

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

(Preventive health care cohort in Vorarlberg)

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Datasets of health care programmes in Vorarlberg documented and managed by the **Agency of Preventive and Social Medicine (Arbeitskreis für Vorsorge- und Sozialmedizin, aks gesundheit GmbH)**

Basic idea:

Merge data of these programmes into one cohort containing information of at least the largest and most comprehensive programme for any member of the cohort. This largest programme accounting for the base dataset of the cohort is the **General Health Examination (Allgemeine Gesundenuntersuchung)** in Vorarlberg 1985-2005 (appr. 185,000 participants corresponding to 50-60% of the adult population, appr. 716,000 examinations)

Subcohorts (other, smaller programmes) add **further examinations and variables**

- „real“ subcohorts: 100% participants of the General Health Examination (additive programmes dependent on the General Health Examination)
- intersecting subcohorts: <100% participating also in the General Health Examination (programmes independent from the General Health Examination, but participation rate usually high)

Objective of the cohort:

Reveal risk factors for diseases, in particular cardiovascular and malignant diseases, for efficient and targeted public health-related planning and decision-making

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Overview

(cf. Stöhr S. & Klenk J. Systematische Aufarbeitung und Dokumentation der aks Daten. Kommentar zur Datenqualität. Master Thesis, Ulm University, 2004)

Intersecting subcohorts

Preventive gynaecological examination (1985-2005)
650,171 examinations in 117,400 women

Skin cancer prevention programme (1989-1994)
12,069 exams in 9382 persons

Colorectal cancer prevention programme (1992-2007)
N = 13,379 participants

Breast cancer prevention programme by mammography screening (1989-2005)
136,254 exams in 53,223 women

Preventive programme for ageing people (2000-2001)
N = 3453 participants

General Health Examination in Vorarlberg (1.1.1985 – 30.6.2005)
185,397 participants
716,679 examinations

Chronic diseases intervention programme

WHO-CINDI 1986
N = 2401 participants

WHO-CINDI 1991
N = 2400 participants

WHO-CINDI 1998
N = 2794 participants

*“real” subcohorts
(additive programmes)*

Preventive programme for postmenopausal women (1991-2000)
N = 5297 women

General Health Examination: the base dataset

- Documentation by aks Jan. 1st 1985 – June 30th 2005 (thereafter by Federation of Social Insurances = Dachverband der Sozialversicherungsträger)
- 716,679 examinations
- 185,397 participants aged ≥ 19 years, 53.9% female; 50-60% of adult population
- Socio-demographic data: age, sex, marital status, occupational status (blue collar, white collar, self-employed)
- Body height, body weight, blood pressure (sys, dia), smoking status, blood glucose, serum uric acid, triglycerides, total cholesterol, gamma-GT, fecal occult blood
- only 1985-1986: dementia, alcohol abuse, status of stress, lack of physical activity
- Closed dataset, however, permanently updated for survival and causes of death → very long follow-up!

Subcohorts: additive programmes

Preventive programme

for ageing people

(„Demenz 2000“, „VHM&PP 65+“)

n	period	Age profile	% female
3453	June 2000 - July 2001	≥ 65 years	58%

- Variables (by questionnaire):

Pre-existing diseases, medications, allergies, smoking, alcohol consumption, nutrition, bone fractures, various ailments (dyspnoea, insomnia, rheumatism, reduction of hearing and vision, vertigo); gynecological information asked from women (intake of hormones, pain and swellings of the breast, number of births, operations of the abdomen and breast); information on living situation and everyday life

Preventive programme for

postmenopausal women („Frauen Plus“)

n	period	Age profile
5297 women	Jan. 1991 – Dec. 2000	≥ 35 years

- HDL-cholesterol

- Bone mineral density by DXA or QCT (n=4750)

- Questionnaire covering various topics: climacteric period, general satisfaction, vitality, cardiovascular risk, osteoporotic risk

Intersecting subcohorts (1)

Preventive gynaecological examination

n	period	Age profile
117,400 women, 650,171 examinations	Jan. 1985 – June 2005	≥ 15 years

- Various examinations documented (breast, uterus, vagina, vulva, ...), e. g. cervical swabs, inspection and palpation of the breast, inspection of the vulva, colposcopy, cytology

Mammography screening programme

n	period	Age profile
53,223 women, 136,254 examination	Jan. 1989 – Dec. 2005	≥ 18 years

- Offered to all (female) participants of the General Health Examination and the Preventive gynaecological examination
- Mammography results; acquisition of breast cancer family history, operations of the breast, use of contraceptives, and breastfeeding

Intersecting subcohorts (2)

Skin cancer prevention

n	period	Age profile	% female
9382 participants, 12,069 examinations	Aug. 1989 – Dec. 1994	≥ 13 years	61%

- Acquisition of risk for skin cancer, skin type

Colorectal cancer prevention

n	period	Age profile	% female
13,379 participants	1992 - 2007	>= 7 Jahre	41%

- Family history of colorectal cancer, fecal occult blood, colorectal cancer risk (adenomas, colorectal cancer syndroms, ulcerative colitis, cancer familiy history)

Intersecting subcohorts (3)

<u>Chronic diseases intervention programme (“CINDI“ of the WHO)</u>	n	period	Age profile	% female
	2401 (CINDI 1986), 2400 (CINDI 1991), 2794 (CINDI 1998)	1986, 1991, 1998	25 – 64 years	50%

- **CINDI** (Countrywide Integrated Non-communicable Diseases Intervention) programme of the **WHO** with the purpose of prevention of chronic diseases in 1986, 1991, and 1998
- Inquiries, additional acquisition of laboratory parameters
- Randomly selected participants aged 25-64 years with residency in Vorarlberg, same proportion females/males (representative random sample)
- All years: Socio-demographic variables (age, sex, marital status, occupation), physical activity, nutrition, smoking, alcohol consumption, information sources for health-related topics
- CINDI 1986: blood pressure (sys, dia), pulse, body height, body weight; serum uric acid, total cholesterol, gamma-GT, blood glucose, HDL-cholesterol, triglycerides
- CINDI 1991: blood glucose, HDL-cholesterol, triglycerides; disease history (in particular, hypertension, cardiovascular disease, pulmonary disease, diabetes, malignant disease, urinary tract infection), medication history (analgesics, hypnotics, contraceptives, and other drugs)
- CINDI 1998: blood glucose, serum uric acid, triglycerides, total cholesterol, HDL-cholesterol, gamma-GT

Scientific publications

- >150 scientific publications in peer-reviewed journals since 2003 (up to April 2023)
(cf. <https://www.i-med.ac.at/msig/mitarbeiter/ulmer/vhmpp.html.de>)
- Often combination with other datasets, registries, and cohorts, and part of multi-center studies (MCS):
 - **National Mortality Registry** (Statistik Austria) (follow-up, causes of death)
 - **Cancer Registry Vorarlberg**
 - **Coronary Angiography Cohort Vorarlberg** (VIVIT [Vorarlberg Institute of Vascular Investigation and Treatment])
 - **Hip fracture dataset Vorarlberg** (2003-2013)
 - **Austrian Dialysis and Transplant Registry** (ÖDTR)

 - ***Me-Can*** (*Metabolic Syndrome and Cancer*) (MCS)
 - ***ESCAPE*** (*European Study of Cohorts for Air Pollution Effects*) (MCS)
 - ***ELAPSE*** (*Effects of Low-Level Air Pollution: A Study in Europe*) (MCS)
 - ***NCD RisC*** (*non-communicable diseases risk factor collaboration*) (MCS)
 - ***ERFC*** (*emerging risk factors collaboration*) (MCS)

Scientific publications_examples (1)

European Heart Journal (2003) 24, 1004–1013



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

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KEYWORDS

Cardiovascular risk factors;
Longitudinal studies;

Aims 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)

Methods and Results 67 413 men and 82 237 women underwent a total of 454 448



Ulmer H, Kelleher C, Diem G, Concini H. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: The Vorarlberg Health Monitoring & Promotion Programme. *Eur. Heart J.* 2003;24:1004–13.

- Stability (tracking) of cardiovascular risk factors during a max. of 15 years:
- BMI (body mass index) very stable
- Triglycerides and gamma-GT not very stable, blood pressure fluctuating
- Stable (vs. fluctuating) triglycerides and gamma-GT associated with higher total mortality, more stable systolic blood pressure with lower total mortality, both in women; no such effects in men

Research Article

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

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Abstract

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

excessive alcohol intake (1–5). However, in recent years, several epidemiologic studies have sparked further interest in elevated GGT as an independent predictor for morbidity and mortality from causes other than liver disease. Particularly, it was reported that GGT is independently associated with cardiovascular disease (6–11) and most cardiovascular risk factors (12–15), and more recently, an association with chronic kidney disease was found (16). In addition, several large-scale studies indicate an independent role of GGT for premature death from all causes (9, 12, 17).

The association of GGT with cancer incidence, however, remains largely unexplored to date. Several experimental models have elucidated the ability of cellular GGT to modulate essential redox

Strasak AM, Rapp K, Brant LJ, Hilbe W, Gregory M, Oberaigner W, Ruttmann E, Concini H, Diem G, Pfeiffer KP, Ulmer H. Association of γ -glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer Res.* 2008;68:3970–7.

- Elevated gamma-GT associated with increased cancer risk in men
- In particular cancer of digestive, respiratory, and urinary organs
- Marked dose-response effect

Scientific publications_examples (2)



Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults

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Borena W, Strohmaier S, Lukanova A, Bjørge T, Lindkvist B, Hallmans G, Edlinger M, Stocks T, Nagel G, Manjer J, Engeland A, Selmer R, Häggström C, Tretli S, Concini H, Jonsson H, Stattin P, Ulmer H. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int. J. Cancer* 2012;131:193–200.

- Me-Can MCS
- Primary hepatic tumors (liver cancer) as endpoint
- BMI, blood glucose, and MetS Index: positively associated with primary hepatic tumors
- Total cholesterol inversely associated

Initial studies have indicated diabetes and obesity to be risk factors for hepatocellular carcinoma; but the association between other metabolic risk factors and primary liver cancer (PLC) has not been investigated. The metabolic syndrome and cancer project (Me-Can) includes cohorts from Norway, Austria and Sweden with data on 578,700 subjects. We used Cox proportional hazard models to calculate relative risks (RRs) of PLC by body mass index (BMI), blood pressure and plasma levels of glucose, cholesterol and triglycerides as continuous standardized variables (z-score with mean = 0 and standard

Article

Repositioning of the global epicentre of non-optimal cholesterol

<https://doi.org/10.1038/s41586-020-2338-1>

NCD Risk Factor Collaboration (NCD-RisC)¹

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High blood cholesterol is typically considered a feature of wealthy western countries^{1,2}. However, dietary and behavioural determinants of blood cholesterol are changing rapidly throughout the world³ and countries are using lipid-lowering medications at varying rates. These changes can have distinct effects on the levels of high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol, which have different effects on human health^{4,5}. However, the trends of HDL and non-HDL cholesterol levels over time have not been previously reported in a global analysis. Here we pooled 1,127 population-based studies that measured blood lipids in 102.6 million individuals aged 18 years and older to estimate trends from 1980 to 2018 in mean total, non-HDL and HDL cholesterol levels for 200 countries. Globally, there was little change in total or non-HDL cholesterol from 1980 to 2018. This was a net effect of increases in low- and middle-income countries, especially in east and southeast Asia, and decreases in high-income western countries, especially those in northwestern Europe, and in central and eastern Europe. As a result, countries with the highest level of non-HDL cholesterol—which is a marker of cardiovascular risk—changed from those in western Europe such as Belgium, Finland, Greenland, Iceland, Norway, Sweden, Switzerland and Malta in 1980 to those in Asia and the Pacific, such as Tokelau, Malaysia, The Philippines and Thailand. In 2017, high non-HDL cholesterol was responsible for an estimated 3.9 million (95% credible interval 3.7 million–4.2 million) worldwide deaths, half of which occurred in east, southeast and south Asia. The global repositioning of lipid-related risk, with non-optimal cholesterol shifting from a distinct feature of high-income countries in northwestern Europe, north America and Australasia to one that affects countries in east and southeast Asia and Oceania should motivate the use of population-based policies and personal interventions to improve nutrition and enhance access to treatment throughout the world.

Blood cholesterol is one of the most important risk factors for ischaemic heart disease (IHD) and ischaemic stroke⁶. Consistent and comparable countries have adopted lipid-lowering medications⁷. These changes are likely to have influenced cholesterol levels substantially in the

NCD Risk Factor Collaboration. Repositioning of the global epicentre of non-optimal cholesterol. *Nature* 2020;582:73-77.

- NCD-RisC MCS
- Total and non-HDL cholesterol decreasing since 1980 in Western industrialized countries, also in Austria
- Increasing in newly industrialized and low-income countries of South-East Asia and Oceania (changing nutritional habits, restricted availability of statins)
- Data for Austria in large part from VHM&PP cohort

Scientific publications_examples (3)

RESEARCH

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Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis

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ABSTRACT OBJECTIVE

To investigate the associations between air pollution and mortality, focusing on associations below current European Union, United States, and World Health Organization standards and guidelines.

DESIGN

Pooled analysis of eight cohorts.

SETTING

Multicentre project Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) in six European countries.

PARTICIPANTS

325 367 adults from the general population recruited

residential air pollution concentrations of ambient fine particulate matter (PM_{2.5}), nitrogen dioxide, ozone, and black carbon.

MAIN OUTCOME MEASURES

Deaths due to natural causes and cause specific mortality.

RESULTS

Of 325 367 adults followed-up for an average of 19.5 years, 47 131 deaths were observed. Higher exposure to PM_{2.5}, nitrogen dioxide, and black carbon was associated with significantly increased risk of almost all outcomes. An increase of 5 µg/m³ in PM_{2.5} was associated with 13% (95% confidence

For numbered affiliations see end of the article

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Research paper

Value of total cholesterol readings earlier versus later in life to predict cardiovascular risk

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ABSTRACT

Background: Prognostic implications of blood cholesterol may differ at different stages of life. This cohort study compares the value of total cholesterol (TC) readings earlier versus later in life for the prediction of coronary atherosclerosis, cardiovascular events, and cardiovascular death.
Methods: In a cardiovascular observation study (CVOS) we performed coronary angiography and prospectively recorded cardiovascular events in 1090 patients over up to 19 years. These patients had participated in a health survey (HS) 15 years prior to the CVOS baseline. TC was measured twice, first at the earlier HS and then later at CVOS recruiting.
Findings: Patients in the highest versus the lowest TC-category of the HS had an OR of 4.30 [2.41–7.65] for significant CAD at angiography, a HR of 1.74 [1.10–2.76] for cardiovascular events, and a HR of 7.55 [1.05–54.49] for cardiovascular death after multivariate adjustment. In contrast, TC as measured at the base-

Strak M, et al. Long-term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ* 2021;374:n1904.

- ELAPSE MCS (various European cohorts)
- Long-term exposure to air pollution (PM_{2.5}, NO₂, black carbon) associated with increased mortality, even below current threshold values
- Increase in mortality risk due to cardiovascular and respiratory diseases
- O₃ (probably) no risk factor

Leiberer A, Ulmer H, Muendlein A, Säly C, Vonbank A, Fraunberger P, Föger B, Brandtner EM, Brozek W, Nagel G, Zitt E, Drexel H, Concin H. Value of total cholesterol readings earlier versus later in life to predict cardiovascular risk. *EBioMed*. 2021;67.

- Total cholesterol measured at 50 years of age on average vs. 15 years later is significantly more accurate to predict cardiovascular risk at an advanced age

Scientific publications_examples (4)

The Association of Excess Body Weight with Risk of ESKD Is Mediated Through Insulin Resistance, Hypertension, and Hyperuricemia

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ABSTRACT

Background Insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia are hypothesized to be important intermediates in the relationship between excess body weight and CKD risk. However, the magnitude of the total effect of excess body weight on ESKD mediated through these four pathways remains to be quantified.

Methods We applied a model for analysis of correlated mediators to population-based data from 100,269 Austrian individuals (mean age 46.4 years). Association of body mass index (BMI) was coalesced with ESKD risk into direct association. Indirect associations were mediated through the triglyceride-glucose (TyG) index (as an indicator of insulin resistance), mean arterial pressure (MAP), uric acid (UA), and total cholesterol (TC).

Results Mean follow-up was 23.1 years with 463 (0.5%) incident ESKD cases. An unhealthy metabolic profile (prevalence 32.4%) was associated with a markedly increased ESKD risk (multivariable adjusted hazard ratio (aHR), 3.57; 95% CI, 2.89 to 4.40), independent of BMI. A 5-kg/m² higher BMI was associated with a 57% increased ESKD risk (aHR_{total association}, 1.57; 1.38 to 1.77). Of this association, 99% (76% to 140%) arose from all mediators jointly; 33% (22% to 49%) through TyG index; 34% (24% to 50%) through MAP; 30% (21% to 45%) through UA; and 2% (-1% to 4%) through TC. The remaining direct association was nonsignificant (aHR_{direct association}, 1.01; 0.88 to 1.14).

Conclusions TyG index, MAP, and UA, but not TC, mediate the association of BMI with ESKD in middle-aged adults. Our findings highlight that in addition to weight reduction, the control of metabolic risk factors might be essential in mitigating the adverse effects of BMI on kidney function.

CLINICAL EPIDEMIOLOGY

Fritz J, Brozek W, Concin H, Nagel G, Kerschbaum J, Lhotta K, Ulmer H, Zitt E. The association of excess body weight with risk of ESKD is mediated through insulin resistance, hypertension, and hyperuricemia. *J. Am. Soc. Nephrol.* 2022;33:1377-89.

→ Hypertension, insulin resistance, and hyperuricemia but not elevated total cholesterol mediate the risk association of excess body weight and end-stage kidney disease

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ORIGINAL ARTICLE



Gamma-glutamyl-transferase is associated with incident hip fractures in women and men ≥ 50 years: a large population-based cohort study

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Abstract

Summary The association of serum gamma-glutamyl-transferase (GGT) with hip fracture risk has not been examined in women and men ≥ 50 years. We show that elevated GGT was associated with increased hip fracture risk, particularly in men. GGT could be a candidate serum marker of long-term hip fracture risk in the elderly.

Introduction We herein examined a possible relation between serum levels of GGT and hip fracture risk in women and men aged ≥ 50 years, which has not been investigated before.

Methods In this population-based prospective cohort study, approximately 41,000 women and nearly 33,000 men ≥ 50 years participating in a medical prevention program 1985–2005 in western Austria were followed up for the occurrence of osteoporotic hip fractures during 2003–2013. ICD-10 based discharge diagnoses for hip fracture included S72.0, S72.1, and S72.2 available from all regional hospitals. GGT-related hip fracture risk was ascertained at each participant's first and last examination during the prevention program. In a subset of 5445 participants, alcohol consumption could be included as a covariate.

Results In men, hip fracture risk rose significantly by 75% and 86% for every tenfold increase of GGT measured at the first and last examination, respectively, and in women, hip fracture risk rose by 22% from the last examination. Elevated GGT (≥ 36 U/l in women, ≥ 56 U/l in men) at the first examination was associated with increased hip fracture risk only in men (HR 1.51, 95% CI 1.25–1.82), and at the last examination in both women (HR 1.14, 95% CI 1.02–1.28) and men (HR 1.61, 95% CI 1.33–1.95). Alcohol consumption had no significant influence on GGT-mediated hip fracture risk in women and men.

Conclusions Our findings identified an association of elevated GGT and hip fracture in women and men ≥ 50 years and suggest GGT as a candidate serum marker of long-term hip fracture risk in an elderly population.

Brozek W, Ulmer H, Pompella A, Nagel G, Leiherer A, Preyer O, Concin H, Zitt E. Gamma-glutamyl-transferase is associated with incident hip fractures in women and men ≥ 50 years: a large population-based cohort study. *Osteoporos. Int.* 2022;33:1295-1307.

→ Gamma-GT as risk factor for hip fractures at age ≥ 50 independent from alcohol consumption, particularly in men

Summary

Strengths & limitations:

- Population-based cohort, but arguably selection for more health-conscious participants (healthy volunteer effect)
- Prospective and standardized data acquisition, long follow-up times
- Vorarlberg as “epidemiologic model region“: relatively isolated because of high mountains (east and south) and borders with non-EU countries (Switzerland, Liechtenstein) with a distinct social insurance system
- Repeated examinations, in particular in the base data set (General Health Examination)
- No new participants because dataset is closed since July 1st, 2005 (as of then, documentation by the Austrian Federation of Social Insurances)

Desired cooperation with other databases and cohorts, concerning:

- Data of the General Health Examination for Vorarlberg since July 1st, 2005
- Information on medication
- Biosamples, biological material