and younger people of both sexes. For the first time, we demonstrate that the low cholesterol effect occurs even among younger respondents, contradicting the previous assessments among cohorts of older people that this is a proxy or marker for frailty occurring with age.



Secular trends in cardiovascular risk factors: an age-period cohort analysis of 698 954 health examinations in 181 350 Austrian men and women

Ulmer H, Kelleher C, Fitz-Simon N, Diem G, Concin H

Blood lipids and blood pressure declined. By contrast, fasting glucose showed a strong rising tendency, most markedly in young males.

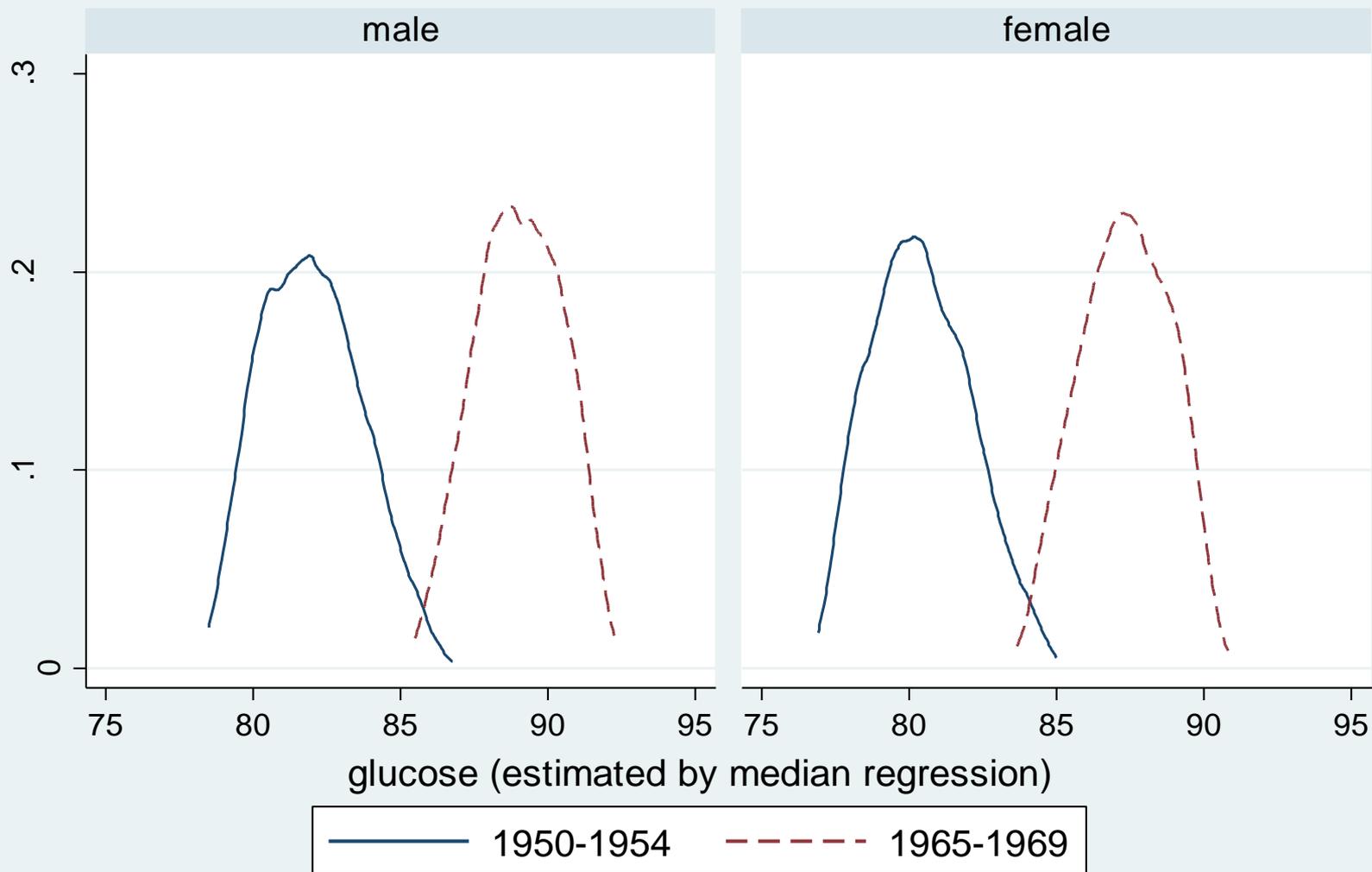
It is well established that morbidity and mortality patterns in cardiovascular diseases vary strongly over time, yet the determinants of such trends remain poorly understood. To assess the potential contribution of secular or cross-generation patterns, we evaluated birth cohort-related trends across the 20th century of risk factors in a large database of Austrian men and women.

Trends in risk factors were investigated for 181 350 adults aged 20–79 years born between 1905 and 1975 undergoing 698 954 health examinations between 1985 and 2005 as participants of the Vorarlberg Health Monitoring and Promotion Programme.

There was clear evidence of cohort-related shifts in all risk factors. Total serum cholesterol and triglyceride declined markedly, particularly in the youngest cohorts, as did systolic and diastolic blood pressure in both men and women. By contrast, fasting glucose showed a strong rising tendency in both sexes and at all ages, most markedly in young males. Average glucose levels were between 4 and 15 mg dL⁻¹ higher in individuals at the same age born 20 years later. In males, body weight expressed in kg m⁻² (body mass index) was increasing as well; however, in women, patterns were most marked at the 90th percentile.

Conclusion. These findings provide strong evidence of population wide secular shifts and suggest that in addition to period influences, most probably through treatment intervention and lifestyle change, determinants across the life-course are programming shifts from childhood onwards.

VHM&PP participant aged 35-39 years



Graphs by sex

Predictive accuracy of the SCORE risk function for cardiovascular disease in clinical practice: a prospective evaluation of 44,649 Austrian men and women

Ulmer H, Kollerits B, Kelleher C, Diem G, Concin H

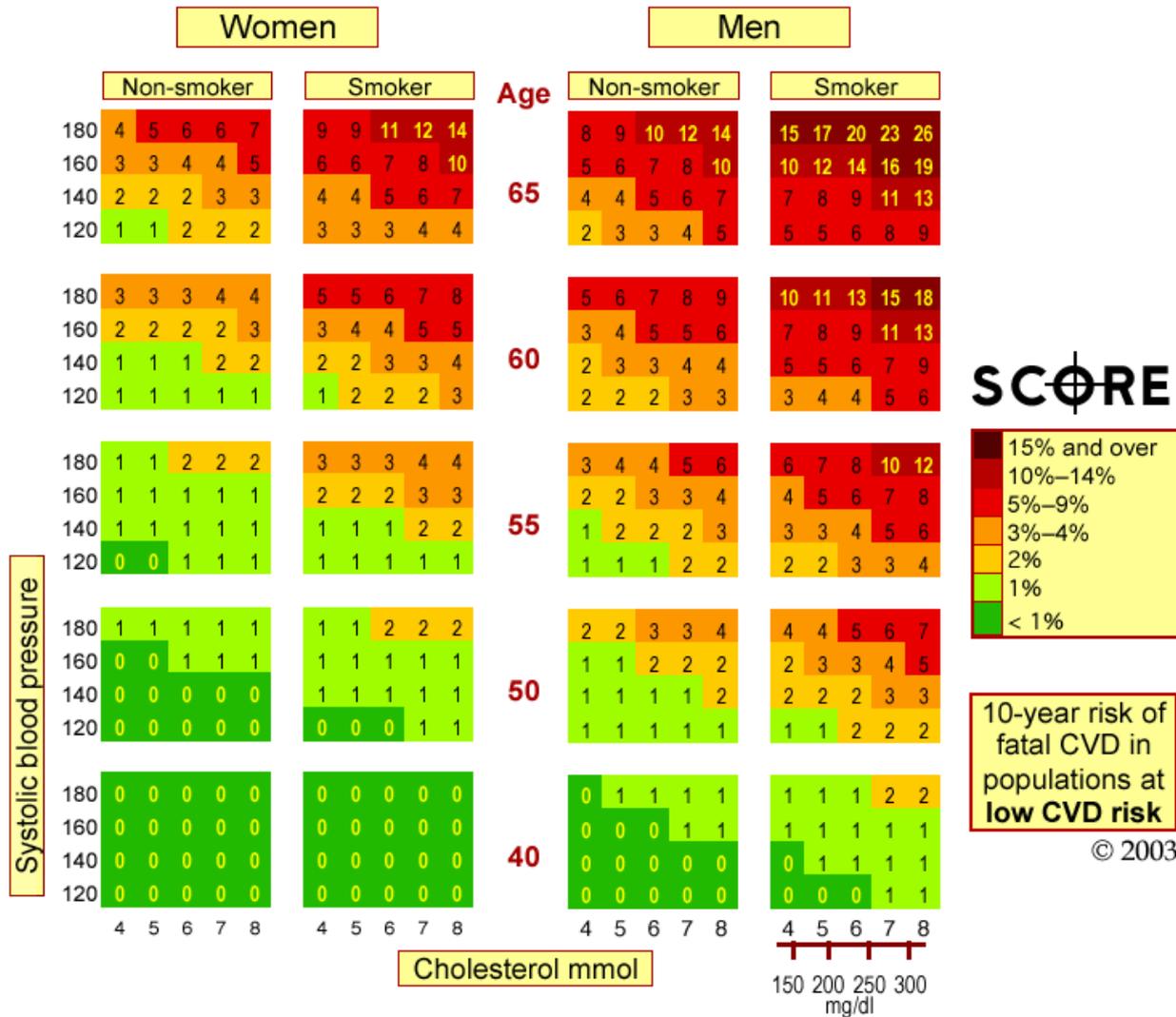
The SCORE overpredicted the mortality pattern in the cohort as a whole, its predictive ability at the individual level still demonstrates a potentially widespread utility in clinical practice.

In 2003, a new risk function for cardiovascular risk in clinical practice was developed by the SCORE project group. The aim of this paper was to evaluate the predictive accuracy of the SCORE in a large Austrian population.

Using the 'SCORE risk function for low-risk regions', we calculated the risk of death from cardiovascular and coronary heart disease events over a 10-year period for 44 649 participants aged 40–65 years in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP). The predicted risks were compared with the 95% confidence intervals (CI) of the observed events.

We observed a total of 487 deaths (1.1%; 95% CI 1.0–1.2) for all cardiovascular disease within 10 years, 371 (1.8%; 95% CI 1.6–2.0) in men and 116 (0.5%; 95% CI 0.4–0.6) in women. The SCORE function overestimated cardiovascular mortality and predicted 666 (1.5%) events, 444 (2.2%) in men and 222 (0.9%) in women. Receiver operating characteristics analyses revealed area under the curve values of 0.76 (95% CI 0.74–0.79) for men and 0.78 (95% CI 0.74–0.82) for women. Multivariable analyses showed that obesity (in men only) increased levels of glucose, gamma-glutamyl transferase, triglycerides (in women only), and blue-collar job status (in women only) significantly contributed to the SCORE as additional independent risk factors.

Although the SCORE overpredicted the mortality pattern in the cohort as a whole, its predictive ability at the individual level still demonstrates a potentially widespread utility in clinical practice.



Gamma-Glutamyltransferase as a Risk Factor for Cardiovascular Disease Mortality: An Epidemiologic Investigation in a Cohort of 163,944 Austrian Adults

Ruttman E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H

This study demonstrates in a large, prospectively observed cohort that gamma-glutamyltransferase is independently associated with cardiovascular mortality.

There is evidence from recent studies that gamma-glutamyltransferase (GGT) is likely to be associated with cardiovascular disease (CVD). However, few studies to date with sufficient sample size and follow-up investigated the association of GGT with CVD mortality.

The relation of GGT to the risk of death from CVD was examined in a cohort of 163 944 Austrian adults that was monitored for up to 17 years. To evaluate GGT as an independent predictor, Cox proportional hazards models were calculated, which adjusted for established risk factors. In both men and women, high GGT was significantly ($P < 0.001$) associated with total mortality from CVD, showing a clear dose-response relationship. Adjusted hazard ratios (95% CI) per log GGT increase were 1.66 (1.40 to 1.98) in men and 1.64 (1.36 to 1.97) in women. In men, subgroup analyses showed that high GGT was positively associated with incident fatal events of chronic forms of coronary heart disease ($P = 0.009$), congestive heart failure ($P < 0.001$), and hemorrhagic ($P = 0.01$) and ischemic stroke ($P < 0.001$). No significant associations were observed for acute myocardial infarction ($P = 0.16$). In women, hazard ratios suggested associations in all subgroups; however, for hemorrhagic and ischemic stroke they were not statistically significant ($P = 0.09$ and $P = 0.07$, respectively). In addition, subgroup analyses stratified by age revealed a stronger relationship of GGT in younger participants. Hazard ratios for total CVD were 2.03 (1.53 to 2.69) in men and 2.60 (1.53 to 4.42) in women younger than 60 years.

This study demonstrates in a large, prospectively observed cohort that GGT is independently associated with cardiovascular mortality.

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Editorial

Gamma-Glutamyltransferase, Atherosclerosis, and Cardiovascular Disease

Triggering Oxidative Stress Within the Plaque

Michele Emdin, MD, PhD; Alfonso Pompella, MD, PhD; Aldo Paolich, MD, PhD

The serum determination of gamma-glutamyltransferase (γ -GT) activity is a low-cost, highly sensitive and accurate, and frequently used laboratory test. Although it is considered to be an index of hepatobiliary dysfunction and alcohol abuse,¹ recent epidemiology and pathology studies have suggested its independent role in the pathogenesis and clinical evolution of cardiovascular diseases brought on by atherosclerosis.²

Article p 2130

The prospective study by Ruttmann and colleagues in 163 944 Austrian adults studied for 17 years shows that γ -GT is independently associated with cardiovascular mortality.³ Serum γ -GT activity had a prognostic impact on fatal events of chronic forms of coronary heart disease, congestive heart failure, and ischemic or hemorrhagic stroke. This was found to be true in both sexes, with a clear dose-response relationship, and with a stronger prognostic significance of γ -GT in younger participants.

These findings from a large unselected cohort unequivocally confirm previous observations that γ -GT is associated with overall mortality and cardiovascular events, in both unselected populations^{4–7} and patients with ascertained coronary artery disease, independent of all confounders including liver function and alcohol use.^{8,9}

Well-Known Versus “Unknown” γ -Glutamyltransferase

γ -GT is the enzyme responsible for the extracellular catabolism of glutathione (GSH, γ -glutamyl-cysteinyl-glycine), the main thiol intracellular antioxidant agent in mammalian cells.¹⁰ It is present, linked through a small lipophilic sequence of its larger subunit, on the cell surface membrane of most cell types; although the same protein is produced in all tissues, differences in the sugar moieties allow that only the liver γ -GT is detectable in serum.¹⁰ Most serum γ -GT is bound to carriers, such as α - and β -lipoproteins and albumin.¹

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
From the Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy (M.E.), and the Department of Experimental Pathology, University of Pisa Medical School, Pisa, Italy (A.P., A.P.).
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(Circulation. 2005;112:2078–2088.)
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Circulation is available at <http://www.circulationaha.org>
DOI: 10.1161/CIRCULATIONAHA.105.571919

This association is likely to occur within hepatocytes, before γ -GT releases in serum, through still-unknown mechanisms.

Serum γ -GT activity is affected by genetic and environmental factors, with heritability estimated at 0.52.¹¹ Within its normal range, it has many other determinants, even stronger than liver function or alcohol consumption.¹ The findings of the Austrian Vorarlberg Health Monitoring and Promotion Program,³ a large unselected Norwegian population,¹² and a prospective study of 7613 middle-age British men⁴ show a strong positive association between serum γ -GT level and body mass index, alcohol use, smoking, total lipoprotein and HDL, serum cholesterol, uric acid, serum triglycerides, heart rate, systolic and diastolic blood pressure, antihypertensive medication, preexisting ischemic heart disease, diabetes mellitus, and blood glucose use of oral contraceptives and menopause; pregnant women had lower values.^{3,5,6,12} γ -GT showed a negative association in men in regard to physical activity and lung function (forced expiratory volume in 1 second) and coffee consumption.^{3,5,6}

Prooxidant Effects of Glutathione Hydrolysis by γ -Glutamyltransferase

Catalytically active γ -GT has been found within atherosclerotic cerebral, carotid, and coronary plaques from autopsy studies and surgical endarterectomy, colocalized with oxidized density lipoproteins (LDL) and CD68⁺ foam cells.^{13–15} As concerns the possible association between γ -GT and inflammatory process, it should also be considered that γ -GT has a key role in the interconversion of the glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4.¹⁶

Although the exact mechanism leading to accumulation of γ -GT within the plaque is unknown, the association of γ -GT to lipoproteins suggests that LDL lipoproteins can carry γ -GT activity inside the plaque,¹⁷ where free iron is also present.¹⁸ In the extracellular milieu, γ -GT is the only enzyme responsible for GSH catabolism by hydrolysis of its γ -glutamyl bond between glutamate and cysteine. This reaction produces cysteinyl-glycine moieties, which are usually taken within intracellular milieu by the action of membrane dipeptidases, as precursors for GSH resynthesis.¹

Cysteinyl-glycine is a powerful reducer of Fe³⁺ in the extracellular milieu—and likely at the plaque level—that is able to simultaneously generate Fe²⁺ and a free thyl radical, subsequent reactions lead to the formation of superoxide anion radical and hydrogen peroxide.² These γ -GT-mediated reactions have been shown to catalyze the oxidation of LDL lipoproteins,¹³ likely contributing to oxidative events influ-

Epidemiology

γ -Glutamyltransferase as a Risk Factor for Cardiovascular Disease Mortality

An Epidemiological Investigation in a Cohort of 163 944 Austrian Adults

Elfriede Ruttmann, MD; Larry J. Brant, PhD; Hans Concini, MD; Günter Diem, MD; Kilian Rapp, MD; Hanno Ulmer, PhD; and the Vorarlberg Health Monitoring and Promotion Program Study Group

Background—There is evidence from recent studies that γ -glutamyltransferase (GGT) is likely to be associated with cardiovascular disease (CVD). However, few studies to date with sufficient sample size and follow-up investigated the association of GGT with CVD mortality.

Methods and Results—The relation of GGT to the risk of death from CVD was examined in a cohort of 163 944 Austrian adults that was monitored for up to 17 years. To evaluate GGT as an independent predictor, Cox proportional hazards models were calculated, which adjusted for established risk factors. In both men and women, high GGT was significantly ($P < 0.001$) associated with total mortality from CVD, showing a clear dose-response relationship. Adjusted hazard ratios (95% CI) per log GGT increase were 1.66 (1.40 to 1.98) in men and 1.64 (1.36 to 1.97) in women. In men, subgroup analyses showed that high GGT was positively associated with incident fatal events of chronic forms of coronary heart disease ($P = 0.009$), congestive heart failure ($P = 0.001$), and ischemic stroke ($P < 0.001$). No significant associations were observed for acute myocardial infarction ($P = 0.16$). In women, hazard ratios suggested associations in all subgroups; however, for hemorrhagic and ischemic stroke they were not statistically significant ($P = 0.09$ and $P = 0.07$, respectively). In addition, subgroup analyses stratified by age revealed a stronger relationship of GGT in younger participants. Hazard ratios for total CVD were 2.03 (1.53 to 2.69) in men and 2.60 (1.53 to 4.42) in women younger than 60 years.

Conclusions—This study demonstrates in a large, prospectively observed cohort that GGT is independently associated with cardiovascular mortality. (Circulation. 2005;112:2130–2137.)

Key Words: arteriosclerosis ■ cardiovascular diseases ■ prevention ■ risk factors ■ gamma-glutamyltransferase

In clinical practice, γ -glutamyltransferase (GGT) is a commonly used diagnostic test. Although GGT is mainly seen as an indicator for liver function and alcohol consumption, several studies showed that it is associated with morbidity and mortality from causes other than liver disease, including cardiovascular disease (CVD).¹ In regard to coronary heart disease, it was observed that serum GGT levels were associated with increased risk of myocardial infarction and cardiac death.^{2–5} More recently, associations with stroke were reported.^{6,7} However, such reports are rare, and consistent evidence is lacking because of the limited number of performed studies.

Editorial p 2078

Although there is no doubt about the use of GGT as a monitor of liver function, there are now indications of GGT having a direct involvement in atherosclerotic plaque forma-

tion.⁸ GGT, present in serum and on the surface of most cell types, is the enzyme responsible for the extracellular catabolism of glutathione, the main antioxidant in mammalian cells, and its role in CVDs may be more complex than is currently thought.⁹ The possible role of GGT in the atherosclerotic process suggests that its predictive value is at least partly independent of self-reported alcohol consumption. On the other hand, alcohol consumption has been recently confirmed to have a protective effect against myocardial infarction.¹⁰

The Vorarlberg Health Monitoring and Promotion Program (VHM&PP), located in western Austria, is one of the world's largest ongoing population-based risk factor surveillance programs.¹¹ Since 1985, approximately two thirds of the adult population in the region have been examined, and the database currently includes information from health examinations of 166 547 men and women. From the outset, mea-

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.105.552547

2130

Longitudinal Change in Serum Gamma-Glutamyltransferase and Cardiovascular Disease Mortality. A Prospective Population-Based Study in 76 113 Austrian Adults

Strasak AM, Kelleher CC, Klenk J, Brant LJ, Ruttmann E, Rapp K, Concin H, Diem G, Pfeiffer KP, Ulmer H

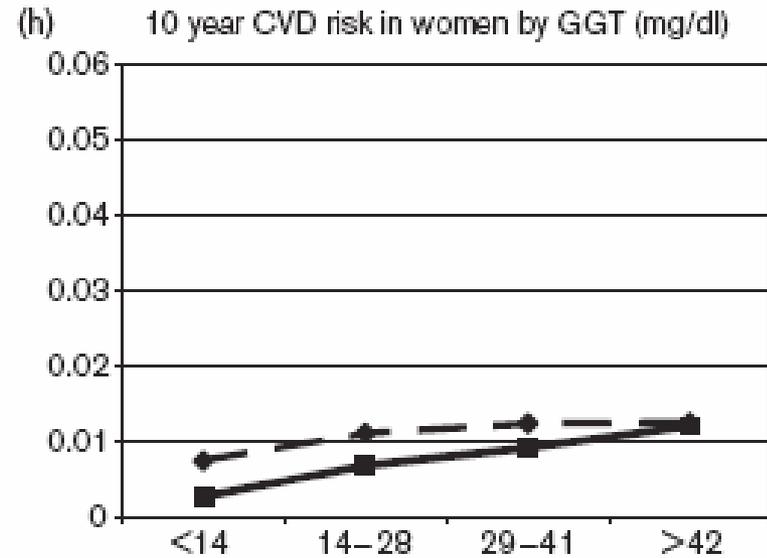
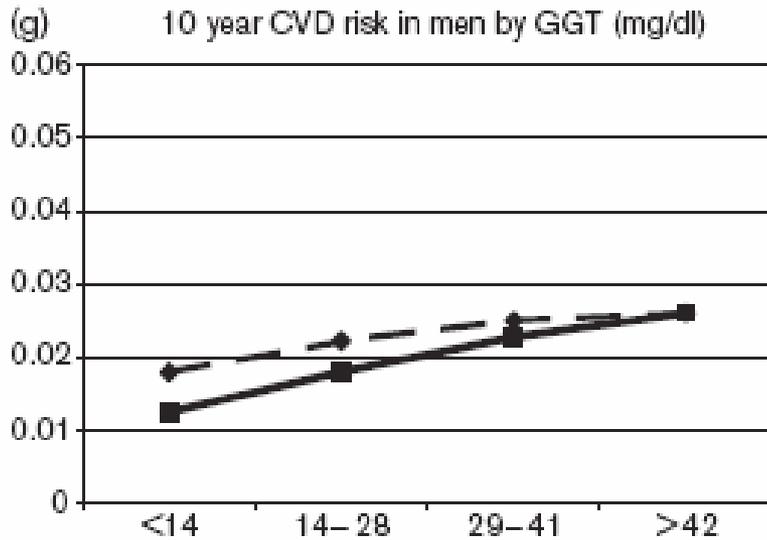
Our study is the first to demonstrate that a longitudinal increase in gamma-glutamyltransferase (GGT), independently of baseline GGT and even within its normal range, significantly increases risk of fatal cardiovascular disease.

The purpose of this study was to investigate the association of longitudinal change in serum γ -glutamyltransferase (GGT) with mortality from cardiovascular disease (CVD).

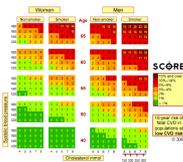
A population-based cohort of 76 113 Austrian men and women with 455 331 serial GGT measurements was prospectively followed-up for a median of 10.2 years after assessment of longitudinal GGT change during an average period of 6.9 years. Cox proportional hazards regression with time-varying covariates was used to evaluate GGT change as an independent predictor for CVD death. Independently of baseline GGT and other classical CVD risk factors, a pronounced increase in GGT (7-year change >9.2 U/L) was significantly associated with increased total CVD mortality in men ($P=0.005$); the adjusted hazard ratio (95% confidence interval) in comparison to stable GGT (7-year change -0.7 to 1.3 U/L) was 1.40 (1.09 to 1.81). Similarly, total CVD risk was elevated for increasing GGT in women, although effects were less pronounced and statistically significant only in subanalyses regarding coronary heart disease. Age of participants significantly modified the relation between GGT change and CVD mortality, with markedly stronger associations to be observable for younger individuals.

Our study is the first to demonstrate that a longitudinal increase in GGT, independently of baseline GGT and even within its normal range, significantly increases risk of fatal CVD.

GGT improves risk prediction



--- SCORE predicted — real CVD mortality



Serum uric Acid and risk of cardiovascular mortality: a prospective long-term study of 83 683 austrian men

Strasak A, Ruttman E, Brant L, Kelleher C, Klenk J, Concin H, Diem G, Pfeiffer K, Ulmer H

Our study demonstrates for the first time in a large prospective male cohort that serum uric acid is independently related to mortality from chronic heart failure and stroke.

The role of serum uric acid (SUA) as an independent risk factor for cardiovascular disease (CVD) remains controversial, and little is known about its prognostic importance for mortality from congestive heart failure (CHF) and stroke. Few large-scale epidemiologic studies with sufficient follow-up have addressed the association of SUA and CVD mortality in apparently healthy men across a wide age range.

A cohort of 83 683 Austrian men (mean age, 41.6 years) was prospectively followed for a median of 13.6 years. We used Cox proportional hazards models adjusted for established risk factors to evaluate SUA as an independent predictor for CVD mortality.

The highest quintile of SUA concentration ($>398.81 \mu\text{mol/L}$) was significantly related to mortality from CHF ($P=0.03$) and stroke ($P<0.0001$); adjusted hazard ratios (95% confidence interval) for the highest vs lowest quintiles of SUA were 1.51 (1.03–2.22) and 1.59 (1.23–2.04), respectively. SUA was not associated, however, with mortality from acute, subacute, or chronic forms of coronary heart disease (CHD) after adjustment for potential confounding factors ($P=0.12$). Age was a significant effect modifier for the relation of SUA to fatal CHF ($P=0.05$), with markedly stronger associations found in younger individuals.

Our study demonstrates for the first time in a large prospective male cohort that SUA is independently related to mortality from CHF and stroke. Although increased SUA is not necessarily a causal risk factor, our results suggest the clinical importance of monitoring and intervention based on the presence of an increased SUA concentration, especially because SUA is routinely measured.

Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: A prospective 21-year follow-up study

Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttman E, Concin H, Diem G, Pfeiffer KP, Ulmer H

These findings, for the first time, demonstrate that serum uric acid is an independent predictor for all major forms of death from CVD including acute, subacute and chronic forms of CHD, CHF and stroke in elderly, post-menopausal women.

The role of serum uric acid (SUA) as a risk factor for cardiovascular disease (CVD) remains controversial. Little is known about its predictive value for mortality from congestive heart failure (CHF) and stroke, particularly in elderly, post-menopausal women.

The relation of SUA to risk of death from total CVD, CHF, stroke and coronary heart disease (CHD) was examined prospectively in a large cohort of 28613 elderly Austrian women (mean age 62.3 years), followed-up for a median of 15.2 years. Adjusted Cox proportional hazards models were calculated to evaluate SUA as an independent predictor for fatal CVD events.

SUA in the highest quartile (≥ 5.41 mg/dL) was significantly associated with mortality from total CVD ($p < 0.0001$), showing a clear dose-response relationship; the adjusted hazard ratio (95%CI) in comparison to the lowest SUA quartile was 1.35 (1.20–1.52). In subgroup analyses SUA was independently predictive for deaths from acute and subacute ($p < 0.0001$) and chronic forms ($p = 0.035$) of CHD, yielding adjusted hazard ratios for the highest versus lowest SUA quartile of 1.58 (1.19–2.10) and 1.25 (1.01–1.56), respectively. SUA was further significantly related to fatal CHF ($p < 0.0001$) and stroke ($p = 0.018$); the adjusted hazard ratios for the highest versus lowest SUA quartile were 1.50 (1.04–2.17) and 1.37 (1.09–1.74), respectively.

These findings, for the first time, demonstrate that SUA is an independent predictor for all major forms of death from CVD including acute, subacute and chronic forms of CHD, CHF and stroke in elderly, post-menopausal women.

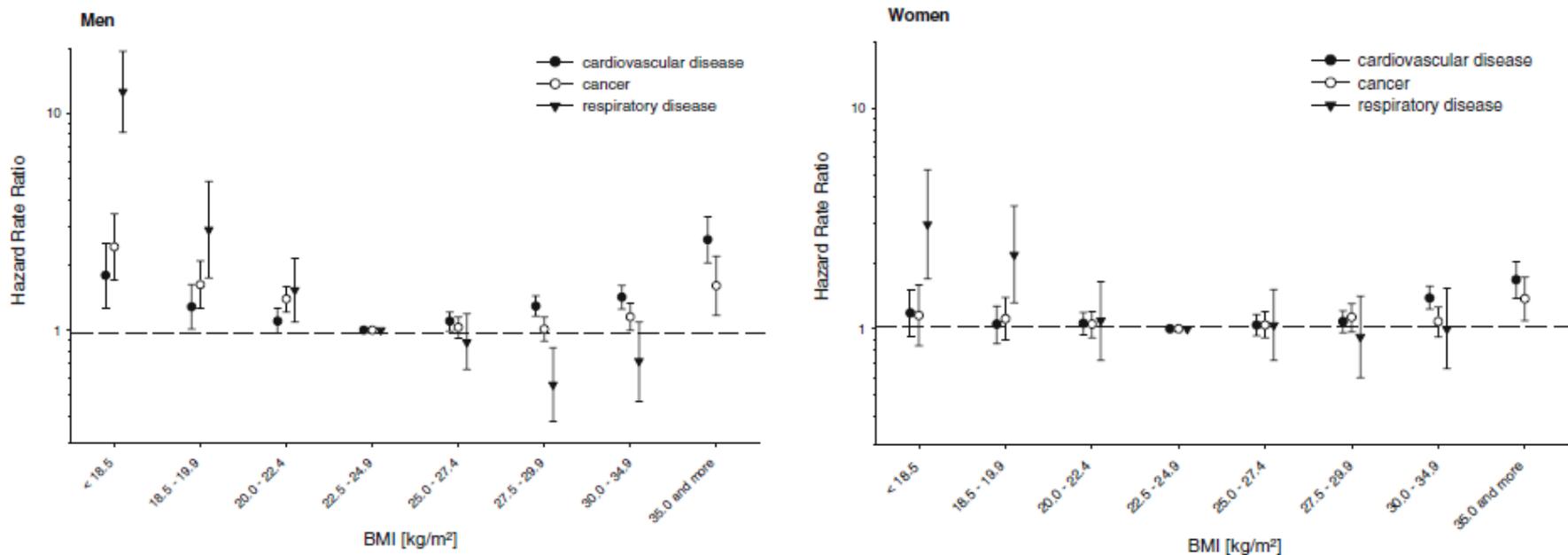
Body mass index and mortality: results of a cohort of 184,697 adults in Austria

Klenk J, Nagel G, Ulmer H, Strasak A, Concin H, Diem G, Rapp K

Underweight and obesity were both associated with higher all-cause mortality in men and women.

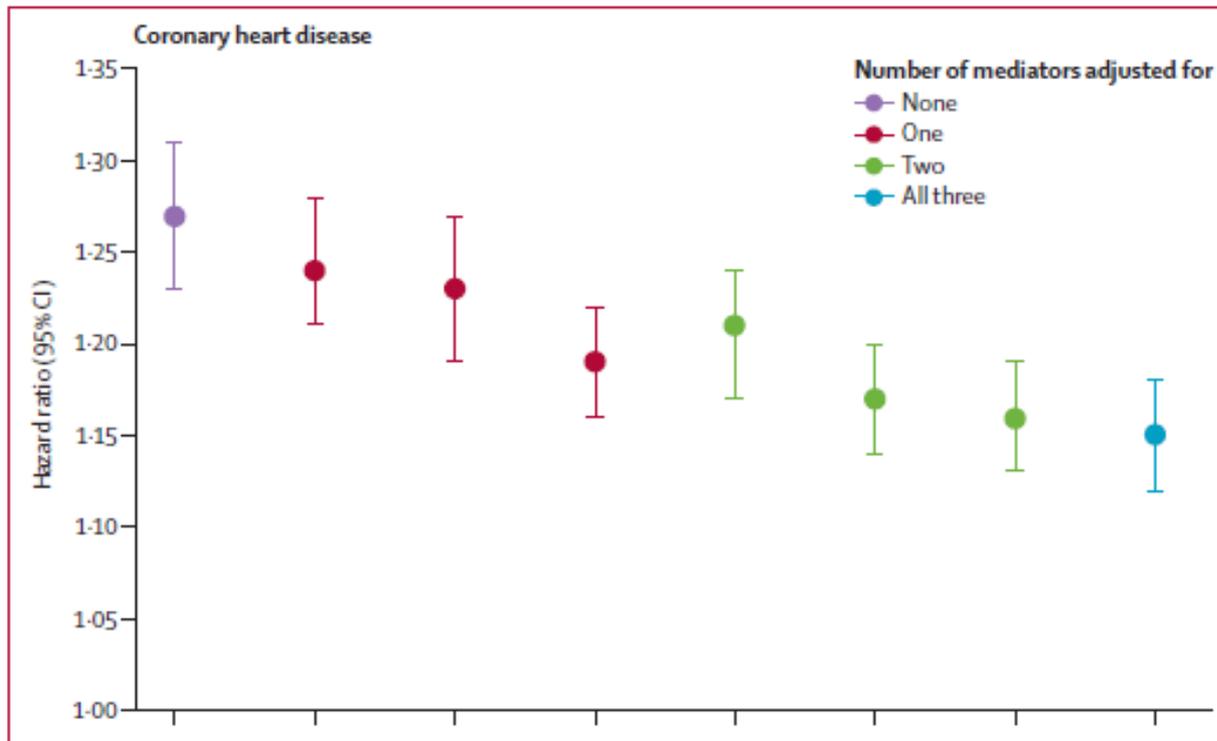
There is still a debate about the role of body mass index (BMI) as a risk factor for all-cause mortality. Most investigations with large sample sizes focused on populations from the United States, studies from Central-European cohorts are not available. We investigated the association between BMI and all-cause mortality and cause-specific mortality within a cohort in Austria. Design of this article is “Cohort study”. The Subjects used were 184,697 men and women (mean age 41.7 ± 15.4 years). Weight and height were measured. Cox proportional hazards models were used to estimate hazard ratios (HR). During a median follow-up of 15.1 years 15,557 deaths (6,077 from cardiovascular disease, 4,443 from cancer and 606 from respiratory disease) were seen. A U-shaped association between BMI and all-cause mortality was observed in men and women. Compared with the reference category (BMI 22.5–24.9 kg/m²) high risks were found both in the highest category of BMI (≥ 35 kg/m²) with HR of 2.13 (95% CI, 1.82–2.48) in men and 1.60 (95% CI, 1.42–1.81) in women and in the lowest category (≤ 18.5 kg/m²) with HR of 2.57 (95% CI, 2.17–3.05) in men and 1.40 (95% CI, 1.21–1.62) in women. Similar patterns were seen among ever-smokers and non-smokers. Increased mortality with increasing BMI was driven by cardiovascular diseases and to a lesser extent by cancers. Respiratory diseases contributed to mortality in the lowest BMI category independently from smoking status. Underweight and obesity were both associated with higher all-cause mortality in men and women.

Fig. 2 Association between BMI and all-cause mortality in men and women in the VHM&PP cohort 1985–2006, stratified by age at enrolment. Hazard Rate Ratios adjusted for smoking status. The reference category is BMI 22.5–24.9 kg/m². Error bars indicate 95% confidence intervals



Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, **Danaei G** on behalf of the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effect)

Metabolic mediators of the effect of body mass index, overweight and obesity on coronary heart disease and stroke: Pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014; 383(9921): 970-83.



Re: Mediators of the Effect of Body Mass Index on Coronary Heart Disease

To the Editor:

The question of how much of the harmful effect of increased body mass index (BMI) on cardiovascular events is mediated through cardiovascular risk factors is of high interest for clinical understanding, public health, and preventive health counseling. Therefore,

TABLE. Total, Direct, and Indirect Effects of Overweight and Obesity on Death from CHD (Compared with Normal Weight) for Metabolic Mediators Systolic Blood Pressure, Total Cholesterol, and Blood Glucose Controlling for Age, Sex, and Smoking Status, VHM&PP Data

Effects	<65 Years		≥65 Years	
	HR (95% CI) ^a	Proportion ^b (95% CI) ^a	HR (95% CI) ^a	Proportion ^b (95% CI) ^a
	Overweight (n = 33,558; 414 Deaths Due to CHD) vs. Normal Weight (n = 56,114; 234 Deaths Due to CHD)		Overweight (n = 4,078; 555 Deaths Due to CHD) vs. Normal Weight (n = 3,522; 471 Deaths Due to CHD)	
Total effect	1.45 (1.21, 1.76)	100%	1.06 (0.93, 1.21)	- ^c
Natural direct effect	1.24 (1.02, 1.52)	58% (10%, 75%)	1.00 (0.88, 1.14)	- ^c
Natural indirect effect	1.17 (1.14, 1.20)	42% (25%, 90%) ^d	1.06 (1.03, 1.10)	- ^c
	Obesity (n = 12,179; 195 Deaths Due to CHD) vs. Normal Weight (n = 56,114; 234 Deaths Due to CHD)		Obesity (n = 1,852; 258 Deaths Due to CHD) vs. Normal Weight (n = 3,522; 471 Deaths Due to CHD)	
Total effect	1.98 (1.58, 2.49)	100%	1.35 (1.15, 1.58)	100%
Natural direct effect	1.44 (1.09, 1.88)	54% (20%, 72%)	1.27 (1.07, 1.50)	80% (40%, 105%)
Natural indirect effect	1.37 (1.25, 1.50)	46% (28%, 80%) ^d	1.06 (0.99, 1.14)	20% (-5%, 60%) ^d

^aBootstrapping with 5,000 samples was used to calculate the uncertainty of the estimates.

^bOn ln(HR) scale.

^cPercentages as proportion of the total effect are not given. Estimates were numerically instable and therefore meaningless due to division by numbers close to zero.

^dThe proportion of the natural indirect effect on the total effect is also called the PERM.¹

CHD indicates coronary heart disease; CI, confidence interval; HR, hazard ratio; PERM, percentage of excess risk mediated.

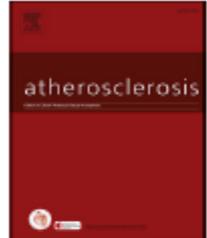


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Mediation analysis of the relationship between sex, cardiovascular risk factors and mortality from coronary heart disease: Findings from the population-based VHM&PP cohort



Josef Fritz ^a, Michael Edlinger ^a, Cecily Kelleher ^b, Susanne Strohmaier ^c,
Gabriele Nagel ^{d, e}, Hans Concin ^e, Elfriede Ruttmann ^f, Margarethe Hochleitner ^g,
Hanno Ulmer ^{a, *}

Können Risikofaktoren den Geschlechterunterschied in der Mortalität der koronaren Herzerkrankung erklären?

Effekt (Männer vs. Frauen)	<50 Jahren		≥50 Jahre	
	Hazard-Ratio (95% CI)	Anteil am Gesamteffekt (%) (95% CI)	Hazard-Ratio (95% CI)	Anteil am Gesamteffekt (%) (95% CI)
Gesamteffekt	4,65 (3,35–5,94)		1,88 (1,76–2,00)	
Indirekter Effekt über den systolischen Blutdruck	1,40 (1,26–1,55)	21,7% (12,4%–30,9%)	0,99 (0,99–0,99)	–1,4% (–1,7% bis –1,1%)
Indirekter Effekt über das Gesamtcholesterin	1,17 (1,11–1,23)	10,0% (6,0%–14,1%)	0,98 (0,97–0,99)	–3,5% (–5,0% bis –2,0%)
Indirekter Effekt über den Blutzucker	1,08 (1,03–1,13)	5,0% (1,9%–8,0%)	1,02 (1,01–1,02)	2,7% (2,2%–3,2%)
Indirekter Effekt über das Rauchverhalten	1,07 (1,03–1,10)	4,2% (2,1%–6,4%)	1,07 (1,05–1,09)	10,3% (7,1%–13,5%)
Indirekter Effekt über die vier Risikofaktoren zusammen	1,87 (1,61–2,14)	40,9% (27,1%–54,7%)	1,05 (1,03–1,08)	8,2% (4,6%–11,7%)

Studies in Cancer Epidemiology

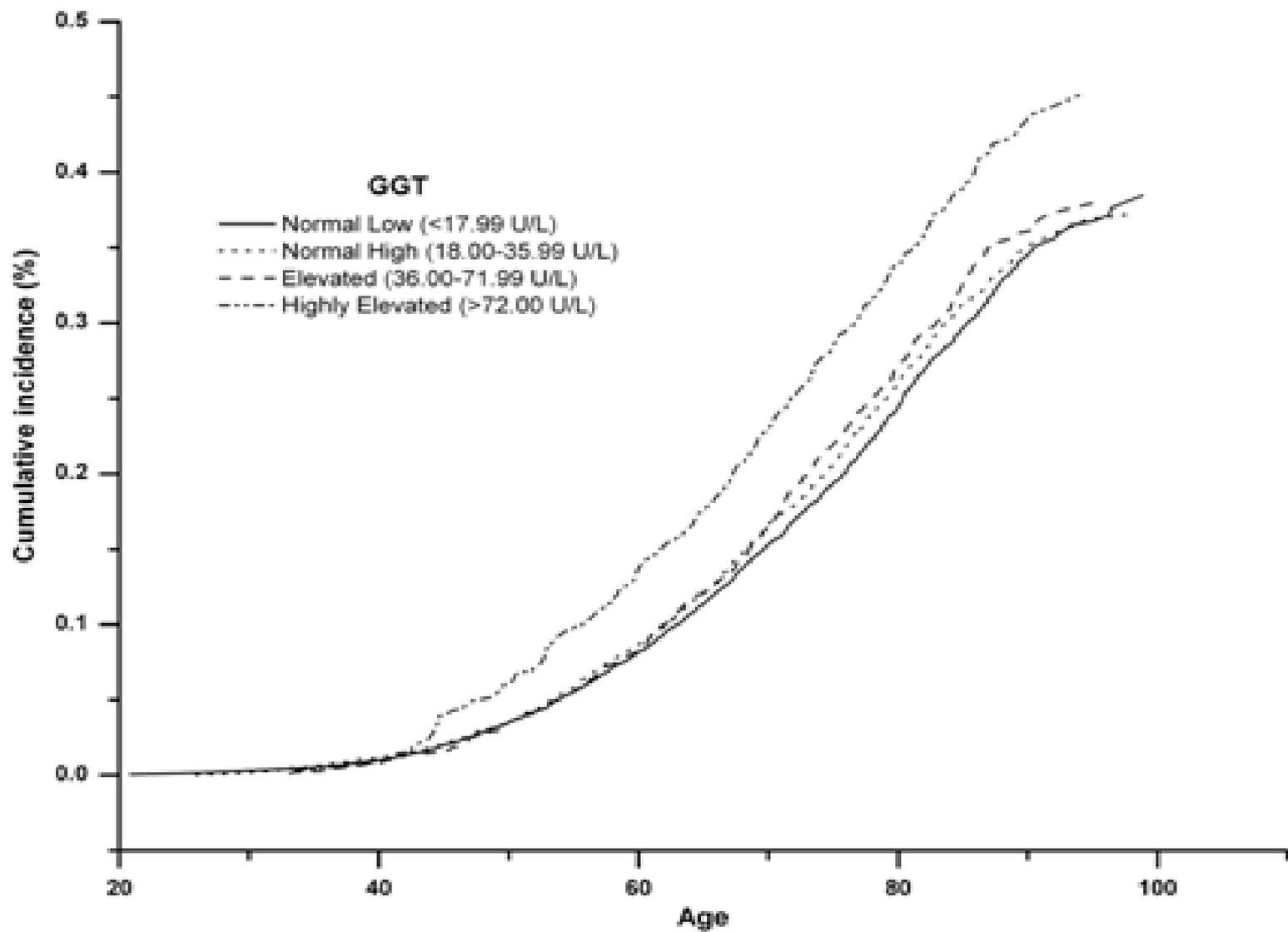
*The Vorarlberg Health Monitoring
& Promotion Programme
(VHM&PP)*

Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women

Strasak AM, Pfeiffer RM, Klenk J, Hilbe W, Oberaigner W, Gregory M, Concin H, Diem G, Pfeiffer KP, Ruttman E, Ulmer H

Our study is the first to demonstrate in a large population-based cohort that high gamma-glutamyltransferase levels significantly increased cancer risk in women.

Although several epidemiologic studies have shown that gammaglutamyltransferase (GGT) is associated with cardiovascular disease and all-cause mortality, its relationship with cancer incidence remains widely unexplored. In experimental models the ability of cellular GGT to modulate crucial redox-sensitive functions has been established, and it may thus play a role in tumor progression. In the present study, we investigated the association of GGT with overall and site-specific cancer incidence in a population-based cohort of 92,843 Austrian women with 349,674 serial GGT measurements, prospectively followed-up for a median of 13.5 years. The relationship between GGT and cancer incidence was analyzed using adjusted Cox regression models with age as underlying time metric with age as underlying time metric including GGT concentrations at baseline and incorporating repeated GGT measurements as a time-dependent variable. During follow-up, 4,884 incidence cancers were observed. Compared to normal low GGT (<17.99 U/L), cancer risk was elevated for all other GGT categories (p for trend < 0.0001), with adjusted hazard ratios (95% confidence intervals) of 1.06 (0.99–1.13) for GGT levels between 18.00 and 35.99 U/L (normal high), 1.12 (1.02–1.22) for GGT levels between 36.00 and 71.99 U/L (elevated) and 1.43 (1.28–1.61) for highly elevated GGT (>72.00 U/L). Very similar results were seen when GGT was analyzed as a time-dependent variable. In cancer-site specific models, elevated GGT statistically significantly increased the risk for malignant neoplasms of digestive organs, the respiratory system/intrathoracic organs, breast and female genital organs and lymphoid and haematopoietic cancers (all, p < 0.006). Our study is the first to demonstrate in a large population-based cohort that high GGT levels significantly increased cancer risk in women.



Association of Gamma-Glutamyltransferase and Risk of Cancer Incidence in Men: A Prospective Study

Strasak A, Rapp K, Brant L, Hilbe W, Gregory M, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H, VHM&PP Study Group

Our findings, for the first time, show that elevated gamma glutamyltransferase is significantly associated with increased cancer risk in men.

Although several epidemiologic studies have shown that γ -glutamyltransferase (GGT) is independently associated with cardiovascular disease and all-cause mortality, its relationship with cancer incidence remains widely unexplored. In several experimental models, the ability of cellular GGT to modulate crucial redox-sensitive functions has been established, and it thus may play a role in tumor progression, as has been repeatedly suggested. We prospectively investigated the association between GGT and risk of overall and site-specific cancer incidence in a large population-based cohort of 79,279 healthy Austrian men with serial GGT measurements. Median follow-up was 12.5 years. Adjusted Cox proportional hazards models were calculated to evaluate GGT as an independent predictor for cancer incidence, and nonparametric regression splines were fitted to flexibly capture the dose-response relationship. Elevated GGT significantly increased overall cancer risk, showing a clear dose-response relationship (P for GGT log-unit increase <0.0001; P for trend <0.0001). In comparison with the reference GGT concentration (25 units/L), we found adjusted relative risks (95% confidence intervals) equaling 1.19 (1.15-1.22) for GGT concentrations of 60 units/L, 1.32 (1.28-1.36) for 100 units/L, 1.67 (1.60-1.75) for 200 units/L, and 2.30 (2.14-2.47) for 400 units/L. In cancer site-specific models, GGT was significantly associated with malignant neoplasms of digestive organs, the respiratory system/intrathoracic organs, and urinary organs (all $P < 0.0001$). Age of participants significantly modified the association of GGT and cancer risk ($P < 0.001$), revealing markedly stronger associations in participants ages ≥ 65 years. Our findings, for the first time, show that elevated GGT is significantly associated with increased cancer risk in men.

Prospective Study of the Association of Serum Gamma-Glutamyltransferase with Cervical Intraepithelial Neoplasia III and Invasive Cervical Cancer

Strasak AM, Goebel G, Concin H, Pfeiffer RM, Brant LJ, Nagel G, Oberaigner W, Concin N, Diem G, Ruttman E, Gruber-Moesenbacher U, Offner F, Pompella A, Pfeiffer KP, Ulmer H

Our findings implicate a role for gamma-glutamyl transferase in the progression of premalignant cervical lesions to invasive cancer.

Epidemiologic studies indicate that elevated levels of γ -glutamyltransferase (GGT), a key enzyme of glutathione metabolism, might be associated with increased cancer risk. Furthermore, preclinical studies support a role for GGT in tumor invasion and progression. However, the relationship between GGT and risks of cervical intraepithelial neoplasia III (CIN-III) and invasive cervical cancer (ICC) have not been evaluated. We investigated the association of enzymatically determined GGT in blood serum with subsequent incidence of CIN-III and ICC in a prospective population-based cohort of 92,843 women ages 18 to 95, of whom 79% had at least one gynecologic examination including Pap smear testing during follow-up. Cox regression was used to compute adjusted hazard ratios (HR) with 95% confidence intervals for the association of GGT with CIN-III and ICC. During median follow-up of 13.8 years, 702 CIN-III and 117 ICC diagnoses were observed. Compared with normal low GGT (<17.99 units/L), risk of ICC was significantly elevated for all other baseline GGT categories, with adjusted HRs of 2.31 (1.49–3.59) for normal high GGT (18.00–35.99 units/L), 2.76 (1.52–5.02) for elevated GGT (36.00–71.99 units/L), and 3.38 (1.63–7.00) for highly elevated GGT [>72.00 units/L; P trend < 0.0001, HR log unit increase 3.45 (1.92–6.19)]. In contrast, associations between GGT serum levels and CIN-III risk were not statistically significant in the main analysis. Exclusion of the first 2 or 5 years of follow-up did not change the results. Effects did not differ by age, body mass index, or socioeconomic status. Our findings implicate a role for GGT in the progression of premalignant cervical lesions to invasive cancer.

Use of penalized splines in extended Cox-type additive hazard regression to flexibly estimate the effect of time-varying serum uric acid on risk of cancer incidence: a prospective, population-based study in 78,850 men

Strasak AM, Lang S, Kneib T, Brant LJ, Klenk J, Hilbe W, Oberaigner W, Ruttmann E, Kaltenbach L, Concini H, Diem G, Pfeiffer KP, Ulmer H

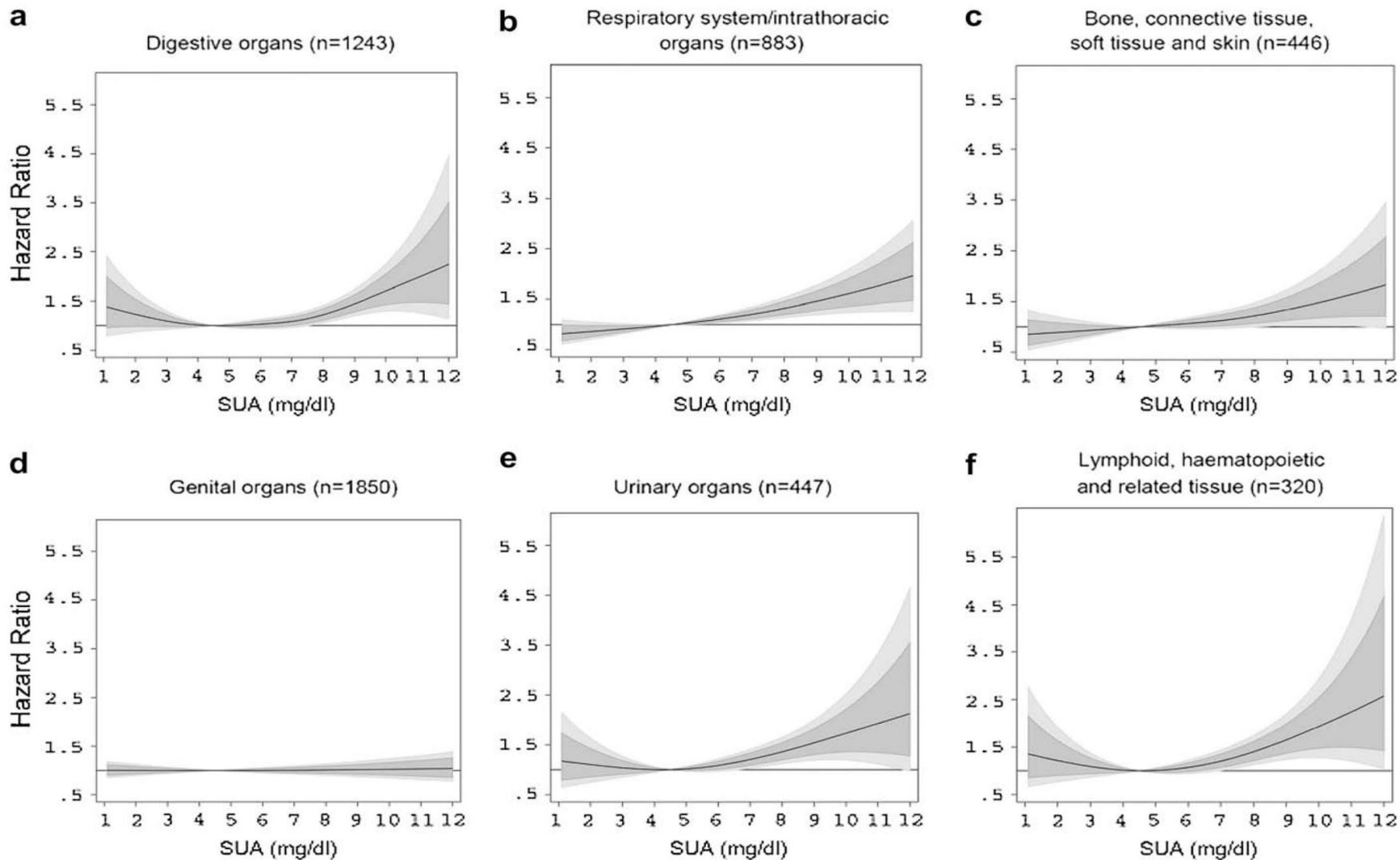
Our study is the first to demonstrate a dose–response association between serum uric acid and cancer incidence in men, simultaneously reporting on the usefulness of a novel methodological framework in epidemiologic research.

We sought to investigate the effect of serum uric acid (SUA) levels on risk of cancer incidence in men and to flexibly determine the shape of this association by using a novel analytical approach.

A population-based cohort of 78,850 Austrian men who received 264,347 serial SUA measurements was prospectively followed-up for a median of 12.4 years. Data were collected between 1985 and 2003. Penalized splines (P-splines) in extended Cox-type additive hazard regression were used to flexibly model the association between SUA, as a time-dependent covariate, and risk of overall and site-specific cancer incidence and to calculate adjusted hazard ratios with their 95% confidence intervals.

During follow-up 5,189 incident cancers were observed. Restricted maximum-likelihood optimizing P-spline models revealed a moderately J-shaped effect of SUA on risk of overall cancer incidence, with statistically significantly increased hazard ratios in the upper third of the SUA distribution. Increased SUA (>8.00 mg/dL) further significantly increased risk for several site-specific malignancies, with P-spline analyses providing detailed insight about the shape of the association with these outcomes.

Our study is the first to demonstrate a dose–response association between SUA and cancer incidence in men, simultaneously reporting on the usefulness of a novel methodological framework in epidemiologic research.



Time-dependent association of total serum cholesterol and cancer incidence in a cohort of 172 210 men and women: a prospective 19-year follow-up study

A.M. Strasak, R. M. Pfeiffer, L. J. Brant, K. Rapp, W. Hilbe, W. Oberaigner, S. Lang, W. Borena, H. Concin, G. Diem, E. Ruttmann, B. Glodny, K. P. Pfeiffer, H. Ulmer, and the VHM&PP Study Group

We observed pronounced inverse associations of total serum cholesterol and overall cancer incidence in both men and women.

The relationship between serum cholesterol and cancer incidence remains controversial.

We investigated the association of total serum cholesterol (TSC) with subsequent cancer incidence in a population-based cohort of 172 210 Austrian adults prospectively followed up for a median of 13.0 years. Cox regression, allowing for time-dependent effects, was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) for the association of TSC with cancer.

We observed pronounced short-term associations of TSC and overall cancer incidence in both men and women. For malignancies diagnosed shortly (<5 months) after baseline TSC measurement, the highest TSC tertile (>235.0 mg/dl in men and >229.0 in women) compared with the lowest tertile (<194.0 mg/dl in men and <190.0 in women) was associated with a significantly lower overall cancer risk [HR = 0.58 (95% CI 0.43–0.78, $P_{\text{trend}} = 0.0001$) in men, HR = 0.69 (95% CI 0.49–0.99, $P_{\text{trend}} = 0.03$) in women]. However, after roughly 5 months from baseline measurement, overall cancer risk was not significantly associated with TSC. The short-term inverse association of TSC with cancer was mainly driven by malignancies of the digestive organs and lymphoid and hematopoietic tissue.

The short-term decrease of cancer risk seen for high levels of TSC may largely capture preclinical effects of cancer on TSC.

Serum triglyceride concentrations and cancer risk in a large cohort study in Austria

Ulmer H, Borena W, Rapp K, Klenk J, Strasak A, Diem G, Concin H, Nagel G

Our findings support the hypothesis that serum triglyceride concentrations are involved in the pathogenesis of lung, rectal, thyroid, prostate, and gynaecological cancers.

Blood lipid levels as part of the metabolic syndrome are thought to be linked to cancer risk. Few epidemiological studies have addressed the association between serum triglyceride (STG) concentrations and cancer risk.

Serum triglyceride concentrations were collected in a health investigation (1988–2003). The analyses included 156 153 subjects (71 693 men and 84 460 women), with 5079 incident cancers in men and 4738 cancers in women, and an average of 10.6 years of follow-up. All malignancies were ascertained from the population cancer registry. Multivariate Cox proportional hazard models stratified by age and sex were used to determine adjusted cancer risk estimates and 95% confidence interval (95% CI).

In men and women combined, higher STG concentrations were associated with increased risk of lung (4th vs 1st quartile: HR, 1.94; 95% CI, 1.47–2.54), rectal (HR, 1.56; 95% CI, 1.00–2.44), and thyroid cancer (HR, 1.96; 95% CI, 1.00–3.84). Serum triglyceride concentrations were inversely associated with non-Hodgkin's lymphoma. In men, STG concentrations were inversely associated with prostate cancer and positively with renal cancer. In women, STG concentrations were positively associated with gynaecological cancers. Stratification by BMI revealed a higher risk of gynaecological cancers in overweight than in normal weight women. No other associations were found.

Our findings support the hypothesis that STG concentrations are involved in the pathogenesis of lung, rectal, thyroid, prostate, and gynaecological cancers.



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