Big data – Statistische Methoden und die größten medizinwissenschaftlichen Erfolge

Hanno Ulmer

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

Contact: hanno.ulmer@i-med.ac.at

Introduction

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.

Introduction

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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 applied for medical research under the name of "Vorarlberg Health Monitoring & Promotion Programme" (VHM&PP).

Introduction

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During the last decade, the research output from analyses of the VHM&PP database was considerable. Original publications on how risk factors track over time, on the way patterns of heart diseases vary by season, and on gender differences and secular trends in chronic disease have all made contributions to medical literature.

The research has provided a novel understanding of how gamma-glutamyltransferase and uric acid are associated with both cardiovascular and cancer outcomes.

Recently VHM&PP contributed to several international pooled analyses which enhanced the understanding on how metabolic factors are involved in the risk of chronic diseases.

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vhmpp, aks

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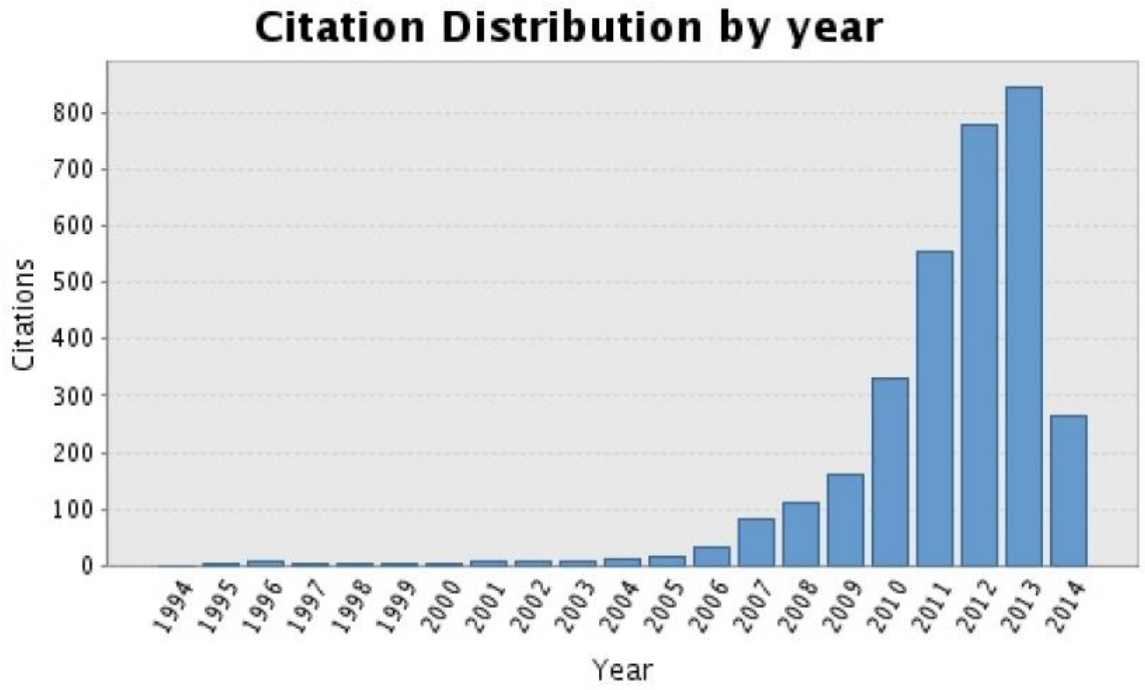
URL: **http://www.researcherid.com/rid/F-9756-2012**

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

My Institutions (more details)

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

Sub-org/Dept:



Total Articles in Publication List: **94**

Articles With Citation Data: **90**

Sum of the Times Cited: **3246**

Average Citations per Article: **36.07**

h-index: **25**

Last Updated: **05/28/2014 12:56 GMT**

How did it get started?

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- 1994 I was introduced by Hans Concin to the aks
- The aks had already a well established IT system (INFORMIX database)
- Results of every health examination performed in Vorarlberg were entered into the database by four data managers
- Data were used mainly for accounting purposes
  GP`s got their payment only when delivering the data sheet (contributes importantly to data quality)
  Reports for GP`s were produced
- Data were not used for research
- However, there were already research activities with data from two health surveys: WHO CINDI 1986 and 1991

What was available in the late 1990s?

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- Results of health examinations of more than 100,000 people
- Routinely collected health data from 1985 onwards
- Health check-up includes consultation with a doctor, a physical examination and a fasting blood test
- Variables in the data set were limited, however all major cardiovascular risk factors were included
- People were systematically re-invited with personal letters to health checks-up.
- Mortality data was recorded as well (to prevent re-invitations of deceased)

VORSORGEUNTERSUCHUNG MÄNNER

Legende für Stammsatz: Grauraster... freilassen DVR-Nr. 0081485

ZUNAME	VORNAME

VERS.-NR.	TAG	MON.	JAHR

GM.-NR.	ANSCHRIFT

ANDERE KRANKK.	19 GKK	05 ÖBB	07 BVA	59 Bauern	40 gew.W.	9A KFA-Breg.	99 nicht vers.

1 LEDIG	2 VERH.	3 VERW.	4 GESCH.	BERUF

VERSICH. DURCH

ZUNAME	VORNAME

VERS.-NR.	TAG	MON.	JAHR

ARZT-NR.	ARZT

Unters.-Datum	1. Untersuchung	2. Untersuchung	3. Untersuchung	4. Untersuchung
Beratungs-Datum	1. Beratung	2. Beratung	3. Beratung	4. Beratung

F. WIEDERBESTELLUNG IN

1 1/2 Jahren	1				
2 1/2 Jahren	2				

D. VORSORGEBERATUNG

31 Risiko familiär (Fragebogen)						33 Risiko aus Unters.-Befund					
Krebs	1					Krebs	1				
Stoffwechsel	2					Übergew.	2				
Kreislauf	3					Zucker	3				
32 Risiko pers. (Fragebogen)						Fettstatus	4				
Streß	1					Harnsäure	5				
Alkoholabusus	2					Herz-Kreisl.	6				
Bewegungsm.	3					Harntrakt	7				
bis 10 Zigar.	4					Magen-Darmtr.	8				
bis 20 Zigar.	5					andere	9				
über 20 Zigar.											
Rauchen seit mehr als 10 Jahren											
Rauchen seit mehr als 20 Jahren											
Exraucher	9										

C. BLUTCHEM. LABOR

Werte eintragen		1	2	3	4
Nüchternblutzucker	22				
Harns., Trigl., Chol. und G-GT kann der unters. Arzt bei Sond. Vers.trägern selbst durchführen; bei Selbstdurchführung nebenst. Kästchen jeweils ankreuzen →		☐	☐	☐	☐
Harnsäure	25				
Triglyceride	26				
Cholesterin	27				
Gamma GT	28				

B. LABORPR.

Harn						18 Stuhl-Blut (ab 40. Lj)					
16 Nitrit pos.	1					positiv	1				
Eiw. pos.	2					19 HGB					
Gluc. pos.	3					über 14	1				
17 Urobil. pos.	1					12–14	2				
Blut pos.	2					10–12	3				
35 Leukoz. vermehrt	1					unter 10	4				
pH. Wert eintragen	2					20 BSG					
Keton pos.	3					15/30	1				
Bilirub. pos.	4					30/60	2				
						über 30/60	3				

Lohs 745*

KS 0200/95/9/8 000

Why was this database not used for research?

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- Only a few people showed interest in medical and epidemiological research (still so)
- Hans Concin always believed that the database has great potential for research and he supported all research activities, however he was almost alone
- Epidemiological and statistical expertise was missing
- It was argued that the data is self-selected, therefore useless, biased to people with a deeper interest in their health
- Computational problems
  a standard PC with SPSS could not handle the data in the late nineties

Milestones on the way to the re-use of the database

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- Another visionary person: Prof. 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, Concin 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) and Ruth Pfeiffer, National Cancer Institute
- Another publication in an international top-ranked journal:
  Ruttmann E, Brant L, Concin H, Diem G, Rapp K, Ulmer H. Gamma-glutamyltransferase as a risk factor for cardiovascular mortality: an epidemiological investigation in 163,944 Austrian adults: Circulation 2005.

Milestones on the way to the re-use of the database

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- The involvement of epidemiologists from nearby located University of Ulm: Prof. Stefan Weiland, Killian Rapp, Jochen Klenk and Gabriele Nagel
- Invitation to collaborate in the Metabolic Syndrome and Cancer (Me-Can) Project
- Participation with VHM&PP data to the Emerging Risk Factor Collaboration (ERFC) and the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration
- Highly motivated Post-Docs and PhD scientists: Elfriede Ruttmann-Ulmer, Alexander Strasak, Wegene Borena, Susanne Strohmaier, Michael Edlinger

A big asset: cancer registry in house

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- Cancer registry and health examinations are both run by the aks
- Cancer registry was established in 1978
- Information about cases from Institute of Pathology (Feldkirch), and hospital discharge diagnoses
- DCO-rate: 1993-97 7% in women and 9% in men, after 1997: 5%, now 3%
- Published in Cancer Incidence in Five Continents Vol. VIII, Vol. IX
- ICD-O-1 (topography, morphology), limited data regarding staging, grading
- High proportion of cancers is histology proven

Health examinations in Vorarlberg (Austria)

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	Total	Men	Women
All VHM&PP participants 1985–2003, no.	174 852	80 224	94 628
Eligible participants for analyses, no.[a]	172 210	79 417	92 793
Age at entry, mean ± SD (range), y	41.6 ± 15.3 (18–96)	41.7 ± 14.6 (18–96)	41.6 ± 15.9 (18–95)
Body mass index, mean ± SD (median), kg/m^2	24.7 ± 4.2 (24.2)	25.3 ± 3.6 (24.9)	24.2 ± 4.6 (23.3)
Total serum cholesterol, mean ± SD (median), mg/dl	215.4 ± 46.7 (211.0)	217.4 ± 47.2 (214.0)	213.7 ± 46.3 (209.0)
Cigarette smoking, %	25.5	30.1	21.5
Follow-up, mean ± SD (median), y	11.6 ± 5.6 (13.0)	11.3 ± 5.6 (12.5)	12.0 ± 5.6 (13.5)
Total person-years at risk	2 004 174	894 645	1 109 529
Incident cancers, no. (%)	9958 (5.8)	5311 (6.7)	4647 (5.0)
Age at cancer diagnosis, mean ± SD (range), y	56.6 ± 12.9 (19–93)	57.1 ± 12.2 (19–93)	55.4 ± 13.8 (19–93)

Challenges on the way to the re-use of the database

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- Data privacy
- Informed consent and ethical approval
- Computational problems (in the beginning)
- Data management and record linkage
- External validity - self selected sample
- Repeated measurements
- Measurement error
- Non-linear relationships

Data management and record linkage

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- Extensive maintenance of personal master data was necessary
- A unique key was necessary for both the health examination data and the cancer registry
- Quality of record linkage with outcome data (morbidity, mortality) was of high importance
- We adapted a method of probabilistic record linkage (Oberaigner Meth Inf Med 2005)
- Mortality record linkage was performed annually with Statistics Austria
- Changes in data acquisition, laboratory reference values etc.
- Secure data transfer

Population based or population biased

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We compared
- the unplanned self selected health examination sample with
- the planned randomly chosen CINDI survey sample

and there were only small differences (Ulmer et al ÖZS 1995).

It seems that the same people who refused to participate in the health survey (response rate 60%), also refused to take part in the general health examinations.

In the landmark Framingham study the random sample forming the cohort had to be “enriched” by volunteers to compensate for its relatively low response rate (69%).

Statistical analysis

In outcome studies, modelling was generally done by Cox proportional hazard regression with calendar time or attained age as time-scale and adjusted for covariates such as birth year, baseline age or smoking status, seperately for males and females.

In some studies, we also made use of time-dependent covariates in the Cox model.

To model continuous risk variables, especially for non-linear relationships, we used spline regression and fractional polynomials.

Non-linear relationships

Penalized Splines in Extended Cox-type additive hazard regression as novel statistical-methodological framework to flexibly model dose-response associations

- Additive extension of the classical Cox model (Kneib/Fahrmeir 2007): Baseline hazards and non-linear effects of covariates are estimated by penalized splines (Eilers/Marx 1996)
- No manual knot tuning through combining penalization of the spline coefficients with automatic choice of the smoothing parameter by restricted maximum likelihood (REML) estimation
- R2BayesX und BayesXsrc (Umlauf 2012)

Penalized splines – graphical illustration

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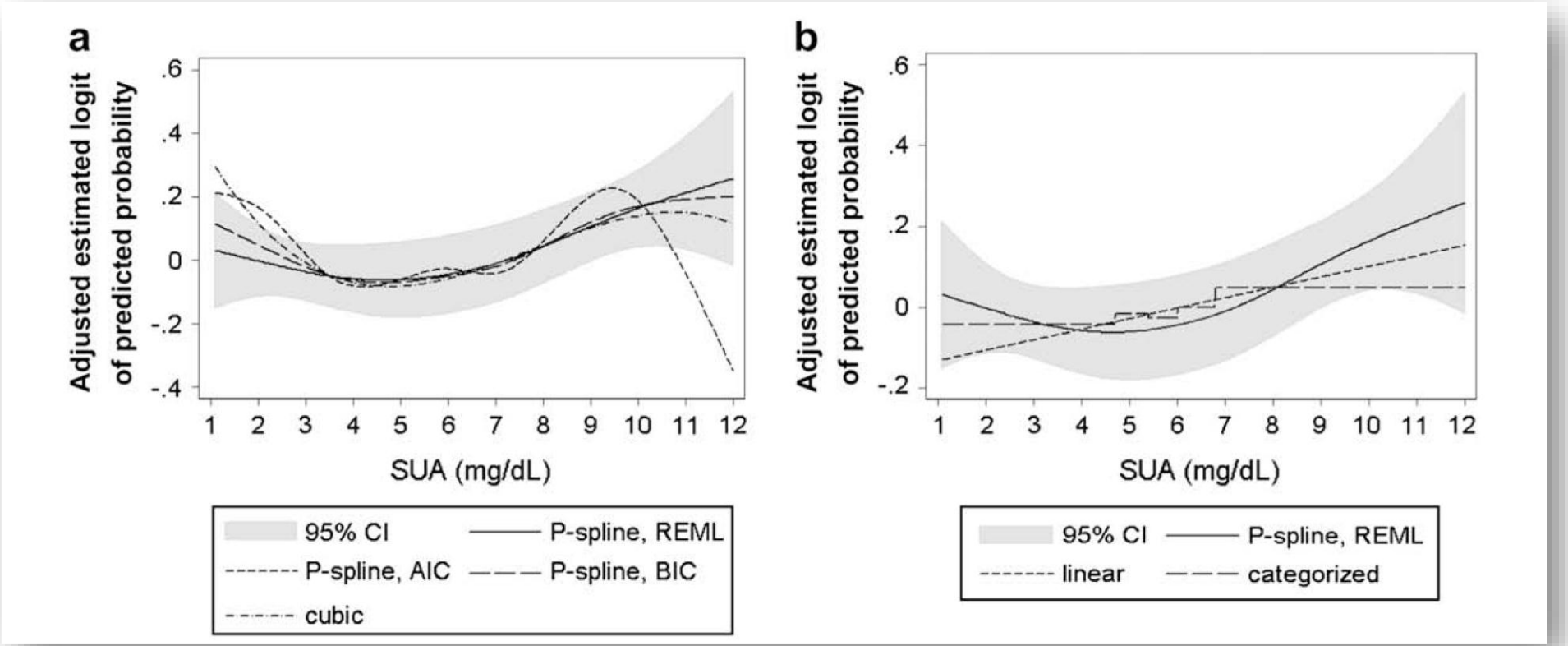

Strasak et al. Ann Epidemiol 2008

Repeated measurements

The use of repeated measurements still statistically challenging:

- Irregular number of repeated measurements per individual
- Irregular time intervals of repeated measurements
- Number and time intervals are not randomly distributed and may be informative

Measurement error

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Repeated measurements allow the correction for random error and within-person variability of the exposure measurements, to counteract regression dilution bias of risk associations.

Regression dilution ratios were estimated with linear mixed effect models

$$y_{ijr} = a + a_i + (b + b_i + c_1|t_{ijr}|)\, y_{ij0} + c_2 t_{ijr} + \sum_{k=1}^{p} \alpha_k x_{ij0,k} + \sum_{l=1}^{q} \beta_l z_{ij0,l} + \varepsilon_{ijr}$$

Regression dilution ratio = $(b+b_i+c_1|t_{ijr}|)$

or GEE models

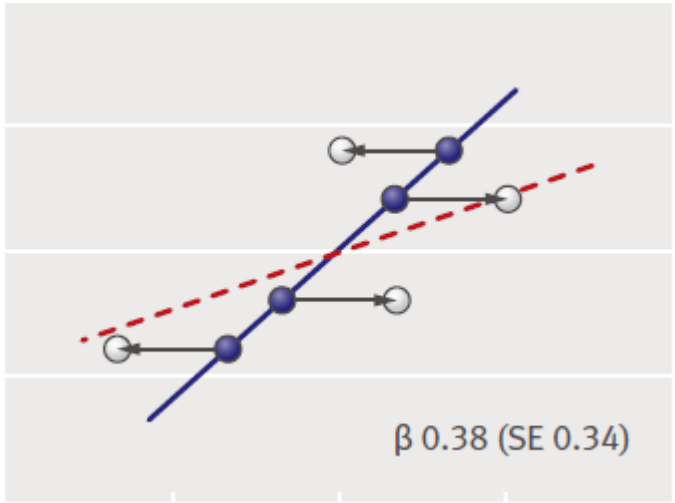
$$Y_{it} = \beta_0 + \beta_1 Y_{it_1} + \beta_2 t + \varepsilon_{it}$$

Regression dilution ratio = (β_1

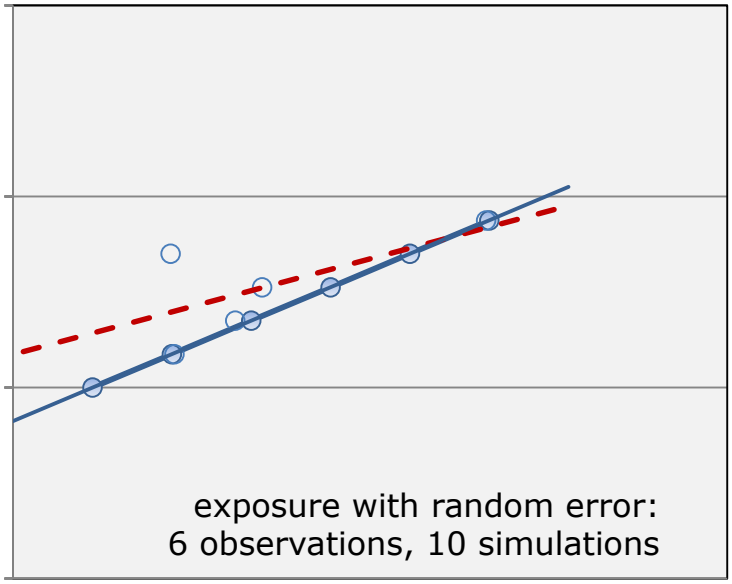
Regression dilution bias

Exposure variables:

- random errors at measurement
- short- and long-term variations of individuals

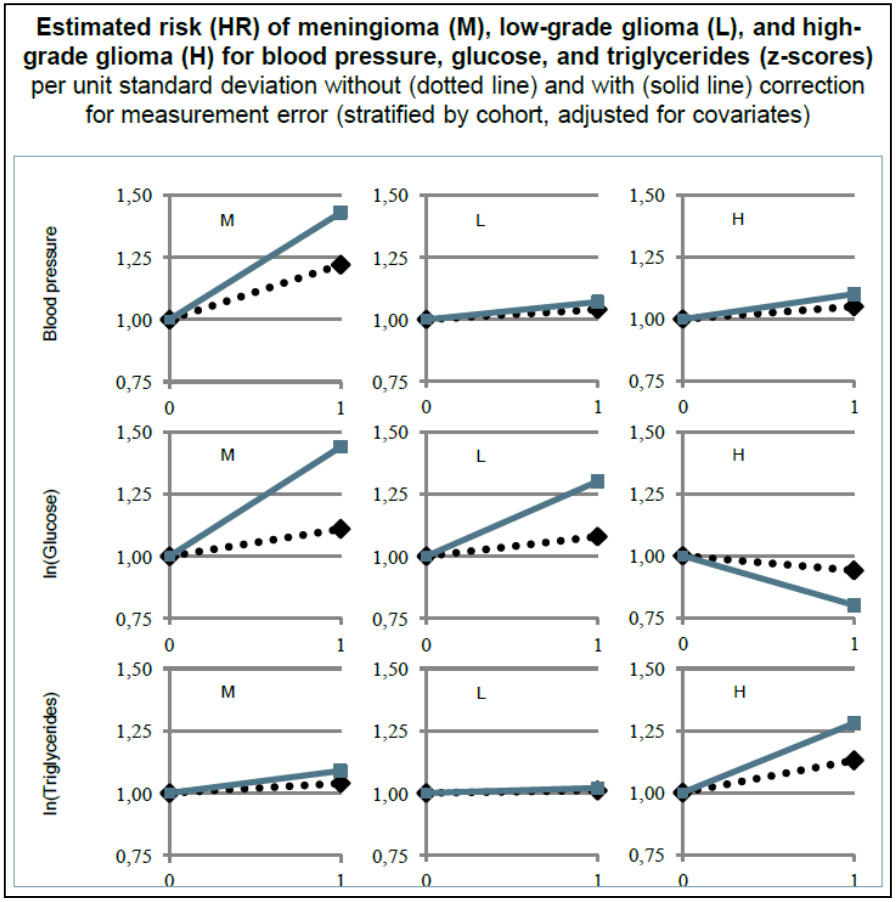


Hutcheon JA et al. Br Med J 2010;340:1402-1406



Underestimation of associations ?

Regression dilution bias



With only one baseline measurement of exposure: bias can lead to substantial underestimation of effects

(same p-value)

Publications

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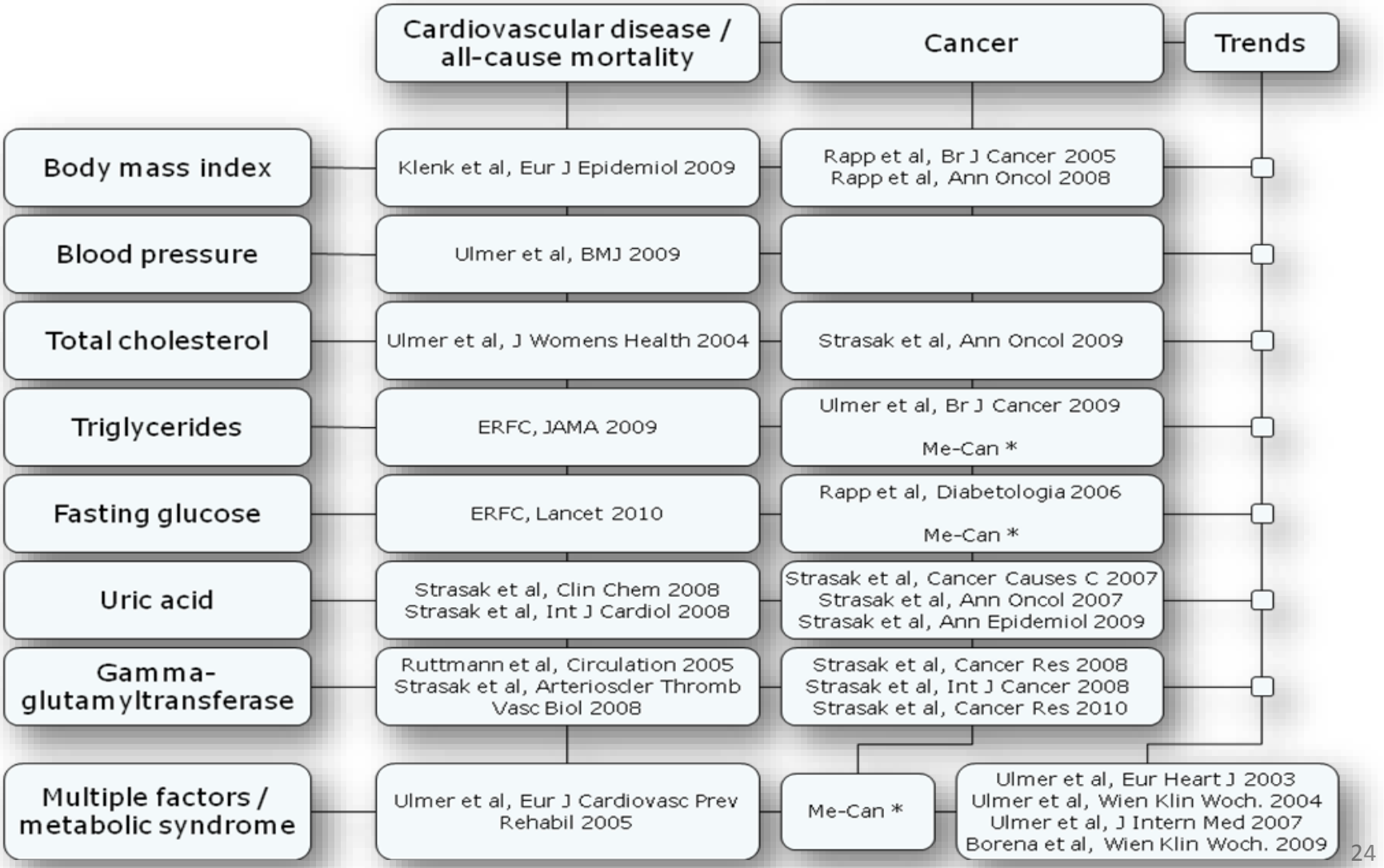


Studies in Cardiovascular Epidemiology

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, Ruttmann 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

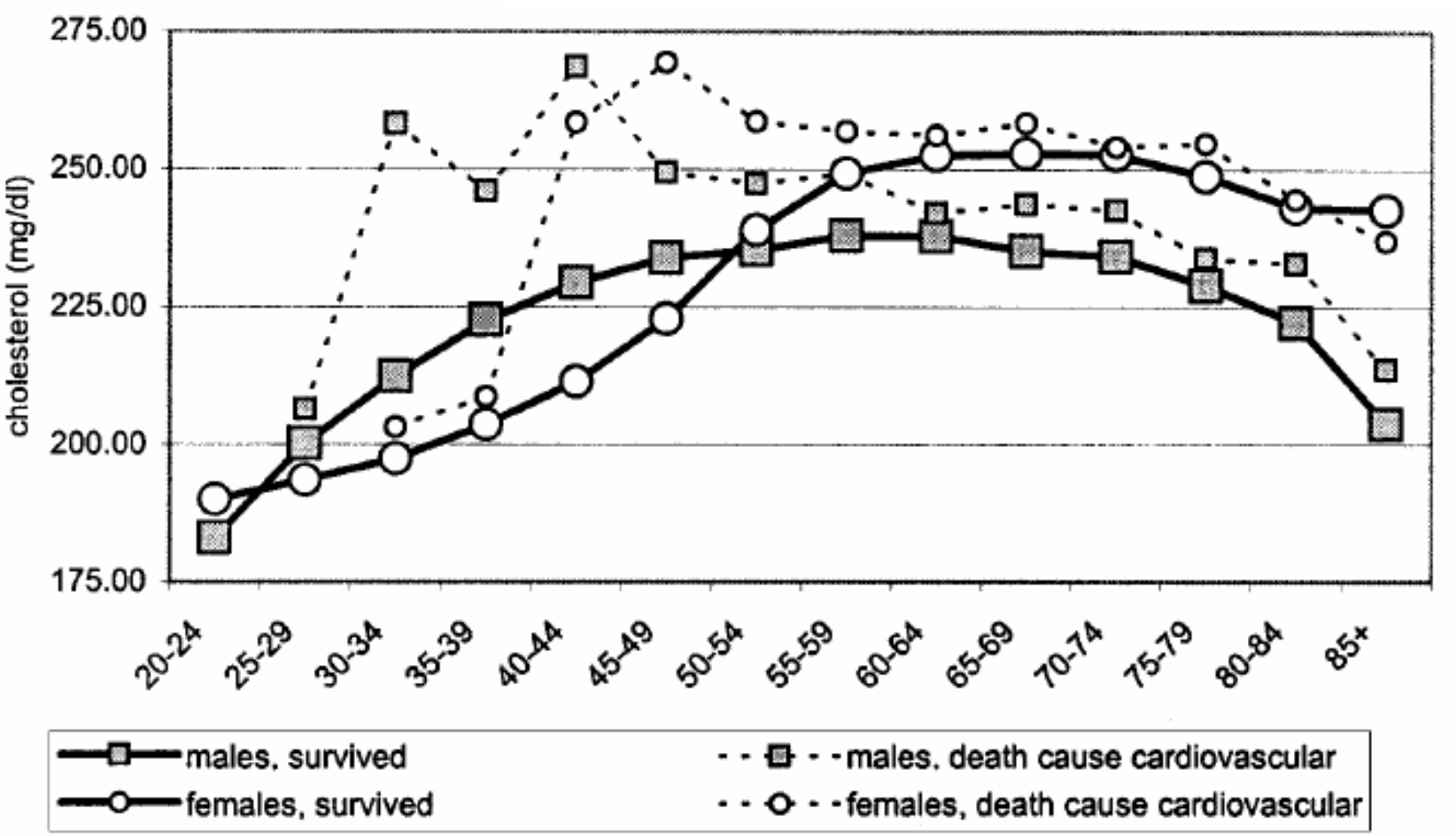
Cholesterol shows pronounced sex-specific differences

To assess the impact of sex-specific patterns in cholesterol levels on all-cause andcardiovascular 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.


275.00
250.00
225.00
200.00
175.00
cholesterol (mg/dl)
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
males, survived
females, survived
males, death cause cardiovascular
females, death cause cardiovascular

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

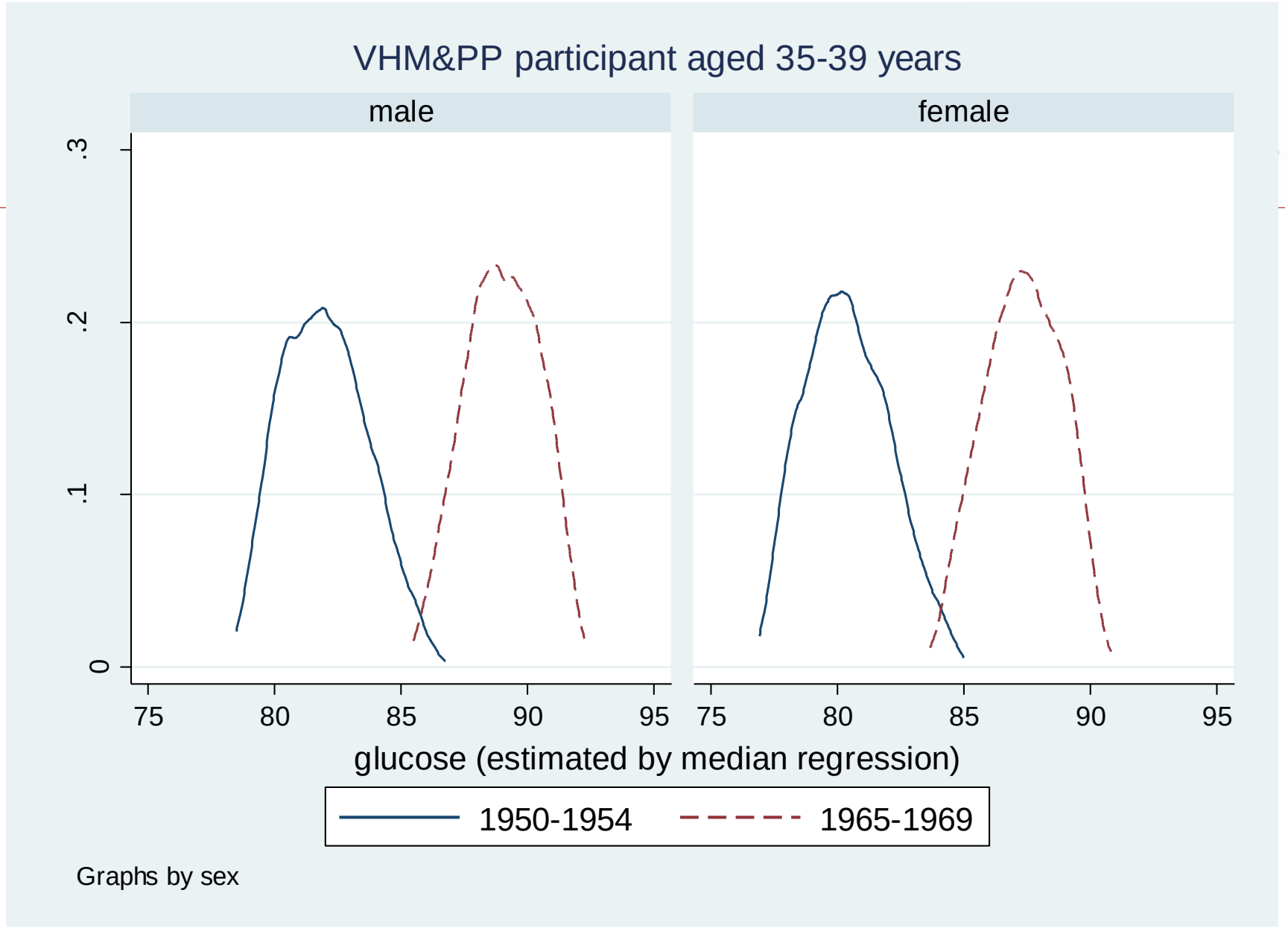
Blood lipids and blood pressure declined. By contrast, fasting glucose showed a strong rising tendency, most markedly in young males.

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
male
female
.3
.2
.1
0
75
80
85
90
95
glucose (estimated by median regression)
1950-1954
1965-1969
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

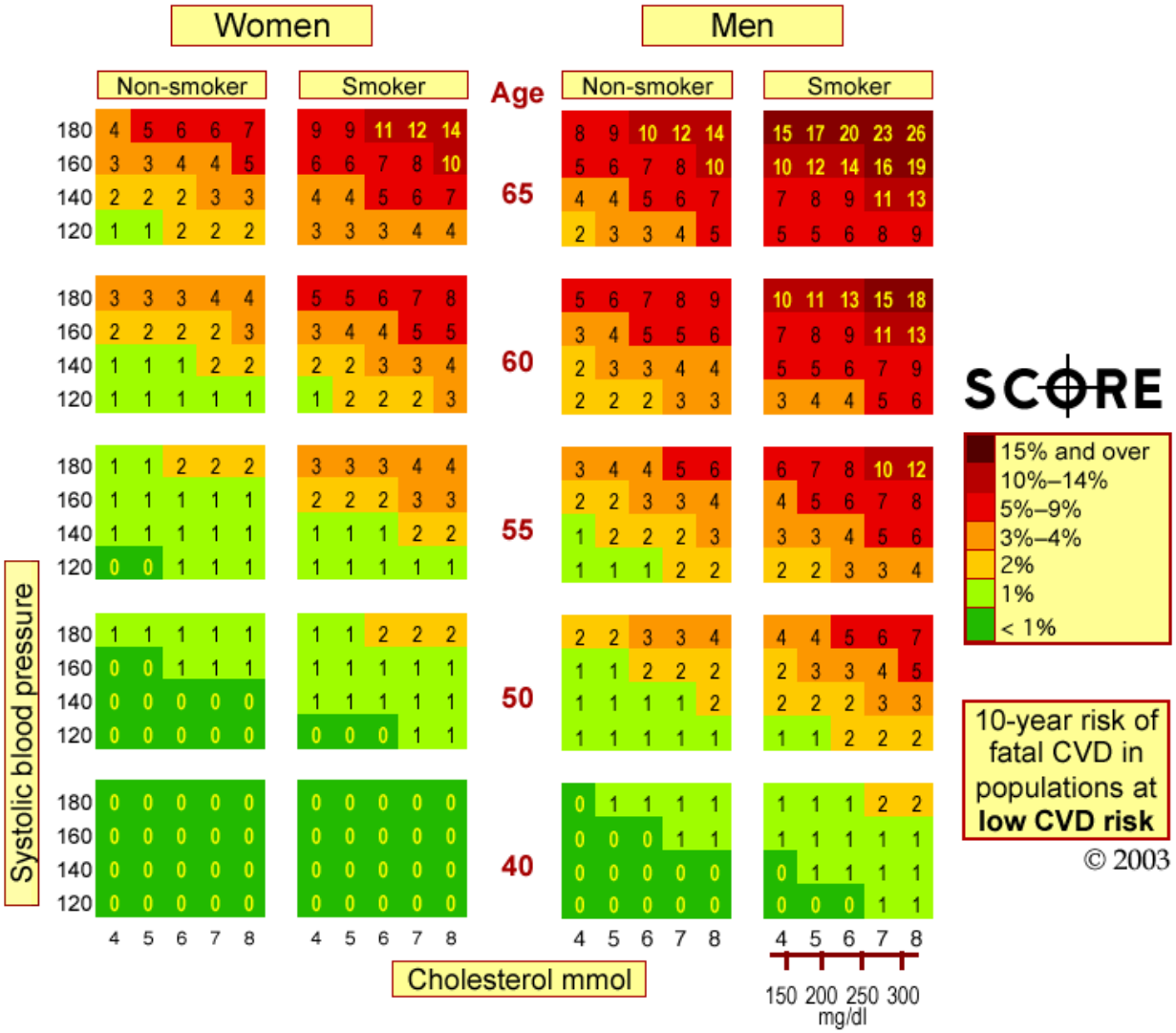
The SCORE overpredicted the mortality pattern in the cohort as a whole, its predictive ability at the individual level still demonstrates a potentially widespread utility in clinical practice.

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.


Women
Men
Non-smoker
Smoker
Non-smoker
Smoker
Age
65
60
55
50
40
Systolic blood pressure
180 160 140 120
4 5 6 7 8
Cholesterol mmol
150 200 250 300
mg/dl
SCORE
15% and over
10%–14%
5%–9%
3%–4%
2%
1%
< 1%
10-year risk of fatal CVD in populations at low CVD risk
© 2003

Editorial

Gamma-Glutamyltransferase, Atherosclerosis, and Cardiovascular Disease

Triggering Oxidative Stress Within the Plaque

Michele Emdin, MD, PhD; Alfonso Pompella, MD, PhD; Aldo Paolicchi, 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.[1,2]

Article p 2130

The prospective study by Ruttman 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-cisteinyl-glycine), the main thiol intracellular antioxidant agent in mammalian cells.[1] 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] 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 men[6] 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 autoptic studies and surgical endoarterectomy, 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 Fe^{3+} in the extracellular milieu—and likely at the plaque level—that is able to simultaneously generate Fe^{2+} and a free thiyl 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-

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.).

Correspondence to Michele Emdin, MD, PhD, Cardiovascular Medicine Dept, Institute of Clinical Physiology, National Research Council (CNR), Via Giuseppe Moruzzi 1, 56124 Pisa, Italy. E-mail emdin@ifc.cnr.it

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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 Concin, 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 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.

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.

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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 formation.[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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From the Department of Medical Statistics, Informatics, and Health Economics, Innsbruck Medical University, Innsbruck, Austria (E.R., H.U.); Gerontology Research Center, National Institute on Aging, Baltimore, Md (L.J.B.); Agency for Preventive and Social Medicine, Bregenz, Austria (H.C., G.D., H.U.); and Department of Epidemiology, University of Ulm, Ulm, Germany (K.R.).

Correspondence to Hanno Ulmer, PhD, Department of Medical Statistics, Informatics, and Health Economics, Innsbruck Medical University, Schoepfstrasse 41, A-6020 Innsbruck, Austria. E-mail hanno.ulmer@uibk.ac.at

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

Ruttmann 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.

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

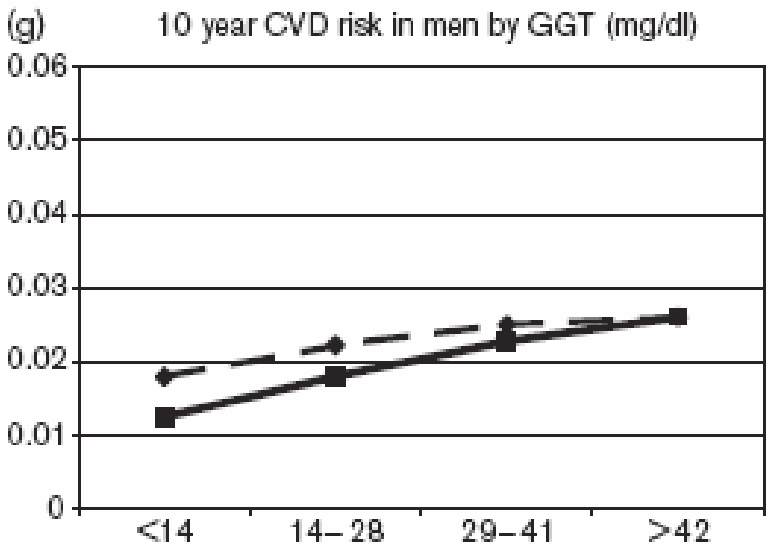
Our study is the first to demonstrate that a longitudinal increase in gamma-glutamyltransferase (GGT), independently of baseline GGT and even within its normal range, significantly increases risk of fatal cardiovascular disease.

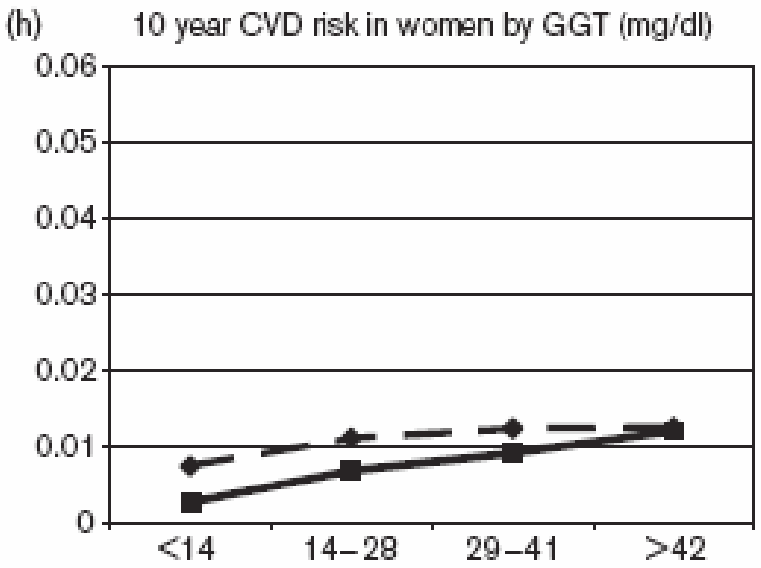
The purpose of this study was to investigate the association of longitudinal change in serum γ-glutamyltransferase (GGT) with mortality from cardiovascular disease (CVD).

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.

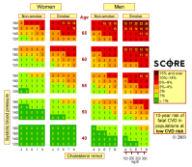
Our study is the first to demonstrate that a longitudinal increase in GGT, independently of baseline GGT and even within its normal range, significantly increases risk of fatal CVD.

GGT improves risk prediction





– – – SCORE predicted ——— real CVD mortality



Gamma-glutamyltransferase (GGT)

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- Several epidemiologic studies have sparked further interest in elevated GGT as an independent predictor for morbidity and mortality from causes other than liver disease
  - GGT independently associated with cardiovascular disease *(Wannamethee 1995, Jousilathi 2000, Ruttmann 2005)*
  - GGT correlated with most cardiovascular risk factors and MetS *(Lee DS 2007, etc.)*
  - Association of GGT with chronic kidney disease *(Ryu 2007)*
  - Independent role of GGT for premature death from all causes *(Ruhl 2009, etc.)*
- Measurement of serum GGT commonly used as an indicator for hepatobiliary disease/congested liver and a biological marker of excessive alcohol intake *(Rollason 1972)*
- There appears to be an interaction effect of high GGT in individuals who smoke and drink *(Breitling 2009)*
- GGT predicts the metabolic syndrome especially through NAFL/NASH *(Rantala 2000, etc.)*

Gamma-glutamyltransferase (GGT)

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- Experimental models elucidated the ability of cellular GGT to modulate crucial redox-sensitive functions, such as antioxidant/antitoxic defenses and cellular proliferative/apoptotic balance, and its role in tumor progression, invasion, and drug resistance has been proposed *(Pompella 2006, Franzini 2006)*
- GGT as a biomarker of exposure to certain cancer-causing xenobiotics, including persistent organic pollutants *(Lee 2006)*
  - e.g. lead, cadmium, dioxins or organochlorine pesticides
- High GGT through genetic factors *(Whitfield 2001)*
- Role of medication and idiosyncratic causes for GGT elevation

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

Strasak A, Ruttmann 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 μmol/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, Ruttmann 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.

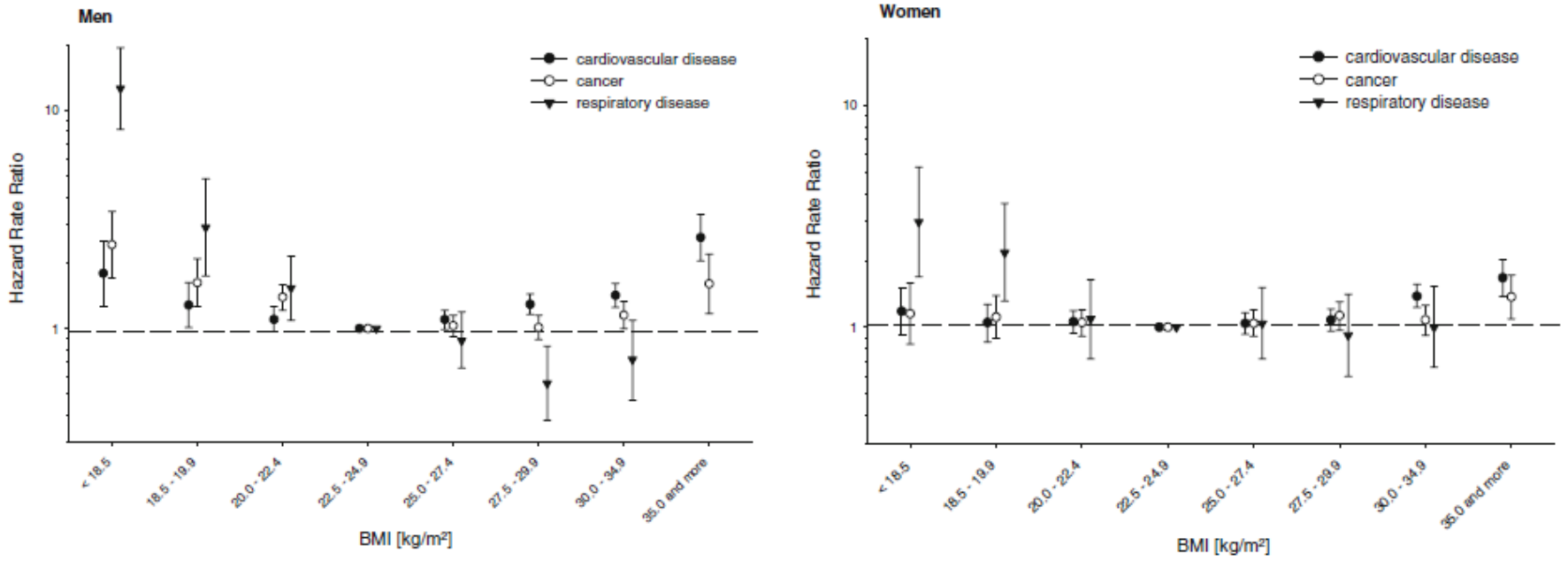
Body mass index and mortality: results of a cohort of 184,697 adults in Austria

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 (C35 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 enrolement. Hazard Rate Ratios adjusted for smoking status. The reference category is BMI 22.5–24.9 kg/m^2. *Error bars* indicate 95% confidence intervals



Studies in Cancer Epidemiology

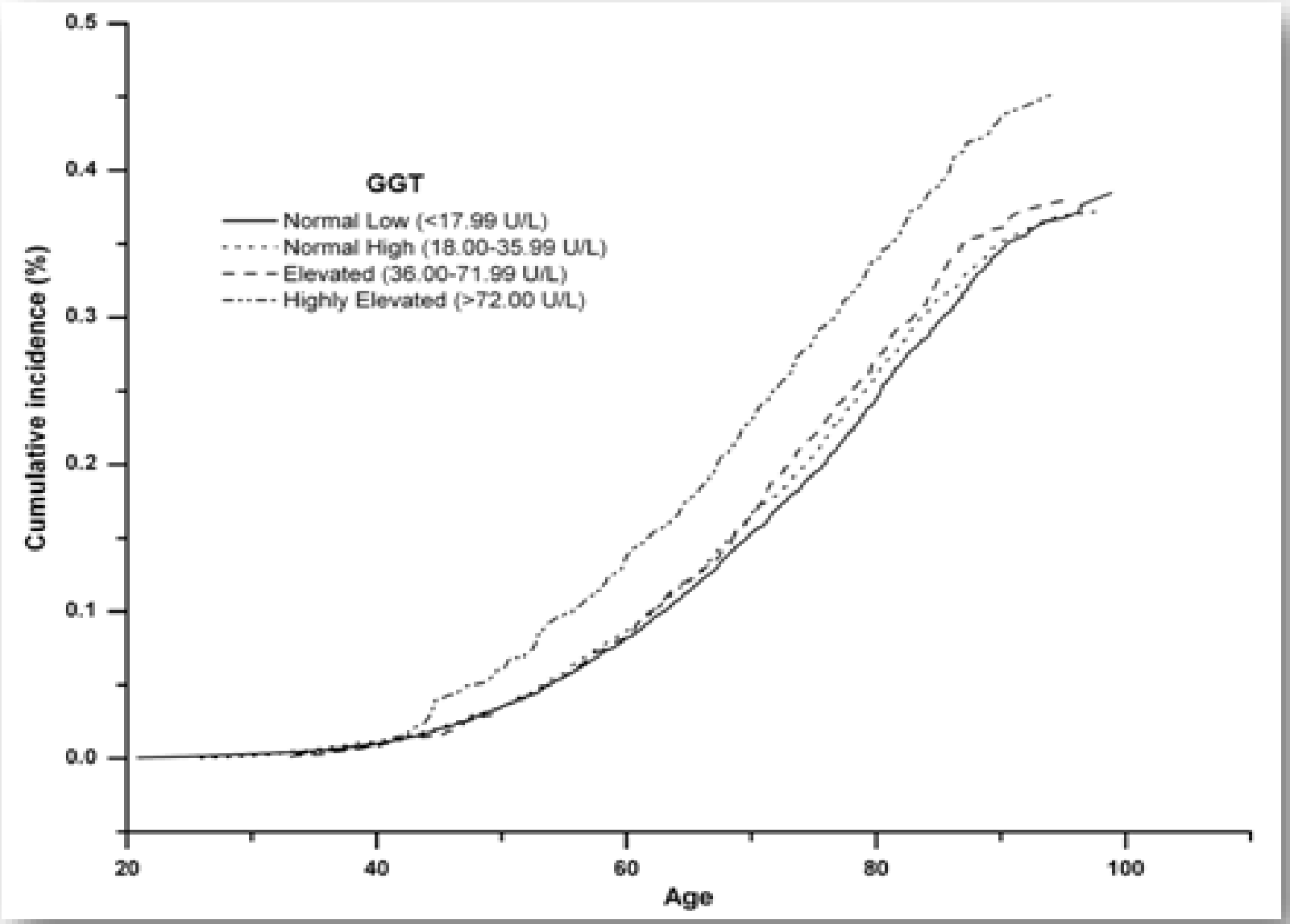
The Vorarlberg Health Monitoring & Promotion Programme (VHM&PP)

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, Ruttmann 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.


GGT
Normal Low (<17.99 U/L)
Normal High (18.00-35.99 U/L)
Elevated (36.00-71.99 U/L)
Highly Elevated (>72.00 U/L)
Cumulative incidence (%)
0.5
0.4
0.3
0.2
0.1
0.0
20
40
60
80
100
Age

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 V65 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, Ruttmann 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, Concin H, Diem G, Pfeiffer KP, Ulmer H

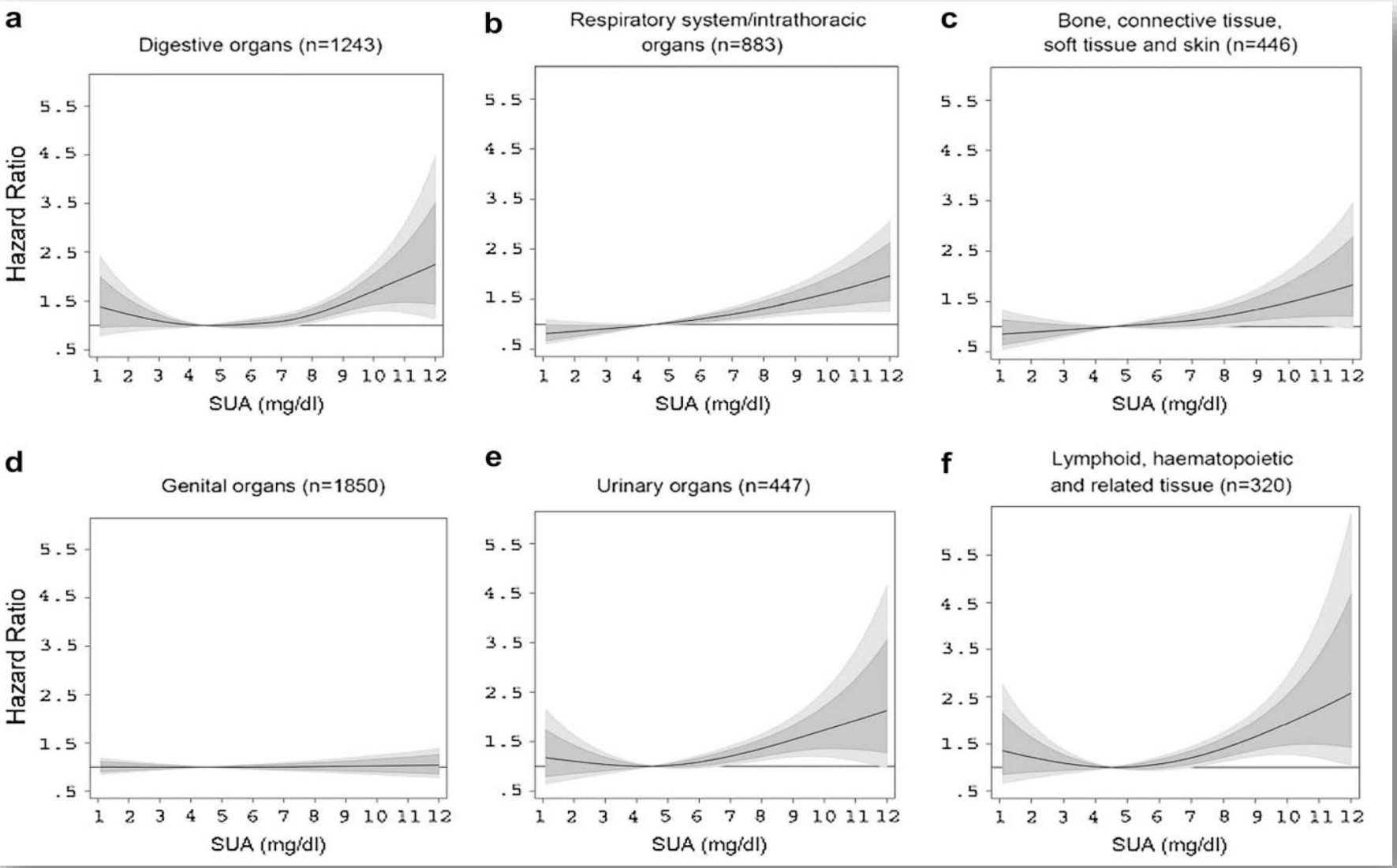
Our study is the first to demonstrate a dose–response association between serum uric acid and cancer incidence in men, simultaneously reporting on the usefulness of a novel methodological framework in epidemiologic research.

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.


a
Digestive organs (n=1243)
b
Respiratory system/intrathoracic organs (n=883)
c
Bone, connective tissue, soft tissue and skin (n=446)
d
Genital organs (n=1850)
e
Urinary organs (n=447)
f
Lymphoid, haematopoietic and related tissue (n=320)
Hazard Ratio
SUA (mg/dl)
.5
1.5
2.5
3.5
4.5
5.5
1 2 3 4 5 6 7 8 9 10 11 12

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_{trend} = 0.0001) in men, HR = 0.69 (95% CI 0.49–0.99, P_{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.

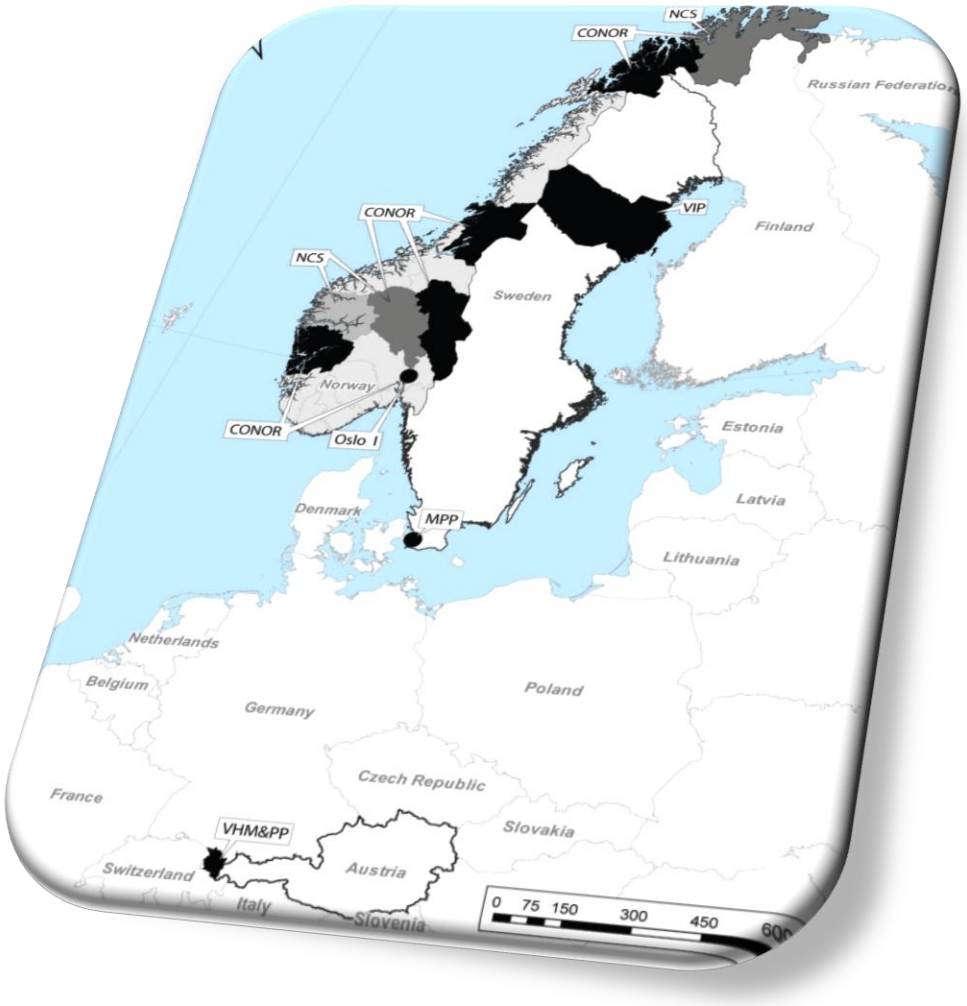
Blood lipid levels as part of the metabolic syndrome are thought to be linked to cancer risk. Few epidemiological studies have addressed the association between serum triglyceride (STG) concentrations and cancer risk.

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.

Me-Can project



In 2006, the **Metabolic syndrome and Cancer projec**t (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).

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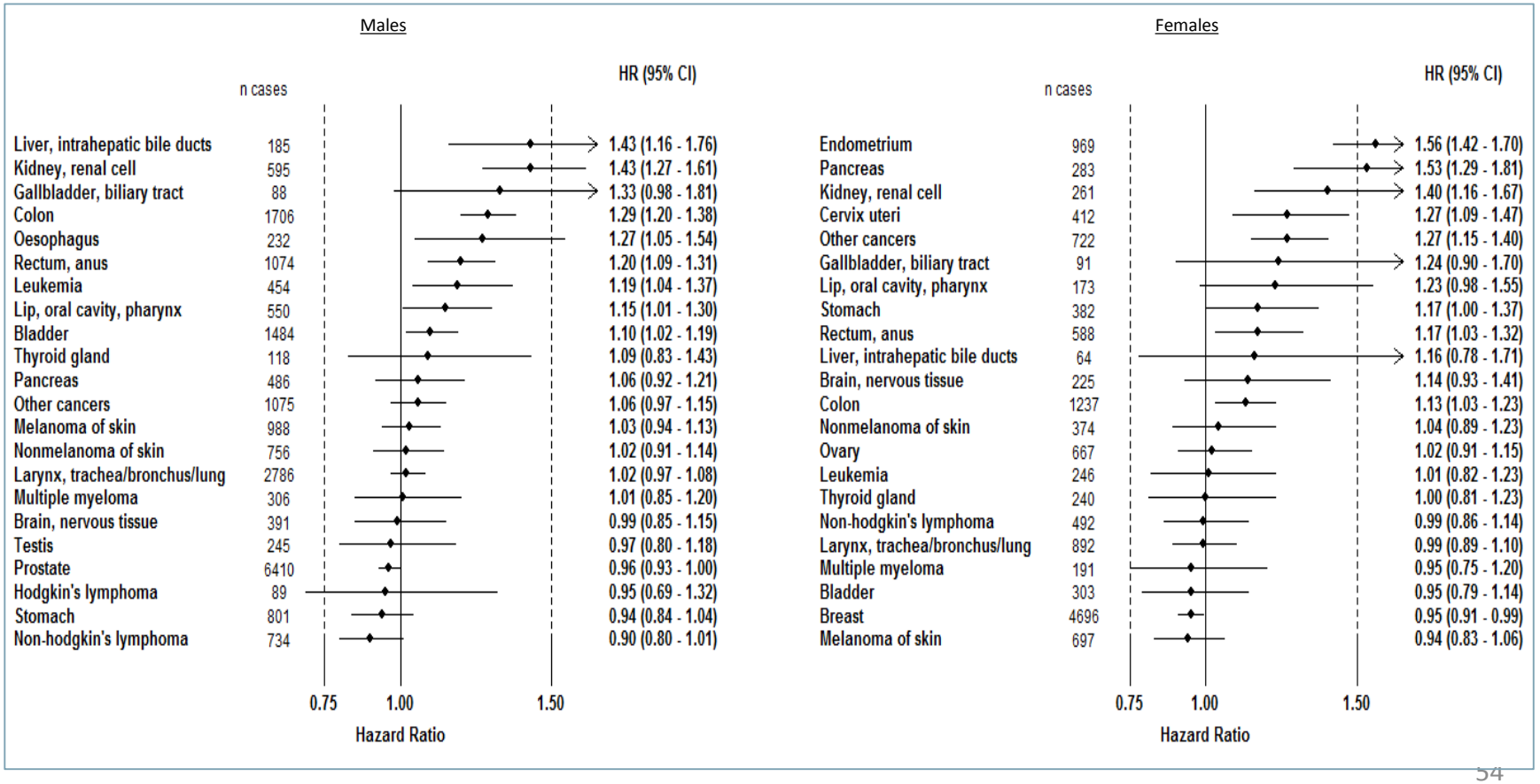
Sex-specific risk estimates of incident cancer by site per unit MetS score (standardised sum of the five separate z-scores)



Emerging Risk Factors Collaboration (ERFC) – University of Cambrige

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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

All our publications are online:

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Me-Can project - Publications

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Me-Can project - Publications

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Emerging Risk Factors Collaboration (ERFC) - Publications with VHM&PP data

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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

Sweden:
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