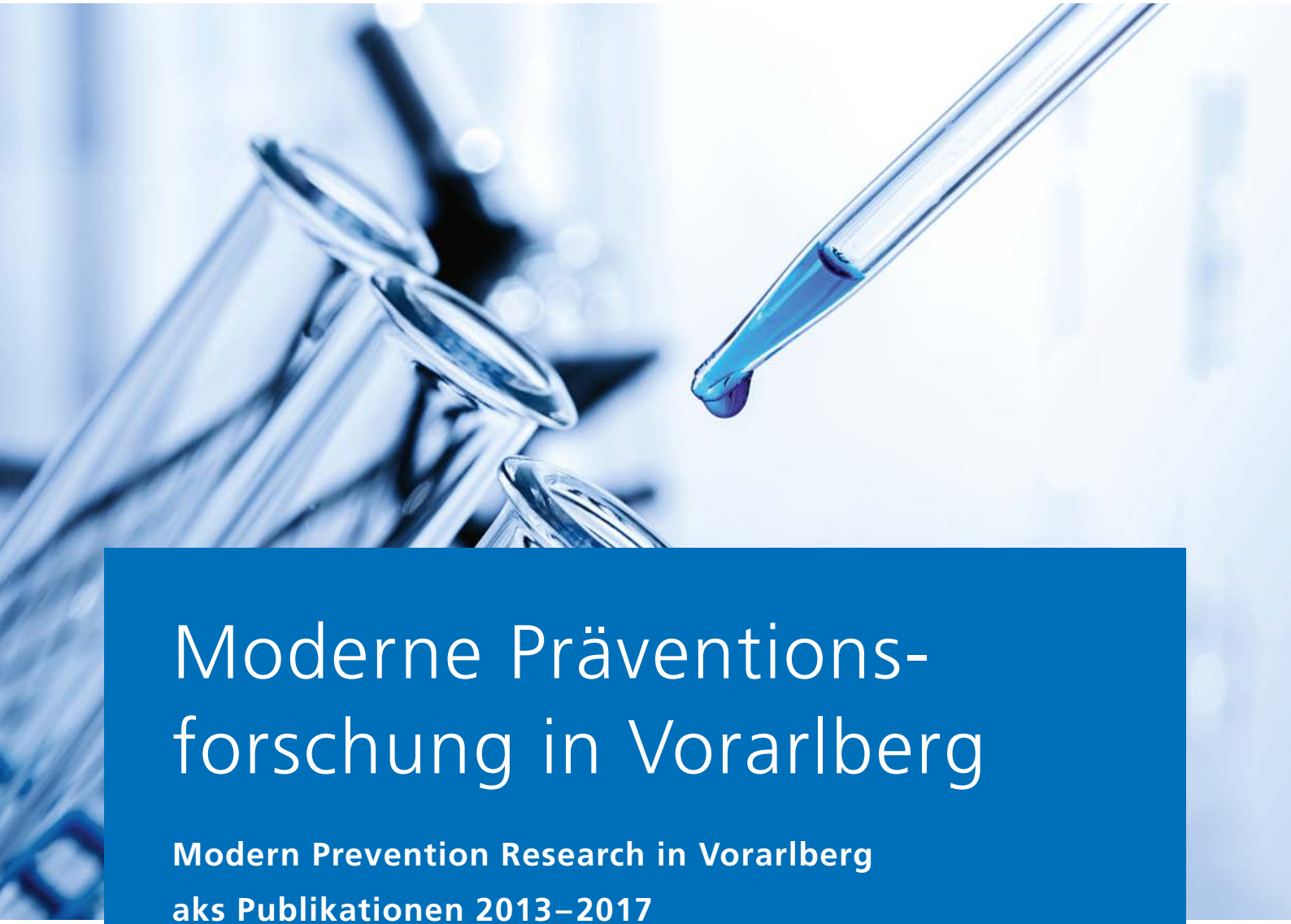
aks gesundheit
im ländle vor ort



Moderne Präventions-forschung in Vorarlberg

Modern Prevention Research in Vorarlberg

aks Publikationen 2013–2017

50 Jahre Vorsorgemedizin und Wissenschaft im Arbeitskreis für Vorsorge- und Sozialmedizin

50 Years of Preventive Medicine and Research in the Agency for Preventive and Social Medicine

Editors
Hans Concin | Gabriele Nagel | Hanno Ulmer | Georg Posch

Vorwort

Hans Concin | Bernhard Föger | Gabriele Nagel | Hanno Ulmer | Georg Posch

Herr Prim. a. D. Dr. Hans Concin
Thema: Leopold Bischof bis heute

Historie der Gesundheitsforschung im aks

Die Entstehung von Krankheiten kann am besten geklärt werden wenn eine große abgeschlossene Kohorte untersucht und über eine lange Zeit beobachtet wird. Genau das war die Idee unseres aks Gründungspräsidenten OMR Dr Leopold Bischof zusammen mit Hofrat Dr. Hermann Girardi von der Vorarlberger Landesregierung. Mit der Einführung von Vorsorgeuntersuchungen durch den aks in Vorarlberg in den 1960er Jahren wurden von Anfang an alle Befunde dokumentiert, zuerst auf Lochkarten, ab den 1980er Jahren standen digitale Speichermedien zur Verfügung. Mit diesen Daten arbeiten wir heute. Die Beteiligung der Vorarlberger Bevölkerung an den aks Vorsorgeprogrammen war sehr hoch und die Befunde für das ganze Bundesland repräsentativ. Später sind diese Gesundheitsprogramme vom Bund österreichweit übernommen worden. Im Jahr 1992 hat Dr. Hans-Peter Bischof einen Wissenschaftlichen Beirat im aks eingesetzt und bis zu seinem Amtsantritt als Gesundheitslandesrat 1993 geführt. Diese Funktion wurde dann mir übertragen.

Konkret vergleichen wir die Ausgangssituation bei der ersten und den folgenden Vorsorgeuntersuchungen mit dem Auftreten von Krankheiten (z.B. Krebs, Hüftfrakturen, Niereninsuffizienz, Atherosklerose) und mit den Todesursachen. Bei circa 700.000 Vorsorgeuntersuchungen stellen solche Auswertungen außerordentliche Anforderungen an den Biostatistiker. Der Dornbirner Hanno Ulmer, zwischenzeitlich Univ. Professor und Direktor des Instituts für Medizinische Statistik, Informatik und Gesundheitsökonomie an der Medizinischen Universität Innsbruck, war der erste dem Auswertungen in diesem riesigen Umfang gelungen sind. Diese Forschungsergebnisse haben international große Beachtung gefunden. Frau Prof. Kelleher, Vizerektorin und Vorstand der Epidemiologie an der Universität Dublin, wird in ihrem Festvortrag am Samstag den 29.04.2017 die internationale Bedeutung unserer Gesundheitsdatenbank reflektieren.

Dank:
Die Vorarlberger Landesregierung hat alle diese Aktivitäten über Jahrzehnte finanziert und tatkräftig unterstützt. Die Kosten der Vorsorgeuntersuchungen und teilweise deren Dokumentation wurden von der Vorarlberger Gebietskrankenkasse getragen.

Herr Prim. Univ. Prof. Dr. Bernhard Föger
Thema: Lancet Publikationen

Die einzigartigen Stärken der beiden, inhaltlich zusammengehörenden Arbeiten zu Übergewicht und Zuckerkrankheit im Lancet 2016 liegt im sehr langen Beobachtungszeitraum (seit 1975), in der enormen Größe beider Studien (19 bzw. 4 Mio Teilnehmer) und in der Verfügbarkeit weltweiter Daten. Ergebnisse der aks-Forschung aus Vorarlberg haben hier wesentlich mitgeholfen, die für die Volksgesundheit wichtige Frage nach der Entwicklung der dieser beiden Komponenten der Wohlstands-erkrankung (metabolisches Syndrom) in Österreich und Mittel-europa zu beleuchten. Übergewicht, mangelnde körperliche Aktivität, und ungesunde Ernährung stellen die wichtigsten, vermeidbaren Risikofaktoren für die Zuckerkrankheit, eine schmerzlose, aber dennoch lebensbedrohliche Stoffwechselstörung, dar. Übergewicht und Zuckerkrankheit sind wichtige Gründe für Gefäßverkalkung (Atherosklerose), Erblindung, Nierenversagen und Amputationen.

In **Mitteleuropa** nahm der Körper-Masse-Index (BMI) in diesen 4 Jahrzehnten bei Frauen um 0,8 kg/m² zu, bei Männern sogar etwas mehr, was in etwa einem Gewichtsanstieg von 2,5 kg entspricht. Im **mittleren Osten, Asien und Südamerika** wurden z.T. deutlich höhere Anstiege verzeichnet. In **Mitteleuropa** nahm Diabetes, gemessen v.a. an der Nüchtern-blutglukose, in den letzten 3 ½ Jahrzehnten bei Frauen nur geringfügig zu, wenn man für das Alter korrigiert. Bei Männern war alterskorrigiert ein Anstieg von etwa 5 % auf 7,5 % zu verzeichnen. Wieder wurden im **mittleren Osten, Asien und Südamerika** wurden z.T. deutlich höhere Anstiege als in Mitteleuropa

verzeichnet. Unabhängig davon kommt es allein durch die Alterung der Bevölkerung in Europa zu einem bedeutenden Anstieg (Altersdiabetes).

Intensive Lebensstilmaßnahmen wie körperliche Aktivität, gesunde Ernährung, Vermeiden von Übergewicht und Nicht-Rauchen sind zentrale Elemente der Diabetes-vorbeugung und sollten v.a. bei jungen Menschen und Risikogruppen Einsatz finden.

Prof. Dr. med. Gabriele Nagel MPH

Thema: Eigene Top-Studien und skandinavische Kooperationen

Nach Angaben der Weltgesundheitsorganisation sind Krebserkrankungen, Herz-Kreislauf-Erkrankungen, Atemwegserkrankungen und Diabetes – für 80% aller Todesfälle nicht übertragbaren Krankheiten weltweit verantwortlich. Ein Zusammenhang zwischen metabolischen Faktoren (wie Körpergewicht, Blutdruck, Blutfetten sowie Blutzucker) und Herz-Kreislauferkrankungen wurde in den vergangenen Jahrzehnten gut belegt.

Wenig bekannt war, ob diese Stoffwechselfaktoren auch das Risiko an Krebs zu erkranken beeinflussen. Gefördert von World Cancer Research Fund in London wurden in einer Kooperation mit Forschern aus Schweden und Norwegen wesentliche Erkenntnisse zu metabolischen Faktoren und Krebserkrankungen gewonnen. In der Me-Can Studie konnten Daten von fast 600.000 Teilnehmern untersucht werden, darunter auch die Vorarlberger Gesundheitsdaten.

Übergewicht und Fettleibigkeit erhöhen das Risiko für Darmkrebs, Speiseröhrenkrebs und Nierenzellkrebs, bei Frauen wirkt sich Übergewicht zudem auf das Risiko für Gebärmutterkrebs aus sowie auf das Brustkrebsrisiko in und nach den Wechseljahren.

Die Untersuchung der großen Me-Can Studie erbrachte zusätzlich Hinweise für eine Risikoerhöhung weiterer selteneren Krebserkrankungen wie Leberkrebs, Bauchspeicheldrüsenkrebs, Gallenblasenkrebs, und Eierstockkrebs. Für einige Krebsarten konnte sogar eine Dosis-Wirkungs-Beziehung festgestellt werden. Das heißt: Je dicker man ist, umso höher ist das Krebsrisiko.

Verschiedene Mechanismen erklären die Zusammenhänge. Zum einen beeinflusst Körperfett die Produktion von Hormonen und Wachstumsfaktoren. Beispielsweise sind Insulin und Leptin in übergewichtigen Menschen erhöht und können das Wachstum von Krebszellen fördern. Zum anderen ist Fettleibigkeit mit einem niedrigen chronischen entzündlichen Zustand verbunden, welche die Krebsentwicklung fördern kann.

Die Ergebnisse wurden in hochrangigen Zeitschriften veröffentlicht und gingen in international vielbeachtete Übersichtsarbeiten ein. Nachdem erfolgreichen Verlauf der ersten Projektphase arbeiten wir an der Fortsetzung des Me-Can Projekts.

Herr Univ. Prof. Dr. Mag. Hanno Ulmer

Thema: Eigene Top-Studien und angelsächsische Kooperationen

Die Vorsorgeprogramme des aks werden seit ihrer Einführung in den 1970er Jahren wissenschaftlich begleitet.

Die wissenschaftliche Ausrichtung stellt sicher, dass die Programme auf dem neuesten Stand der Forschung sind. Durch die regelmäßige Evaluation der Vorsorgeprogramme ist eine weltweite einzigartige Datenbank mit vorsorgemedizinischen Daten entstanden. Unter Einhaltung größtmöglichen Datenschutzes werden diese Daten anonym für wissenschaftliche Publikationen genutzt. Eine Publikation im Jahre 2005 im weltweit führenden Fachjournal Circulation über die Relevanz des Leberwerts Gamma-glutamyl Transferase für die Entstehung von Herz-Kreislauferkrankungen hat die Aufmerksamkeit der Fachwelt auf die aks Daten gerichtet. In der Folge sind internationale Spitzenuniversitäten auf den aks zugekommen, mit der Bitte die vorsorgemedizinischen Daten des aks für ihre Publikationen verwenden zu dürfen.

Zu diesen Universitäten gehören die University of Cambridge, das Imperial College London (beide England) und die Harvard University in Boston (USA). Mittlerweile sind in Zusammenarbeit mit diesen Institutionen rund 15 Publikationen entstanden, die zu den meist zitierten Arbeiten im Fachgebiet zählen.

Herr Mag. Georg Posch

Thema: Strategie, Konzept und Ausblick der Wissenschaft im aks

Die übergreifende Vision der Wissenschaftsabteilung der aks gesundheit GmbH ist es, durch wissenschaftliche Exzellenz das Verständnis der Entstehung von Volkskrankheiten und Gesundheitsphänomenen zu erhöhen und somit einen wesentlichen Beitrag zur Verbesserung der Bevölkerungsgesundheit zu leisten. Die aks gesundheit GmbH hat die epidemiologische Wichtigkeit und Einzigartigkeit ihres Datenpools erkannt. Durch renommierte und strategisch optimal angelegte Forschungskooperationen sowie dem Enthusiasmus der Beteiligten wird aus der Masse an Datensätzen erfolgreich Wissen generiert. Dieses Potenzial wird weltweit als große Chance gesehen. Die aks gesundheit GmbH nutzt diese Chance um Wissenslücken in der Gesundheit zu schließen und Handlungsbedarfe für die Praxis und Politik, vor allem auch auf kommunaler Ebene, aufzuzeigen.

Die Gesundheit der Bevölkerung verbessern

Gesundheitsdaten und wissenschaftliche Erkenntnisse sind die Basis eines evidenzbasierten Vorgehens um die größten gesundheitlichen Herausforderungen, mit denen wir derzeit konfrontiert sind, zu bekämpfen. Erst durch das Verständnis, welche Zusammenhänge zwischen bestimmten Risikofaktoren bestehen und welche Risikofaktoren mit welchen Krankheiten korrelieren, können wirksame Maßnahmen geplant und umgesetzt werden. In diesem Sinne sind die Erfassung, Analyse und Interpretation von Gesundheitsdaten die zentralen Bestandteile eines public health-orientierten Vorgehens.

… durch Intensivierung bestehender und Etablierung neuer Kooperationen

Die aks gesundheit GmbH wird weiterhin ein wesentlicher Player auf der internationalen Drehscheibe hochrangiger wissenschaftlicher Forschungsprojekte sein. Erst durch die Auswertung von Daten und Interpretation dieser Ergebnisse erlangen diese an Relevanz und Wert. Der Erfolg bisheriger Kooperationen und den Beitrag, den die aks gesundheit GmbH zur weltweiten Wissensgenerierung bspw. im Bereich Krebsforschung oder Herz-Kreislaufkrankheiten erzielen konnte, sprechen für sich. Dementsprechend soll die Mitarbeit an universitärer Spitzenforschung weiterhin forciert werden. Das bestehende Netzwerk reicht von universitären Kooperationen in Österreich, Deutschland, England, Schweden, Norwegen und den USA. Die beiden Hauptkooperationsstränge mit dem Department für Medizinische Statistik, Informatik und Gesundheitsökonomie der Medizinischen Universität Innsbruck sowie dem Institut für Epidemiologie und Medizinischen Biometrie der Universität Ulm werden weiter intensiviert. Um die regionale Fachexpertise verstärkt zu bündeln, wird nun auch eine enge Zusammenarbeit mit dem Vorarlberg Institute for vascular Investigation and Treatment (VIVIT) am Landeskrankenhaus Feldkirch etabliert.

… durch Dissemination der Ergebnisse den Anstoß zum Handeln geben

Die aks gesundheit GmbH hat sich zur zentralen Aufgabe gemacht, die Erkenntnisse der Forschung zu streuen. Bereits jetzt verzeichnet die aks gesundheit GmbH viele Publikationen in den renommiertesten Journals der Gesundheitsbranche (z.B. The Lancet). Zudem werden Ergebnisse bei diversen wissenschaftlichen Konferenzen präsentiert. Allerdings müssen neue Erkenntnisse die isolierte Welt der Forschung verlassen um in der Umsetzung von gesundheitspolitischen Maßnahmen Berücksichtigung zu finden. Daher ist es eine der wesentlichen Herausforderungen der Zukunft, die Ergebnisse auch strukturiert, einfach verständlich und transparent für die Praxis und Politik, vor allem auch auf kommunaler Ebene, aufzubereiten. Schlussendlich ist es das Ziel, dass auch die Österreichische und vor allem die Vorarlberger Bevölkerung davon profitiert.

Übersicht über wissenschaftliche Arbeiten

Inhalt in chronologischer Reihenfolge

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Lifestyle-related biomarkers and endometrial cancer survival: Elevated gamma-glutamyltransferase as an important risk factor

Michael Edlinger [a], Nicole Concin [b], Hans Concin [c], Gabriele Nagel [c,d], Hanno Ulmer [a], Georg Göbel [a,*]

[a] Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Austria
[b] Department of Obstetrics and Gynaecology, Innsbruck Medical University, Austria
[c] Agency for Preventive and Social Medicine, Bregenz, Austria
[d] Institute of Epidemiology and Medical Biometry, Ulm University, Germany

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ABSTRACT

Background: Lifestyle seems to play an important role in endometrial cancer mortality, but it remains unclear which biomarkers are involved. The aim of this study was to assess the extent of the association between lifestyle-related biomarkers and the survival of endometrial cancer patients. *Methods*: A sub-cohort of 242 endometrial cancer patients, from a population-based study of the more than 90,000 female participants of the Vorarlberg Health Monitoring and Promotion Programme, was followed for a median duration of twelve years. Besides age, tumour staging, and histology, also pre-diagnostic levels of body mass index, blood pressure, triglycerides, total cholesterol, glucose, gamma-glutamyltransferase (GGT), and serum uric acid were analysed in Cox proportional hazards regression models to estimate multivariate mortality risks. *Results*: During follow-up 89 deaths occurred of which 49 were cancer-related. Survival was associated with age, tumour stage, and histology. Of the biomarkers, $\log_{10}$-transformed GGT showed a large effect on cancer-related mortality (HR = 3.35, 95% CI 1.12–10.03), whereas the other parameters did not appear with significant effects after adjustment for the other factors. *Conclusion*: Elevated level of GGT, a lifestyle-related marker, was associated with poor survival among endometrial cancer patients.

1. Introduction

Endometrial cancer is the sixth most common incident cancer in women worldwide, with an age-standardised incidence of 8.2 per 100,000 women per year. In Western Europe and North America the rates are higher with 11.2 and 16.4 per 100,000 respectively [1]. Recent 5-year relative survival in the United States of America is estimated at about 80% overall [2], but decreases dramatically for advanced stages. Most endometrial carcinomas are adenocarcinomas [3] and staged surgically with the FIGO system [4]. Commonly treatment involves surgery and, in an adjuvant setting, chemotherapy, radiotherapy or a combination of both [5]. The incidence of this cancer type is known to be clearly positively associated with obesity [6], but risk factors also include increasing age, unopposed oestrogen therapy, nulliparity, diabetes, and hypertension [7]. However, the specific determinants of patients' survival is still widely unexplored and the role of lifestyle only beginning to become unravelled.

Cancer mortality in general has been associated with lifestyle-related factors like smoking and nutrition, but there is evermore interest in lifestyle-related biomarkers, for aetiological and for prognostic reasons. For example, an association has been reported between elevated gamma-glutamyltransferase (GGT) and general cancer mortality from a USA population study [8]. GGT seems to be involved in tumour progression by oxidative stress pathways [9–11] and it is a marker of excessive alcohol intake [12]. Alcohol consumption, metabolic factors, and oxidative stress have been linked to the cancer process [13].

High blood pressure, high blood glucose, overweight, and high cholesterol are among the most important risk factors related to overall mortality worldwide and probably involved in a large amount of cancer deaths [14]. In the Me-Can project several of these metabolic factors were found to be associated with mortality from specific cancers [15,16]. Specifically, fatal uterine corpus cancer was related to body mass index and to a lesser extent associated with blood pressure, glucose and triglycerides [17]. Furthermore, in a review of the associations of serum uric acid and GGT, these two metabolic and oxidative stress markers also

* Corresponding author at: Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Schöpfstraße 41, 6020 Innsbruck, Austria. Tel.: +43 512 9003 70911; fax: +43 512 9003 73922.
E-mail addresses: Michael.Edlinger@i-med.ac.at (M. Edlinger), Nicole.Concin@i-med.ac.at (N. Concin), Hans.Concin@lhkb.at (H. Concin), Gabriele.Nagel@uni-ulm.de (G. Nagel), Hanno.Ulmer@i-med.ac.at (H. Ulmer), Georg.Goebel@i-med.ac.at (G. Göbel).

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PLOS ONE

Total Serum Cholesterol and Cancer Incidence in the Metabolic Syndrome and Cancer Project (Me-Can)

Susanne Strohmaier[1], Michael Edlinger[1], Jonas Manjer[2], Tanja Stocks[3,4], Tone Bjørge[5,6], Wegene Borena[1], Christel Häggström[3], Anders Engeland[5,6], Gabriele Nagel[7,8], Martin Almquist[9], Randi Selmer[6], Steinar Tretli[10], Hans Concin[8], Göran Hallmans[11], Håkan Jonsson[12], Pär Stattin[3,13], Hanno Ulmer[1]*

1 Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria, **2** Department of Surgery, Malmö University Hospital, Lund University, Malmö, Sweden, **3** Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden, **4** Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, **5** Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway, **6** Norwegian Institute of Public Health, Oslo/Bergen, Norway, **7** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **8** Agency for Preventive and Social Medicine, Bregenz, Austria, **9** Department of Surgery, Skåne University Hospital Lund and Lund University, Lund, Sweden, **10** Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, Oslo, Norway, **11** Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden, **12** Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden, **13** Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, United States of America

Abstract

Objective: To investigate the association between total serum cholesterol (TSC) and cancer incidence in the Metabolic syndrome and Cancer project (Me-Can).

Methods: Me-Can consists of seven cohorts from Norway, Austria, and Sweden including 289,273 male and 288,057 female participants prospectively followed up for cancer incidence (n = 38,978) with a mean follow-up of 11.7 years. Cox regression models with age as the underlying time metric were used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) for quintiles of cholesterol levels and per 1 mmol/l, adjusting for age at first measurement, body mass index (BMI), and smoking status. Estimates were corrected for regression dilution bias. Furthermore, we performed lag time analyses, excluding different times of follow-up, in order to check for reverse causation.

Results: In men, compared with the 1st quintile, TSC concentrations in the 5th quintile were borderline significantly associated with decreasing risk of total cancer (HR = 0.94; 95%CI: 0.88, 1.00). Significant inverse associations were observed for cancers of the liver/intrahepatic bile duct (HR = 0.14; 95%CI: 0.07, 0.29), pancreas cancer (HR = 0.52, 95% CI: 0.33, 0.81), non-melanoma of skin (HR = 0.67; 95%CI: 0.46, 0.95), and cancers of the lymph−/hematopoietic tissue (HR = 0.68, 95%CI: 0.54, 0.87). In women, hazard ratios for the 5th quintile were associated with decreasing risk of total cancer (HR = 0.86, 95%CI: 0.79, 0.93) and for cancers of the gallbladder (HR = 0.23, 95%CI: 0.08, 0.62), breast (HR = 0.70, 95%CI: 0.61, 0.81), melanoma of skin (HR = 0.61, 95%CI: 0.42, 0.88), and cancers of the lymph−/hematopoietic tissue (HR = 0.61, 95%CI: 0.44, 0.83).

Conclusion: TSC was negatively associated with risk of cancer overall in females and risk of cancer at several sites in both males and females. In lag time analyses some associations persisted, suggesting that for these cancer sites reverse causation did not apply.

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

* E-mail: hanno.ulmer@i-med.ac.at

Introduction

Since the 1980s several epidemiological studies have reported an association between higher total serum cholesterol (TSC) levels and lower overall or site-specific cancer incidence and mortality [1–9], whereas others found higher cancer risk in people with high TSC levels [10–13], no significant relation [14–18], or a U-shaped association, that is both low and high TSC levels being significantly associated with increased cancer risk [19].

It has been suggested that the observed inverse associations have to be attributed to an effect of preclinical cancer or disease on cholesterol levels (i.e. metabolic depression or increased utilization of cholesterol during carcinogenesis [20]) rather than reflecting a true causal relationship. The hypothesis of reverse causation is strongly supported by a recent Mendelian randomization study

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Metabolic Factors Associated with Risk of Renal Cell Carcinoma

Christel Häggström[1]*, Kilian Rapp[2], Tanja Stocks[1,3], Jonas Manjer[4], Tone Bjørge[5,6], Hanno Ulmer[7], Anders Engeland[5,6], Martin Almqvist[4], Hans Concin[8], Randi Selmer[6], Börje Ljungberg[1], Steinar Tretli[9], Gabriele Nagel[2,8], Göran Hallmans[10], Håkan Jonsson[11], Pär Stattin[1,12]

1 Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Umeå, Sweden, **2** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **3** Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, **4** Department of Surgery, Skåne University Hospital, Lund University, Malmö, Sweden, **5** Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway, **6** Norwegian Institute of Public Health, Oslo/Bergen, Norway, **7** Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria, **8** Agency for Preventive and Social Medicine, Bregenz, Austria, **9** Institute of Population-based Cancer Research, The Cancer Registry of Norway, Oslo, Norway, **10** Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden, **11** Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden, **12** Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, New York, United States of America

Abstract

Previous studies have shown that obesity and hypertension are associated with increased risk of renal cell carcinoma (RCC), but less is known about the association to other metabolic factors. In the Metabolic Syndrome and Cancer project (Me-Can) data on body mass index (BMI, kg/m2), blood pressure, and circulating levels of glucose, cholesterol, and triglycerides were collected from 560,388 men and women in cohorts from Norway, Austria, and Sweden. By use of Cox proportional hazard models, hazard ratios (HR) were calculated for separate and composite metabolic exposures. During a median follow-up of 10 years, 592 men and 263 women were diagnosed with RCC. Among men, we found an increased risk of RCC for BMI, highest vs. lowest quintile, (HR = 1.51, 95% CI 1.13–2.03), systolic blood pressure, (HR = 3.40, 95% CI 1.91–6.06), diastolic blood pressure, (HR = 3.33, 95% CI 1.85–5.99), glucose, (HR = 3.75, 95% CI 1.46–9.68), triglycerides, (HR = 1.79, 95% CI 1.00–3.21) and a composite score of these metabolic factors, (HR = 2.68, 95% CI 1.75–4.11). Among women we found an increased risk of RCC for BMI, highest vs. lowest quintile, (HR = 2.21, 95% CI 1.32–3.70) and the composite score, (HR = 2.29, 95% CI 1.12–4.68). High levels of the composite score were also associated with risk of death from RCC among both men and women. No multiplicative statistical or biological interactions between metabolic factors on risk of RCC were found. High levels of BMI, blood pressure, glucose and triglycerides among men and high BMI among women were associated with increased risk of RCC.

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* E-mail: christel.haggstrom@urologi.umu.se

Introduction

The highest incidence of renal cell carcinoma (RCC) is found in North America and Europe and the incidence has been increasing world-wide until recently [1,2]. The increase can be partly explained by improved detection by use of ultra sound and magnetic resonance imaging [3], but it may also be due to an increasing prevalence of risk factors [1].

Established life-style related risk factors for RCC are obesity, hypertension, and smoking [1,2], and these risk factors have been estimated to account for up to 50% of the cases [4]. Previous studies have reported that diabetes type 2 among women [5] and high BMI and blood pressure among men [6] are independent risk factors for RCC, however, those studies had no data of blood lipids, which may be a mediator of these associations. Another study reported that high levels of triglycerides were associated with risk of RCC [7], and found that the association was stronger among obese subjects, however, no data for smoking or hypertension was included in that study.

Thus, less is known about lipids [7,8] and glucose [7,9] and it is also unclear if any of the metabolic factors independently increase the risk, or if they are part of the same pathway, or interact on risk of RCC. Most studies for metabolic factors and risk of RCC have used dichotomized levels of exposure, however, it remains to be shown if there is a threshold with a distinct risk increase, or if the association between increasing levels of metabolic factors and risk is linear.

The aim of this study was to investigate the associations between metabolic factors, separately and jointly, and the risk of RCC and death from RCC taking random measurement error into account.

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RESEARCH ARTICLE Open Access

Blood pressure and falls in community-dwelling people aged 60 years and older in the VHM&PP cohort

Diana Klein[1*], Gabriele Nagel[2,3], Andrea Kleiner[2], Hanno Ulmer[4], Barbara Rehberger[3], Hans Concin[3] and Kilian Rapp[1,2]

Abstract

Background: Falls are one of the major health problems in old people. Different risk factors were identified but only few epidemiological studies analysed the influence of conventionally measured blood pressure on falls. The objective of our study was to investigate the relationship between systolic and diastolic blood pressure and falls.

Methods: In 3,544 community-dwelling Austrian women and men aged 60 years and older, data on falls within the previous three months were collected by questionnaire. Blood pressure was measured by general practitioners within the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) 90 to 1095 days before the fall assessment. A multiple logistic regression analysis was conducted. The models were stratified by gender and adjusted by age, number of medical conditions and subjective feeling of illness.

Results: In total, 257 falls in 3,544 persons were reported. In women, high systolic and diastolic blood pressure was associated with a decreased risk of falls. An increase of systolic blood pressure by 10 mmHg and of diastolic blood pressure by 5 mmHg reduced the risk of falling by 9% (OR 0.91, 95% CI 0.84-0.98) and 8% (OR 0.92, 95% CI 0.85-0.99), respectively. In men, an increased risk of falls was observed in participants with low systolic or low diastolic blood pressure.

Conclusions: Blood pressure was associated with the risk of falls. Hypertensive values decreased the risk in women and low blood pressure increased the risk in men.

Keywords: Falls, Blood pressure, Hypotension, Risk factors

Background

Falls are one of the major health problems in old people. About one third of people aged 65 years and older report at least one fall per year [1]. Consequences can be injuries such as fractures of the hip, the humerus or the forearm, fear of falling, loss of independence and increased mortality [2-4]. Different risk factors for falls including functional limitations and several diseases have been identified [5]. Cardiovascular diseases, for example, have been found to be associated with falls, mostly as a result of hypotensive episodes [6,7]. Blood pressure (BP) is one of the leading risk factors for cardiovascular diseases. Increasing BP has been shown to be linearly associated with cardiovascular disease and mortality. Therefore, low BP values have been usually regarded as a protective factor for different diseases and death [8,9].

In old people, however, there is evidence that the positive relationship between BP and mortality is weakened and that a low BP may even increase mortality [10-12]. For example, in the INVEST-study a J-curve between BP and adverse outcomes (all-cause mortality, nonfatal myocardial infarction or nonfatal stroke) was observed with an increased risk in participants with a very low and a very high BP [13].

Orthostatic hypotension has been shown to be a risk factor for recurrent falls in nursing home residents [14] and in people living in apartments for the elderly [15]. However, assessing orthostatic hypotension is relatively

* Correspondence: diana.klein@rbk.de
[1]Department of Clinical Gerontology, Robert-Bosch-Hospital, Stuttgart, Germany
Full list of author information is available at the end of the article

Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

Ole Raaschou-Nielsen, Zorana J Andersen, Rob Beelen, Evangelia Samoli, Massimo Stafoggia, Gudrun Weinmayr, Barbara Hoffmann, Paul Fischer, Mark J Nieuwenhuijsen, Bert Brunekreef, Wei W Xun, Klea Katsouyanni, Konstantina Dimakopoulou, Johan Sommar, Bertil Forsberg, Lars Modig, Anna Oudin, Bente Oftedal, Per E Schwarze, Per Nafstad, Ulf De Faire, Nancy L Pedersen, Claes-Göran Östenson, Laura Fratiglioni, Johanna Penell, Michal Korek, Göran Pershagen, Kirsten T Eriksen, Mette Sørensen, Anne Tjønneland, Thomas Ellermann, Marloes Eeftens, Petra H Peeters, Kees Meliefste, Meng Wang, Bas Bueno-de-Mesquita, Timothy J Key, Kees de Hoogh, Hans Concin, Gabriele Nagel, Alice Vilier, Sara Grioni, Vittorio Krogh, Ming-Yi Tsai, Fulvio Ricceri, Carlotta Sacerdote, Claudia Galassi, Enrica Migliore, Andrea Ranzi, Giulia Cesaroni, Chiara Badaloni, Francesco Forastiere, Ibon Tamayo, Pilar Amiano, Miren Dorronsoro, Antonia Trichopoulou, Christina Bamia, Paolo Vineis, Gerard Hoek**

Summary

Background **Ambient air pollution is suspected to cause lung cancer. We aimed to assess the association between long-term exposure to ambient air pollution and lung cancer incidence in European populations.**

Methods **This prospective analysis of data obtained by the European Study of Cohorts for Air Pollution Effects used data from 17 cohort studies based in nine European countries. Baseline addresses were geocoded and we assessed air pollution by land-use regression models for particulate matter (PM) with diameter of less than 10 µm (PM_{10}), less than 2·5 µm ($PM_{2·5}$), and between 2·5 and 10 µm (PM_{coarse}), soot ($PM_{2·5absorbance}$), nitrogen oxides, and two traffic indicators. We used Cox regression models with adjustment for potential confounders for cohort-specific analyses and random effects models for meta-analyses.**

Findings **The 312 944 cohort members contributed 4 013 131 person-years at risk. During follow-up (mean 12·8 years), 2095 incident lung cancer cases were diagnosed. The meta-analyses showed a statistically significant association between risk for lung cancer and PM_{10} (hazard ratio [HR] 1·22 [95% CI 1·03–1·45] per 10 µg/m³). For $PM_{2·5}$ the HR was 1·18 (0·96–1·46) per 5 µg/m³. The same increments of PM_{10} and $PM_{2·5}$ were associated with HRs for adenocarcinomas of the lung of 1·51 (1·10–2·08) and 1·55 (1·05–2·29), respectively. An increase in road traffic of 4000 vehicle-km per day within 100 m of the residence was associated with an HR for lung cancer of 1·09 (0·99–1·21). The results showed no association between lung cancer and nitrogen oxides concentration (HR 1·01 [0·95–1·07] per 20 µg/m³) or traffic intensity on the nearest street (HR 1·00 [0·97–1·04] per 5000 vehicles per day).**

Interpretation **Particulate matter air pollution contributes to lung cancer incidence in Europe.**

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*Joint last authors

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Danish Cancer Society Research Center, Copenhagen, Denmark (O Raaschou-Nielsen PhD, Z J Andersen PhD, K T Eriksen PhD, M Sørensen PhD, A Tjønneland DMSc); **Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark** (Z J Andersen); **Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands** (R Beelen PhD, Prof B Brunekreef PhD, M Eeftens MSc, K Meliefste BSc, M Wang MSc, G Hoek PhD); **Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece** (E Samoli PhD, Prof K Katsouyanni PhD, K Dimakopoulou MSc, Prof A Trichopoulou MD, C Bamia PhD); **Department of Epidemiology, Lazio Regional Health Service, Local Health Unit ASL RME, Rome, Italy** (M Stafoggia MSc, G Cesaroni MSc, C Badaloni MSc, F Forastiere PhD); **Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany** (G Weinmayr PhD, G Nagel PhD); **IUF–Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany** (G Weinmayr, Prof B Hoffmann MD); **Medical**

Introduction

Lung cancer is one of the most common cancers and has a poor prognosis. Active smoking is the main cause, but occupational exposures, residential radon, and environmental tobacco smoke are also established risk factors. Furthermore, lower socioeconomic position has been associated with a higher risk for lung cancer.[1] Ambient air pollution, specifically particulate matter with absorbed polycyclic aromatic hydrocarbons and other genotoxic chemicals, is suspected to increase the risk for lung cancer. Results of several epidemiological studies have shown higher risks for lung cancer in association with various measures of air pollution[2–11] and suggested an association mainly in non-smokers[4,12] and never-smokers[13,14] and in individuals with low fruit consumption.[4,13] In developed countries, overall lung cancer incidence rates have stabilised during the past few decades, but major shifts have been recorded in the frequencies of different histological types of lung cancer, with substantial relative increases in adenocarcinomas and decreases in squamous-cell carcinomas.[15] Changes in tobacco blends[15] and ambient air pollution[16,17] might have contributed to these shifts.

Within the European Study of Cohorts for Air Pollution Effects (ESCAPE), we aimed to analyse data from 17 European cohort studies with a wide range of exposure levels to investigate the following hypotheses: that ambient air pollution at the residence (specifically particulate matter) is associated with risk for lung cancer; that the association between air pollution and risk for lung cancer is stronger for non-smokers and people with low fruit intake; and that the association with air pollution is stronger for adenocarcinomas and squamous-cell carcinomas than for all lung cancers combined.

Methods

Study design and participants

This study is a prospective analysis of data obtained by ESCAPE—an investigation into the long-term effects of

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PLOS ONE

The Age-Specific Quantitative Effects of Metabolic Risk Factors on Cardiovascular Diseases and Diabetes: A Pooled Analysis

Gitanjali M. Singh[1☯], Goodarz Danaei[2,3☯], Farshad Farzadfar[4], Gretchen A. Stevens[5], Mark Woodward[6,7], David Wormser[8], Stephen Kaptoge[8], Gary Whitlock[9], Qing Qiao[10], Sarah Lewington[9], Emanuele Di Angelantonio[8], Stephen vander Hoorn[11], Carlene M. M. Lawes[12], Mohammed K. Ali[13], Dariush Mozaffarian[1,3,14], Majid Ezzati[15]*, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group; Asia-Pacific Cohort Studies Collaboration (APCSC)[¶], Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE)[¶], Emerging Risk Factor Collaboration (ERFC)[¶], Prospective Studies Collaboration (PSC)[¶]

1 Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, United States of America, **2** Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, United States of America, **3** Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, **4** Diabetes Research Centre and Endocrinology and Metabolism Research Centre, Tehran University of Medical Sciences, Tehran, Iran, **5** Department of Health Statistics and Information Systems, World Health Organization, Geneva, Switzerland, **6** The George Institute for Global Health, University of Sydney, Australia, **7** Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, United States of America, **8** Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom, **9** Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom, **10** Department of Public Health, University of Helsinki, Helsinki, Finland, **11** Department of Statistics, University of Melbourne, Melbourne, Australia, **12** National Institute for Health Innovation, University of Auckland, Auckland, New Zealand, **13** Hubert Department of Global Health, Emory University, Atlanta, Georgia, United States of America, **14** Division of Cardiovascular Medicine and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States of America, **15** Medical Research Council-Health Protection Agency Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

Abstract

Background: The effects of systolic blood pressure (SBP), serum total cholesterol (TC), fasting plasma glucose (FPG), and body mass index (BMI) on the risk of cardiovascular diseases (CVD) have been established in epidemiological studies, but consistent estimates of effect sizes by age and sex are not available.

Methods: We reviewed large cohort pooling projects, evaluating effects of baseline or usual exposure to metabolic risks on ischemic heart disease (IHD), hypertensive heart disease (HHD), stroke, diabetes, and, as relevant selected other CVDs, after adjusting for important confounders. We pooled all data to estimate relative risks (RRs) for each risk factor and examined effect modification by age or other factors, using random effects models.

Results: Across all risk factors, an average of 123 cohorts provided data on 1.4 million individuals and 52,000 CVD events. Each metabolic risk factor was robustly related to CVD. At the baseline age of 55–64 years, the RR for 10 mmHg higher SBP was largest for HHD (2.16; 95% CI 2.09–2.24), followed by effects on both stroke subtypes (1.66; 1.39–1.98 for hemorrhagic stroke and 1.63; 1.57–1.69 for ischemic stroke). In the same age group, RRs for 1 mmol/L higher TC were 1.44 (1.29–1.61) for IHD and 1.20 (1.15–1.25) for ischemic stroke. The RRs for 5 kg/m^2 higher BMI for ages 55–64 ranged from 2.32 (2.04–2.63) for diabetes, to 1.44 (1.40–1.48) for IHD. For 1 mmol/L higher FPG, RRs in this age group were 1.18 (1.08–1.29) for IHD and 1.14 (1.01–1.29) for total stroke. For all risk factors, proportional effects declined with age, were generally consistent by sex, and differed by region in only a few age groups for certain risk factor-disease pairs.

Conclusion: Our results provide robust, comparable and precise estimates of the effects of major metabolic risk factors on CVD and diabetes by age group.

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Body mass index and metabolic factors predict glomerular filtration rate and albuminuria over 20 years in a high-risk population

Gabriele Nagel[1,2*], Emanuel Zitt[3,4], Raphael Peter[1,2], Alfonso Pompella[5], Hans Concin[1] and Karl Lhotta[3,4]

Abstract

Background: The number of individuals suffering from chronic kidney disease (CKD) is increasing. Therefore, early identification of modifiable predictors of CKD is highly desirable. Previous studies suggest an association between body mass index (BMI), metabolic factors and CKD.

Methods: Data of 241 high risk patients with information on renal function and albuminuria from the Renal Disease in Vorarlberg (RENVOR) study (2010–2011) were linked with long-term measurements of metabolic factors in the same patients from the population-based Vorarlberg Health Monitoring & Prevention Program (VHM&PP) cohort study (1988–2005). Actual estimated glomerular filtration rate (eGFR) and urinary albumin creatinine ratio (ACR) were determined. BMI, blood pressure, fasting glucose, total cholesterol, triglycerides and Gamma-glutamyltransferase (GGT) were available from previous health examinations performed up to 25 years ago. Linear regression models were applied to identify predictors of current renal function.

Results: At all-time points BMI was significantly inversely associated with actual eGFR and positively with actual albuminuria in men, but not in women. Serum GGT and triglycerides were significantly positively associated with albuminuria in men at all-time points. Fasting glucose levels more than 20 years earlier were associated with increased albuminuria in women and reduced eGFR in men, whereas at later time points it was associated with albuminuria in men.

Conclusions: BMI, serum GGT, and triglycerides are long-term predictors of renal function in men. In women however, anthropometric and metabolic parameters seem to be less predictive of eGFR and albuminuria.

Keywords: Body mass index, Glomerular filtration rate, Albuminuria, Obesity, Gamma glutamyltransferase, Epidemiology

Background

According to the World Health Organisation (WHO) obesity is one of the greatest public health challenges in the 21st century. Obesity causes 2-8% of health costs and 10-13% of deaths in Europe [1]. Not only is obesity a well-known risk factor for diabetes, cardiovascular disease and cancer, but it is also increasingly being recognised as contributing to the development of chronic kidney disease (CKD). According to a Swedish study, 16% of chronic renal failure cases in men and 11% in women can be attributed to obesity [2]. A recent study of over a million individuals showed that overweight and obesity in adolescence increased the risk for end-stage renal failure three- and sevenfold 25 years later [3].

The metabolic syndrome (MetS) is a cluster of different metabolic risk factors, such as obesity, hypertension, insulin resistance/hyperglycaemia and dyslipidaemia [4]. Obesity is linked to the metabolic syndrome, which is clearly associated with CKD [5]. Beyond the metabolic factors (elevated fasting glucose, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol) and hypertension included in the definition of the metabolic syndrome, serum levels of the enzyme gamma

* Correspondence: gabriele.nagel@aks.or.at
[1]Agency for Preventive and Social Medicine, Rheinstraße 61, 6900 Bregenz, Austria
[2]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
Full list of author information is available at the end of the article

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ORIGINAL PAPER

Pooled cohort study on height and risk of cancer and cancer death

Sara Wirén · Christel Häggström · Hanno Ulmer · Jonas Manjer · Tone Bjørge · Gabriele Nagel · Dorthe Johansen · Göran Hallmans · Anders Engeland · Hans Concin · Håkan Jonsson · Randi Selmer · Steinar Tretli · Tanja Stocks · Pär Stattin

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Abstract
Purpose To assess the association between height and risk of cancer and cancer death.
Methods The metabolic syndrome and cancer project is a prospective pooled cohort study of 585,928 participants from seven cohorts in Austria, Norway, and Sweden. Hazard ratios (HRs) and 95 % confidence intervals (CIs) for cancer incidence and death were estimated in height categories and per 5-cm increment for each cancer site using Cox proportional hazards model.
Results During a mean follow-up of 12.7 years (SD = 7.2), 38,862 participants were diagnosed with cancer and 13,547 participants died of cancer. Increased height (per 5-cm increment) was associated with an increased overall cancer risk in women, HR 1.07 (95 % CI 1.06–1.09), and in men, HR 1.04 (95 % CI 1.03–1.06). The highest HR was seen for malignant melanoma in women, HR 1.17 (95 % CI 1.11–1.24), and in men HR 1.12 (95 % CI 1.08–1.19). Height was also associated with increased risk of cancer death in women, HR 1.03 (95 % CI 1.01–1.16), and in men, HR 1.03 (95 % CI 1.01–1.05). The highest HR was observed for breast cancer death in postmenopausal women (>60 years), HR 1.10 (95 % CI 1.00–1.21), and death from renal cell carcinoma in men, HR 1.18 (95 % CI 1.07–1.30). All these associations were independent of body mass index.
Conclusion Height was associated with risk of cancer and cancer death indicating that factors related to height such as hormonal and genetic factors stimulate both cancer development and progression.

S. Wirén (✉) · C. Häggström · T. Stocks · P. Stattin
Department of Surgery and Perioperative Sciences, Urology and Andrology, Umeå University, 901 87 Umeå, Sweden
e-mail: sara.wiren@urologi.umu.se

H. Ulmer
Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria

J. Manjer
Department of Plastic Surgery, Skåne University Hospital Malmö, Lund University, Malmö, Sweden

T. Bjørge · A. Engeland
Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

T. Bjørge · A. Engeland · R. Selmer
Norwegian Institute of Public Health, Oslo/Bergen, Norway

G. Nagel
Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

G. Nagel · H. Concin
Agency for Preventive and Social Medicine, Bregenz, Austria

D. Johansen
Department of Surgery, Skåne University Hospital Lund, Lund, Sweden

G. Hallmans
Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden

H. Jonsson
Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

S. Tretli
Institute of Population-based Cancer Research, Cancer Registry of Norway, Oslo, Norway

Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants

*The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects)**

Summary

Background Body-mass index (BMI) and diabetes have increased worldwide, whereas global average blood pressure and cholesterol have decreased or remained unchanged in the past three decades. We quantified how much of the effects of BMI on coronary heart disease and stroke are mediated through blood pressure, cholesterol, and glucose, and how much is independent of these factors.

Methods We pooled data from 97 prospective cohort studies that collectively enrolled 1·8 million participants between 1948 and 2005, and that included 57 161 coronary heart disease and 31 093 stroke events. For each cohort we excluded participants who were younger than 18 years, had a BMI of lower than 20 kg/m², or who had a history of coronary heart disease or stroke. We estimated the hazard ratio (HR) of BMI on coronary heart disease and stroke with and without adjustment for all possible combinations of blood pressure, cholesterol, and glucose. We pooled HRs with a random-effects model and calculated the attenuation of excess risk after adjustment for mediators.

Findings The HR for each 5 kg/m² higher BMI was 1·27 (95% CI 1·23–1·31) for coronary heart disease and 1·18 (1·14–1·22) for stroke after adjustment for confounders. Additional adjustment for the three metabolic risk factors reduced the HRs to 1·15 (1·12–1·18) for coronary heart disease and 1·04 (1·01–1·08) for stroke, suggesting that 46% (95% CI 42–50) of the excess risk of BMI for coronary heart disease and 76% (65–91) for stroke is mediated by these factors. Blood pressure was the most important mediator, accounting for 31% (28–35) of the excess risk for coronary heart disease and 65% (56–75) for stroke. The percentage excess risks mediated by these three mediators did not differ significantly between Asian and western cohorts (North America, western Europe, Australia, and New Zealand). Both overweight (BMI ≥25 to <30 kg/m²) and obesity (BMI ≥30 kg/m²) were associated with a significantly increased risk of coronary heart disease and stroke, compared with normal weight (BMI ≥20 to <25 kg/m²), with 50% (44–58) of the excess risk of overweight and 44% (41–48) of the excess risk of obesity for coronary heart disease mediated by the selected three mediators. The percentages for stroke were 98% (69–155) for overweight and 69% (64–77) for obesity.

Interpretation Interventions that reduce high blood pressure, cholesterol, and glucose might address about half of excess risk of coronary heart disease and three-quarters of excess risk of stroke associated with high BMI. Maintenance of optimum bodyweight is needed for the full benefits.

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*Members of the Writing and Pooling, and Collaborating Group are listed at end of paper

Correspondence to: Goodarz Danaei, Department of Global Health and Population, Harvard School of Public Health, Boston, MA 02115, USA
gdanaei@hsph.harvard.edu

Introduction

Cardiovascular diseases, especially coronary heart disease and stroke, are the leading causes of death worldwide.[1] High body-mass index (BMI) is an important cardiovascular disease risk factor,[2–4] and raised blood pressure, cholesterol, and glucose partly mediate its effects.[5,6] Present behavioural interventions for weight management are only effective in the short term,[7,8] most weight-loss drugs lack either sustained efficacy or an acceptable safety profile,[9,10] and surgical methods are recommended only for very obese individuals.[11,12] This situation has created concerns about a potentially massive worldwide increase in cardiovascular diseases as a result of increased BMI and prevalence of overweight and obesity in most countries.[13–15] By contrast, effective clinical and public health interventions for blood pressure and cholesterol are available, as evidenced by large decreases in these measures in some countries despite rises in obesity.[14,16,17] Therefore, an important clinical and public health question is: to what extent can the adverse effects of high BMI be mitigated by targeting its metabolic mediators?

To answer this question we need a detailed understanding of how much of the effect of excess weight on cardiovascular disease is mediated by these metabolic factors, separately and in combinations, which are relevant for individual patients or populations. Whether the extent

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Changes of Body Mass Index in Relation to Mortality: Results of a Cohort of 42,099 Adults

Jochen Klenk[1,2], Kilian Rapp[1,2], Hanno Ulmer[3], Hans Concin[4], Gabriele Nagel[1,4]*

1 Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **2** Clinic for Geriatric Rehabilitation, Robert-Bosch Hospital, Stuttgart, Germany, **3** Department of Medical Statistics, Informatics and Health Economics, Medical University, Innsbruck, Austria, **4** Agency for Preventive and Social Medicine, Bregenz, Austria

Abstract

Background: High Body-Mass-Index (BMI) is associated with increased all-cause mortality, but little is known about the effect of short- and long-term BMI change on mortality. The aim of the study was to determine how long-term weight change affects mortality.

Methods and findings: Within a population-based prospective cohort of 42,099 Austrian men and women (mean age 43 years) with at least three BMI measurements we investigated the relationship of BMI at baseline and two subsequent BMI change intervals of five years each with all-cause mortality using Cox proportional Hazard models. During median follow-up of 12 years 4,119 deaths were identified. The lowest mortalities were found in persons with normal weight or overweight at baseline and stable BMI over 10 years. Weight gain ($\geq$0.10 kg/m^2/year) during the first five years was associated with increased mortality in overweight and obese people. For weight gain during both time intervals mortality risk remained significantly increased only in overweight (Hazard Ratio (HR): 1.39 (95% confidence interval: 1.01; 1.92)) and obese women (1.85 (95% confidence interval: 1.18; 2.89)). Weight loss ($<$ $-$0.10 kg/m^2/year) increased all-cause mortality in men and women consistently. BMI change over time assessed using accepted World Health Organisation BMI categories showed no increased mortality risk for people who remained in the normal or overweight category for all three measurements. In contrast, HRs for stable obese men and women were 1.57 (95% CI: 1.31; 1.87) and 1.46 (95% CI: 1.25; 1.71) respectively.

Conclusion: Our findings highlight the importance of weight stability and obesity avoidance in prevention strategy.

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* E-mail: gabriele.nagel@uni-ulm.de

Introduction

Over the last decades, the prevalence of overweight and obesity has increased in most industrialized countries and reached alarming dimensions [1]. Many diseases are linked to excess body-weight such as type II diabetes, coronary heart disease, stroke or various types of cancer [2–5]. Several studies have shown a relationship between obesity and increased all-cause mortality [6–11]. For overweight, little to no increased mortality risk has been reported [6–11].

BMI is a common clinical measure for overweight and obesity. Although many previously published studies have been limited to a single BMI measurement, some studies suggest that changes in BMI over time may be of greater significance to public health. However, the impact of BMI change on all-cause mortality remains controversial.

Several studies found a relationship between BMI loss and elevated all-cause mortality [12–18]. The observed associations between BMI gain and all-cause mortality are inconsistent. Some authors reported positive associations [12,13,15,19–21], while others did not find any relationship [14,16,17]. Data on the effects of long- term weight changes in population-based cohorts are sparse.

Methodological problems like reverse causation or lack of knowledge about the intention of weight loss make causality difficult to interpret [22,23]. In addition, weight change may be associated with pre-existing disease or subclinical conditions.

In order to clarify the effect of long-term BMI change patterns, we conducted a prospective study to analyse the effect of BMI at baseline and two subsequent BMI change intervals of five years each on all-cause mortality in a cohort of 42,099 Austrian men and women.

Methods

Study Population

The Vorarlberg Health Monitoring & Prevention Program (VHM&PP) is a population-based risk factor surveillance program in Vorarlberg, the westernmost province of Austria. The program is administrated by the Agency of Social and Preventive Medicine (aks). All adults (aged $\geq$19 years) within the province were invited to participate. Enrolment is voluntary and costs for one examination per year are covered by the participant's compulsory health insurance. The screening examinations take place in the practices of local physicians according to a standard protocol.

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RESEARCH ARTICLE Open Access

Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580 000 subjects within the Me-Can project

Björn Lindkvist[1,14*], Dorthe Johansen[2], Tanja Stocks[3], Hans Concin[4], Tone Bjørge[5,6], Martin Almquist[7], Christel Häggström[3], Anders Engeland[5,6], Göran Hallmans[8], Gabriele Nagel[9], Håkan Jonsson[10], Randi Selmer[6], Hanno Ulmer[11], Steinar Tretli[12], Pär Stattin[3] and Jonas Manjer[2,13]

Abstract

Background: Obesity is associated with an increased risk of esophageal adenocarcinoma (EAC) and a decreased risk of esophageal squamous cell carcinoma (ESCC). However, little is known about the risk of EAC and ESCC related to other metabolic risk factors. We aimed to examine the risk of EAC and ESCC in relation to metabolic risk factors, separately and combined in a prospective cohort study.

Methods: The Metabolic Syndrome and Cancer cohort includes prospective cohorts in Austria, Norway and Sweden, with blood pressure, lipids, glucose and BMI available from 578 700 individuals. Relative risk (RR) for EAC and ESCC was calculated using Cox's proportional hazards analysis for metabolic risk factors categorized into quintiles and transformed into z-scores. The standardized sum of all z-scores was used as a composite score for the metabolic syndrome (MetS).

Results: In total, 324 histologically verified cases of esophageal cancer were identified (114 EAC, 184 ESCC and 26 with other histology). BMI was associated with an increased risk of EAC (RR 7.34 (95% confidence interval, 2.88-18.7) top versus bottom quintile) and negatively associated with the risk of ESCC (RR 0.38 (0.23-0.62)). The mean value of systolic and diastolic blood pressure (mid blood pressure) was associated with the risk of ESCC (RR 1.77 (1.37-2.29)). The composite MetS score was associated with the risk of EAC (RR 1.56 (1.19-2.05) per one unit increase of z-score) but not ESCC.

Conclusions: In accordance with previous studies, high BMI was associated with an increased risk of EAC and a decreased risk of ESCC. An association between high blood pressure and risk of ESCC was observed but alcohol consumption is a potential confounding factor that we were not able to adjust for in the analysis. The MetS was associated with EAC but not ESCC. However this association was largely driven by the strong association between BMI and EAC. We hypothesize that this association is more likely to be explained by factors directly related to obesity than the metabolic state of the MetS, considering that no other metabolic factor than BMI was associated with EAC.

Keywords: Esophageal cancer, Esophageal adenocarcinoma, Esophageal squamous cell carcinoma, Obesity, Hypertension

* Correspondence: bjorn.lindkvist@vgregion.se
[1]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[14]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden
Full list of author information is available at the end of the article

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Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: Results from the ESCAPE and TRANSPHORM projects

Meng Wang [a,*], Rob Beelen [a], Massimo Stafoggia [b], Ole Raaschou-Nielsen [c], Zorana Jovanovic Andersen [c,d], Barbara Hoffmann [e,f], Paul Fischer [g], Danny Houthuijs [g], Mark Nieuwenhuijsen [h,i], Gudrun Weinmayr [f,j], Paolo Vineis [k], Wei W. Xun [k,l], Konstantina Dimakopoulou [m], Evangelia Samoli [m], Tiina Laatikainen [n,o], Timo Lanki [n], Anu W. Turunen [n], Bente Oftedal [p], Per Schwarze [p], Geir Aamodt [p], Johanna Penell [q], Ulf De Faire [q], Michal Korek [q], Karin Leander [q], Göran Pershagen [q], Nancy L. Pedersen [r], Claes-Göran Östenson [s], Laura Fratiglioni [t], Kirsten Thorup Eriksen [c], Mette Sørensen [c], Anne Tjønneland [c], Bas Bueno-de-Mesquita [g,u], Marloes Eeftens [a,v,w], Michiel L. Bots [x], Kees Meliefste [a], Ursula Krämer [e], Joachim Heinrich [y], Dorothea Sugiri [e], Timothy Key [z], Kees de Hoogh [aa], Kathrin Wolf [ab], Annette Peters [ab], Josef Cyrys [ab,ac], Andrea Jaensch [j], Hans Concin [ad], Gabriele Nagel [j,ad], Ming-Yi Tsai [v,w], Harish Phuleria [v,w], Alex Ineichen [v,w], Nino Künzli [v,w], Nicole Probst-Hensch [v,w], Emmanuel Schaffner [v,w], Alice Vilier [ae,af,ag], Françoise Clavel-Chapelon [ae,af,ag], Christophe Declerq [ah], Fulvio Ricceri [ai], Carlotta Sacerdote [aj], Alessandro Marcon [ak], Claudia Galassi [aj], Enrica Migliore [aj], Andrea Ranzi [al], Giulia Cesaroni [b], Chiara Badaloni [b], Francesco Forastiere [b], Michail Katsoulis [am], Antonia Trichopoulou [am], Menno Keuken [an], Aleksandra Jedynska [an], Ingeborg M. Kooter [an], Jaakko Kukkonen [ao], Ranjeet S. Sokhi [ap], Bert Brunekreef [a,x], Klea Katsouyanni [m], Gerard Hoek [a]

[a] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[b] Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
[c] Danish Cancer Society Research Center, Copenhagen, Denmark
[d] Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[e] IUF, Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[f] University of Düsseldorf, Düsseldorf, Germany
[g] National Institute of Public Health and the Environment, Bilthoven, The Netherlands
[h] Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[i] Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública — CIBERESP), Madrid, Spain
[j] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[k] MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom
[l] University College London, London, United Kingdom
[m] Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens, Athens, Greece
[n] National Institute for Health and Welfare, Kuopio, Finland
[o] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[p] Norwegian Institute of Public Health, Oslo, Norway
[q] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[r] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[s] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[t] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[u] School of Public Health, Imperial College London, London, United Kingdom
[v] Swiss Tropical and Public Health Institute, Basel, Switzerland
[w] University of Basel, Basel, Switzerland
[x] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[y] Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center of Environmental Health, Neuherberg, Germany
[z] Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom
[aa] MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom
[ab] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Abbreviations: BMI, body mass index; CTS, California Teachers Study; Cu, copper; CVD, cardiovascular disease; ESCAPE, European Study of Cohorts for Air Pollution Effects; Fe, iron; HRs, hazard ratios; K, potassium; LOOCV, leave-one-out cross validation; LUR, Land Use Regression models; Ni, nickel; PM, particulate matter; S, sulfur; SES, socio-economic status; Si, silicon; TRANSPHORM, Transport related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter; V, vanadium; XRF, X-ray fluorescence; Zn, zinc.

* Corresponding author at: Institute for Risk Assessment Sciences, Division Environmental Epidemiology, Utrecht University, P.O. Box 80178, 3508 TD Utrecht, The Netherlands. Tel.: +31 6 16697117; fax: +31 30 2539499.
E-mail address: M.Wang@uu.nl (M. Wang).

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A Prospective Study on Metabolic Risk Factors and Gallbladder Cancer in the Metabolic Syndrome and Cancer (Me-Can) Collaborative Study

Wegene Borena[1], Michael Edlinger[1], Tone Bjørge[2,3], Christel Häggström[4], Björn Lindkvist[5], Gabriele Nagel[6,10], Anders Engeland[2,3], Tanja Stocks[4,7], Susanne Strohmaier[1], Jonas Manjer[8], Randi Selmer[2], Steinar Tretli[9], Hans Concin[10], Goran Hallmans[11], Håkan Jonsson[12], Pär Stattin[4], Hanno Ulmer[1]*

1 Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria, **2** Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway, **3** Norwegian Institute of Public Health, Oslo/Bergen, Norway, **4** Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden, **5** Department of Internal Medicine, Division of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Gothenburg, Sweden, **6** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **7** Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, **8** Department of Surgery, Malmö University Hospital, Lund University, Malmö, Sweden, **9** Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, Oslo, Norway, **10** Agency for Preventive and Social Medicine, Bregenz, Austria, **11** Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden, **12** Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

Abstract

Objective: To investigate the association between metabolic risk factors (individually and in combination) and risk of gallbladder cancer (GBC).

Methods: The metabolic syndrome and cancer project (Me-Can) includes cohorts from Norway, Austria, and Sweden with data on 578,700 men and women. We used Cox proportional hazard regression models to calculate relative risks of GBC by body mass index (BMI), blood pressure, and plasma levels of glucose, cholesterol, and triglycerides as continuous standardised variables and their standardised sum of metabolic syndrome (MetS) z-score. The risk estimates were corrected for random error in measurements.

Results: During an average follow-up of 12.0 years (SD = 7.8), 184 primary gallbladder cancers were diagnosed. Relative risk of gallbladder cancer per unit increment of z-score adjusted for age, smoking status and BMI (except for BMI itself) and stratified by birth year, sex and sub-cohorts, was for BMI 1.31 (95% confidence interval 1.11, 1.57) and blood glucose 1.76 (1.10, 2.85). Further analysis showed that the effect of BMI on GBC risk is larger among women in the premenopausal age group (1.84 (1.23, 2.78)) compared to those in the postmenopausal age group (1.29 (0.93, 1.79)). For the other metabolic factors no significant association was found (mid blood pressure 0.96 (0.71, 1.31), cholesterol 0.84 (0.66, 1.06) and serum triglycerides 1.16 (0.82, 1.64)). The relative risk per one unit increment of the MetS z-score was 1.37 (1.07, 1.73).

Conclusion: This study showed that increasing BMI and impaired glucose metabolism pose a possible risk for gallbladder cancer. Beyond the individual factors, the results also showed that the metabolic syndrome as an entity presents a risk constellation for the occurrence of gallbladder cancer.

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* E-mail: Hanno.Ulmer@i-med.ac.at

Introduction

Primary gallbladder cancer (GBC) is the most common biliary tract tumour and the sixth most common cancer affecting the gastrointestinal tract [1,2]. It is a disease typically characterised by late diagnosis and poor outcome with a five year survival of only about 32% [3]. Although the presence of gallstones is considered to be an important risk factor, several other unidentified factors may be important in the development of gallbladder carcinoma. About 10 to 25% of patients with this disease do not have associated cholelithiasis and only a small proportion (1 to 3%) of patients that do have gallstones actually develop cancer [4].

Metabolic syndrome (MetS) is a constellation of factors related to insulin resistance including obesity, impaired glucose tolerance, dyslipidaemia and hypertension with varying definitions [5]. It has consistently been associated with an increased risk of cardiovascular diseases and diabetes type 2 [6,7], and recently with risk of cancer at some sites like colorectal, prostate and liver cancers

Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project

Rob Beelen, Ole Raaschou-Nielsen, Massimo Stafoggia, Zorana Jovanovic Andersen, Gudrun Weinmayr, Barbara Hoffmann, Kathrin Wolf, Evangelia Samoli, Paul Fischer, Mark Nieuwenhuijsen, Paolo Vineis, Wei W Xun, Klea Katsouyanni, Konstantina Dimakopoulou, Anna Oudin, Bertil Forsberg, Lars Modig, Aki S Havulinna, Timo Lanki, Anu Turunen, Bente Oftedal, Wenche Nystad, Per Nafstad, Ulf De Faire, Nancy L Pedersen, Claes-Göran Östenson, Laura Fratiglioni, Johanna Penell, Michal Korek, Göran Pershagen, Kirsten Thorup Eriksen, Kim Overvad, Thomas Ellermann, Marloes Eeftens, Petra H Peeters, Kees Meliefste, Meng Wang, Bas Bueno-de-Mesquita, Dorothea Sugiri, Ursula Krämer, Joachim Heinrich, Kees de Hoogh, Timothy Key, Annette Peters, Regina Hampel, Hans Concin, Gabriele Nagel, Alex Ineichen, Emmanuel Schaffner, Nicole Probst-Hensch, Nino Künzli, Christian Schindler, Tamara Schikowski, Martin Adam, Harish Phuleria, Alice Vilier, Françoise Clavel-Chapelon, Christophe Declercq, Sara Grioni, Vittorio Krogh, Ming-Yi Tsai, Fulvio Ricceri, Carlotta Sacerdote, Claudia Galassi, Enrica Migliore, Andrea Ranzi, Giulia Cesaroni, Chiara Badaloni, Francesco Forastiere, Ibon Tamayo, Pilar Amiano, Miren Dorronsoro, Michail Katsoulis, Antonia Trichopoulou, Bert Brunekreef, Gerard Hoek

Summary

Background **Few studies on long-term exposure to air pollution and mortality have been reported from Europe. Within the multicentre European Study of Cohorts for Air Pollution Effects (ESCAPE), we aimed to investigate the association between natural-cause mortality and long-term exposure to several air pollutants.**

Methods **We used data from 22 European cohort studies, which created a total study population of 367 251 participants. All cohorts were general population samples, although some were restricted to one sex only. With a strictly standardised protocol, we assessed residential exposure to air pollutants as annual average concentrations of particulate matter (PM) with diameters of less than 2·5 μm ($PM_{2·5}$), less than 10 μm (PM_{10}), and between 10 μm and 2·5 μm (PM_{coarse}), $PM_{2·5}$ absorbance, and annual average concentrations of nitrogen oxides (NO_2 and NO_x), with land use regression models. We also investigated two traffic intensity variables—traffic intensity on the nearest road (vehicles per day) and total traffic load on all major roads within a 100 m buffer. We did cohort-specific statistical analyses using confounder models with increasing adjustment for confounder variables, and Cox proportional hazards models with a common protocol. We obtained pooled effect estimates through a random-effects meta-analysis.**

Findings **The total study population consisted of 367 251 participants who contributed 5 118 039 person-years at risk (average follow-up 13·9 years), of whom 29 076 died from a natural cause during follow-up. A significantly increased hazard ratio (HR) for $PM_{2·5}$ of 1·07 (95% CI 1·02–1·13) per 5 μg/m³ was recorded. No heterogeneity was noted between individual cohort effect estimates (I^2 p value=0·95). HRs for $PM_{2·5}$ remained significantly raised even when we included only participants exposed to pollutant concentrations lower than the European annual mean limit value of 25 μg/m³ (HR 1·06, 95% CI 1·00–1·12) or below 20 μg/m³ (1·07, 1·01–1·13).**

Interpretation **Long-term exposure to fine particulate air pollution was associated with natural-cause mortality, even within concentration ranges well below the present European annual mean limit value.**

Funding **European Community's Seventh Framework Program (FP7/2007–2011).**

Introduction

Studies have shown the effects of long-term exposure to air pollution on mortality,[1,2] with most, especially those in the USA, reporting on the mass concentration of particulate matter (PM) smaller than 10 μm (PM_{10}) or 2·5 μm ($PM_{2·5}$) in diameter. Few European studies have investigated $PM_{2·5}$, partly because of the low availability of routine monitoring data. However, some European studies have shown associations between mortality and nitrogen dioxide (NO_2) or nitrogen oxides (NO_x).[3–8]

In urban areas, NO_2, NO_x, and $PM_{2·5}$ absorbance (a marker for black carbon or soot) have larger spatial concentration contrasts than PM because they are more closely related to motorised traffic. Interest in the health effects of coarse particles (2·5–10 μm in diameter) has also increased.[9] However, the comparability of previous studies is limited by the different exposure methods used.[10]

In the framework of the multicentre European Study of Cohorts for Air Pollution Effects (ESCAPE), we added standardised exposure assessment for PM, NO_2, and NO_x to health data from 22 ongoing cohort studies across Europe. The objective of ESCAPE was to investigate the association between long-term exposure to air pollution and mortality. In this Article, we report associations for natural-cause mortality. Cause-specific results will be published separately.

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Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands (R Beelen PhD, M Eeftens MSc, K Meliefste BSc, M Wang MSc, Prof B Brunekreef PhD, G Hoek PhD); **Danish Cancer Society Research Center, Copenhagen, Denmark** (O Raaschou-Nielsen PhD, Z J Andersen PhD, K T Eriksen PhD); **Department of Epidemiology, Lazio Regional Health Service, Rome, Italy** (M Stafoggia MSc, G Cesaroni MSc, C Badaloni MSc, F Forastiere MD); **Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark** (Z J Andersen); **Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany** (G Weinmayr PhD, Prof G Nagel PhD); **IUF – Leibniz Research Institute for Environmental Medicine, Germany and Medical Faculty, University of Düsseldorf, Düsseldorf, Germany** (G Weinmayr, Prof B Hoffman MD, D Sugiri MSc, Prof U Krämer PhD); **Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany** (K Wolf PhD, Prof A Peters PhD, R Hampel PhD); **Department of Hygiene, Epidemiology and Medical Statistics, Medical School,**

ORIGINAL ARTICLE

Air Pollution and Nonmalignant Respiratory Mortality in 16 Cohorts within the ESCAPE Project

Konstantina Dimakopoulou[1], Evangelia Samoli[1], Rob Beelen[2], Massimo Stafoggia[3], Zorana Jovanovic Andersen[4,5], Barbara Hoffmann[6], Paul Fischer[7], Mark Nieuwenhuijsen[8,9], Paolo Vineis[10], Wei Xun[10], Gerard Hoek[2], Ole Raaschou-Nielsen[4], Anna Oudin[11], Bertil Forsberg[11], Lars Modig[11], Pekka Jousilahti[12], Timo Lanki[13], Anu Turunen[13], Bente Oftedal[14], Per Nafstad[14,15], Per E. Schwarze[14], Johanna Penell[16], Laura Fratiglioni[17], Niklas Andersson[16,18], Nancy Pedersen[19], Michal Korek[16], Ulf De Faire[16], Kirsten Thorup Eriksen[4], Anne Tjønneland[4], Thomas Becker[20], Meng Wang[2], Bas Bueno-de-Mesquita[7,10,21], Ming-Yi Tsai[22,23,24], Marloes Eeftens[2,22,23], Petra H. Peeters[10,25], Kees Meliefste[2], Alessandro Marcon[26], Ursula Krämer[6], Thomas A.J. Kuhlbusch[27], Mohammad Vossoughi[6], Timothy Key[28], Kees de Hoogh[10], Regina Hampel[29], Annette Peters[29], Joachim Heinrich[30], Gudrun Weinmayr[6,31], Hans Concin[32], Gabriele Nagel[31,32], Alex Ineichen[22,23], Bénédicte Jacquemin[8,33,34], Morgane Stempfelet[35], Alice Vilier[34,36,37], Fulvio Ricceri[38], Carlotta Sacerdote[39], Xanthi Pedeli[1], Michalis Katsoulis[40], Antonia Trichopoulou[40], Bert Brunekreef[2,25], and Klea Katsouyanni[1,41]

[1]Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens, Athens, Greece; [2]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; [3]Department of Epidemiology, Lazio Regional Health Service, Italy; [4]Danish Cancer Society Research Center, Copenhagen, Denmark; [5]Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [6]IUF–Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; [7]National Institute for Public Health and the Environment, Bilthoven, The Netherlands; [8]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; [9]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), Madrid, Spain; [10]MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, United Kingdom; [11]Division of Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [12]National Institute for Health and Welfare, Department of Chronic Disease Prevention, Helsinki, Finland; [13]Department of Environmental Health, National Institute for Health and Welfare, Kuopio, Finland; [14]Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway; [15]Institute of Health and Society, University of Oslo, Oslo, Norway; [16]Institute of Environmental Medicine, [17]Aging Research Center, Department of Neurobiology, Care Sciences and Society, and [19]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [18]Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden; [20]Department of Environmental Science, Aarhus University, Roskilde, Denmark; [21]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands; [22]Swiss Tropical and Public Health Institute, Basel, Switzerland; [23]University of Basel, Basel, Switzerland; [24]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington; [25]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [26]Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy; [27]Institute of Energy and Environmental Technology e.V., Air Quality & Sustainable Nanotechnology, Duisburg, Germany; [28]Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; [29]Institute of Epidemiology II and [30]Institute of Epidemiology I, Helmholtz Center Munich, German Research Center of Environmental Health, Neuherberg, Germany; [31]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [32]Agency for Preventive and Social Medicine, Bregenz, Austria; [33]Respiratory and Environmental Epidemiology Team and [36]Nutrition, Hormones and Women's Health Team, Inserm, Centre for Research in Epidemiology and Population Health (CESP), Villejuif, France; [34]University Paris Sud, Villejuif, France; [35]InVS, French Institute for Public Health Surveillance, Saint Maurice, France; [37]IGR, Villejuif, France; [38]Human Genetics Foundation, Turin, Italy; [39]Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza-University of Turin and Center for Cancer Prevention, Turin, Italy; [40]Hellenic Health Foundation, Athens, Greece; and [41]Environmental Research Group and Department of Primary Care & Public Health Sciences, King's College London, London, United Kingdom

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Long-term Exposure to Air Pollution and Cardiovascular Mortality

An Analysis of 22 European Cohorts

Rob Beelen,[a] *Massimo Stafoggia,*[b] *Ole Raaschou-Nielsen,*[c] *Zorana Jovanovic Andersen,*[c,d] *Wei W. Xun,*[e,f] *Klea Katsouyanni,*[g] *Konstantina Dimakopoulou,*[g] *Bert Brunekreef,*[a,h] *Gudrun Weinmayr,*[i,j] *Barbara Hoffmann,*[j] *Kathrin Wolf,*[k] *Evangelia Samoli,*[g] *Danny Houthuijs,*[l] *Mark Nieuwenhuijsen,*[m,n] *Anna Oudin,*[o] *Bertil Forsberg,*[o] *David Olsson,*[o] *Veikko Salomaa,*[p] *Timo Lanki,*[p] *Tarja Yli-Tuomi,*[p] *Bente Oftedal,*[q] *Geir Aamodt,*[q] *Per Nafstad,*[q,r] *Ulf De Faire,*[s] *Nancy L. Pedersen,*[t] *Claes-Göran Östenson,*[u] *Laura Fratiglioni,*[v] *Johanna Penell,*[s] *Michal Korek,*[s] *Andrei Pyko,*[s] *Kirsten Thorup Eriksen,*[c] *Anne Tjønneland,*[c] *Thomas Becker,*[w] *Marloes Eeftens,*[a] *Michiel Bots,*[h] *Kees Meliefste,*[a] *Meng Wang,*[a] *Bas Bueno-de-Mesquita,*[l] *Dorothea Sugiri,*[j] *Ursula Krämer,*[j] *Joachim Heinrich,*[x] *Kees de Hoogh,*[e] *Timothy Key,*[y] *Annette Peters,*[k] *Josef Cyrys,*[k,z] *Hans Concin,*[aa] *Gabriele Nagel,*[i,aa] *Alex Ineichen,*[bb,cc] *Emmanuel Schaffner,*[bb,cc] *Nicole Probst-Hensch,*[bb,cc] *Julia Dratva,*[bb,cc] *Regina Ducret-Stich,*[bb,cc] *Alice Vilier,*[dd,ee,ff] *Françoise Clavel-Chapelon,*[dd,ee,ff] *Morgane Stempfelet,*[gg] *Sara Grioni,*[hh] *Vittorio Krogh,*[hh] *Ming-Yi Tsai,*[bb,cc,ii] *Alessandro Marcon,*[jj] *Fulvio Ricceri,*[kk] *Carlotta Sacerdote,*[ll] *Claudia Galassi,*[ll] *Enrica Migliore,*[ll] *Andrea Ranzi,*[mm] *Giulia Cesaroni,*[b] *Chiara Badaloni,*[b] *Francesco Forastiere,*[b] *Ibon Tamayo,*[n,nn] *Pilar Amiano,*[n,nn] *Miren Dorronsoro,*[n,nn] *Michail Katsoulis,*[oo] *Antonia Trichopoulou,*[oo] *Paolo Vineis,*[e] *and Gerard Hoek*[a]

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From the [a]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; [b]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [c]Danish Cancer Society Research Center, Copenhagen, Denmark; [d]Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, CSS, København K, Denmark; [e]MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, St Mary's Campus, London, United Kingdom; [f]University College London, CeLSIUS, London, United Kingdom; [g]Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, University of Athens, Athens, Greece; [h]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [i]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [j]IUF–Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, and Medical Faculty, University of Düsseldorf, Düsseldorf, Germany; [k]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [l]National Institute for Public Health and the Environment, Bilthoven, The Netherlands; [m]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, and Parc de Recerca Biomèdica de Barcelona–PRBB (office 183.05) C. Doctor Aiguader, Barcelona, Spain; [n]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), Melchor Fernández Almagro 3-5, Madrid, Spain; [o]Division of Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [p]National Institute for Health and Welfare, Kuopio, Finland; [q]Norwegian Institute of Public Health, Oslo, Norway; [r]Institute of Health and Society, University of Oslo, Oslo, Norway; [s]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [t]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [u]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [v]Aging Research Center, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden; [w]Department of Environmental Science, Aarhus University, Roskilde, Denmark; [x]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center of Environmental Health, Neuherberg, Germany; [y]Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; [z]Environmental Science Center, University of Augsburg, Augsburg, Germany; [aa]Agency for Preventive and Social Medicine, Bregenz, Austria; [bb]Swiss Tropical and Public Health Institute, Basel, Switzerland; [cc]University of Basel, Basel, Switzerland; [dd]Inserm, Centre for Research in Epidemiology and Population Health (CESP), U1018, Nutrition, Hormones and Women's Health Team, Villejuif, France; [ee]University Paris Sud, UMRS 1018, Villejuif, France; [ff] IGR, Villejuif, France; [gg]French Institute for Public Health Surveillance (InVS) 12, Saint-Maurice, France; [hh]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [ii]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA; [jj]Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy; [kk]Human Genetics Foundation–HuGeF, Turin, Italy; [ll]Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza—University of Turin and Center for Cancer Prevention, Turin, Italy; [mm]Environmental Health Reference Centre, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy; [nn]Public Health Division of Gipuzkoa, Basque Government, Gipuzkoa, Spain; and [oo]Hellenic Health Foundation, Athens, Greece.

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Original Research Article

Change in Height, Weight, and Body Mass Index: Longitudinal Data from Austria

RAPHAEL SIMON PETER,[1,2]* ELLA FROMM,[2] JOCHEN KLENK,[2,3] HANS CONCIN,[1] AND GABRIELE NAGEL[1,2]
[1]*Agency for Preventive and Social Medicine, Bregenz, Austria*
[2]*Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany*
[3]*Department of Clinical Gerontology, Robert-Bosch Hospital, Stuttgart, Germany*

Objectives: To quantify changes in height, weight and their compound effect on the body mass index (BMI) in a large cohort of Central-European men and women.

Methods: The Vorarlberg health monitoring and prevention program (VHM&PP) is a population-based risk factor surveillance program in Vorarlberg. Data of health examinations during January 1985 to June 2005 were available including 714,181 height and weight measurements in 185,192 persons (53.9% women). We estimated yearly percentage change of anthropometric parameters over the age range from 20 to 85 years within intervals of 5 years.

Results: We found that weight increased until the age of 70 years (from the age of 20 years: +24.8% in men and +27.6% in women), with the highest increase in men aged 20–25 years (1.07% per year). Height was shown to decrease starting from the age group 45–50 years. This decrease accelerated with age, and was more pronounced in women than in men.

Conclusions: Weight is strongly related to aging. In older individuals height loss affects BMI and masks weight loss to some degree. Am. J. Hum. Biol. 26:690–696, 2014.

Weight gain until midlife is associated with impaired quality of life (Strandberg et al., 2003) and functional limitations in old age (Houston et al., 2005). In older individuals weight loss is associated with higher mortality (Wedick et al., 2002). Besides weight loss, age related height loss is also associated with negative health outcomes. Height loss may indicate osteoporosis and predicts fractures in women and men (Moayyeri et al., 2008). Wannamethee et al. (2006) found height loss in older men was associated with increased total mortality and higher risk for major coronary heart disease events. Considering the interrelationship between weight change, height change and health, understanding the natural pattern of those changes throughout life is important to identify suitable target populations for lifestyle interventions.

Studies based on successive cross sectional surveys show that mean height as well as mean BMI is higher in younger birth cohorts (Cavelaars et al., 2000; Hermanussen et al., 2001; Lahti-Koski et al., 2001; Rosengren et al., 2000). Changes in height, weight and BMI with aging in cross sectional studies may be the combined result of age and cohort effects as well as selective survival. Longitudinal studies with long-term follow-up on individual level are required to isolate the age effect on these anthropometric parameters.

Most of the studies on longitudinal height change were performed in small samples with <500 individuals per gender (Chumlea et al., 1988; Flynn et al., 1992; Galloway et al., 1990; Miall et al., 1967; Parízková and Eiselt, 1971). Some data from larger cohorts are available for the US (Borkan et al., 1983; Cline et al., 1989; Sorkin et al., 1999a), Australia (Chandler and Bock, 1991), and Sweden with data only for women (Noppa et al., 1980).

We found several longitudinal studies on weight or BMI change from the US (Barone et al., 2006; Juhaeri et al., 2003; Lewis et al., 2000; McTigue et al., 2002, Sheehan et al., 2003; Stevens et al., 1991), from Norway (Drøyvold et al., 2006; Jacobsen et al., 2001), from Sweden (Caman et al., 2013) and one from the Netherlands (Nooyens et al., 2009). Most of these studies examined either the age related change in body height, or in weight, or in BMI. Because BMI is a function of weight and height, changes in all three parameters over adult life within the same study population would be of interest. Data from large scale epidemiological studies covering a wide age range are scarce.

Our objective was therefore to quantify changes in height, weight and their compound effect on BMI in a large cohort of Central-European men and women. The large sample size and the data structure allowed us to calculate individual changes over a wide age range, from 20 to 85 years within intervals of 5 years.

METHODS

Study population

Subjects of this study were women and men participating in voluntary health examinations organized by the "Arbeitskreis für Vorsorge- und Sozialmedizin" (aks) on behalf of the Vorarlberg state government. All Vorarlberg residents aged 19 years or older were invited to participate. Follow-up of study participants was performed through biennial reinvitation. Costs for one examination per year are covered by the participant's compulsory health insurance. Health examinations were carried out by physicians in general or internal medicine. Details of the program and characteristics of the study population

Additional Supporting Information may be found in the online version of this article.

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*Correspondence to: Raphael Peter, Institute of Epidemiology and Medical Biometry, Helmholtzstr. 22, 89081 Ulm, Germany. E-mail: raphael.peter@uni-ulm.de

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OPEN

Prostate Cancer, Prostate Cancer Death, and Death from Other Causes, Among Men with Metabolic Aberrations

Christel Häggström,[a] *Tanja Stocks,*[a,b] *Gabriele Nagel,*[c,d] *Jonas Manjer,*[e] *Tone Bjørge,*[f,g] *Göran Hallmans,*[h] *Anders Engeland,*[f,g] *Hanno Ulmer,*[i] *Björn Lindkvist,*[e] *Randi Selmer,*[g] *Hans Concin,*[d] *Steinar Tretli,*[j] *Håkan Jonsson,*[k] *and Pär Stattin*[a]

Background: Few previous studies of metabolic aberrations and prostate cancer risk have taken into account the fact that men with metabolic aberrations have an increased risk of death from causes other than prostate cancer. The aim of this study was to calculate, in a real-life scenario, the risk of prostate cancer diagnosis, prostate cancer death, and death from other causes.

Methods: In the Metabolic Syndrome and Cancer Project, prospective data on body mass index, blood pressure, glucose, cholesterol, and triglycerides were collected from 285,040 men. Risks of prostate cancer diagnosis, prostate cancer death, and death from other causes were calculated by use of competing risk analysis for men with normal (bottom 84%) and high (top 16%) levels of each factor, and a composite score.

Results: During a mean follow-up period of 12 years, 5,893 men were diagnosed with prostate cancer, 1,013 died of prostate cancer, and 26,328 died of other causes. After 1996, when prostate-specific antigen testing was introduced, men up to age 80 years with normal metabolic levels had 13% risk of prostate cancer, 2% risk of prostate cancer death, and 30% risk of death from other causes, whereas men with metabolic aberrations had corresponding risks of 11%, 2%, and 44%.

Conclusions: In contrast to recent studies using conventional survival analysis, in a real-world scenario taking risk of competing events into account, men with metabolic aberrations had lower risk of prostate cancer diagnosis, similar risk of prostate cancer death, and substantially higher risk of death from other causes compared with men who had normal metabolic levels.

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Prostate cancer incidence is up to 20-fold higher in industrialized countries compared with developing countries,[1] and nutrition and other lifestyle factors have been suggested as a cause for this difference.[2] To date, many studies have investigated the putative etiological association between metabolic aberrations and prostate cancer risk, with inconsistent results.[3–8] We have previously investigated this within the Metabolic Syndrome and Cancer Project by use of Cox regression analysis, and we found no associations between metabolic aberrations and prostate cancer risk.[9] In contrast, high levels of BMI, blood pressure, and a composite score of all metabolic factors were associated with increased risk of prostate cancer death.

However, men with metabolic aberrations have a higher risk of death from cardiovascular disease and other diseases,[10] and such events are censored in studies of etiologic risk using conventional methods similar to the Cox model, despite the fact that they are considered competing events in analysis of prostate cancer. Few studies to date have taken risk of competing events into account when assessing a person's risk of prostate cancer in a real-world scenario. This risk—previously denoted as actual risk,[11] cumulative absolute risk,[12] real-world probabilities,[13] and crude probabilities[14]—can be calculated by cumulative incidence functions.

The aim of this study was to assess the risk of prostate cancer diagnosis, prostate cancer death, and death from other causes for men with normal metabolic levels and metabolic aberrations in a real-world scenario by use of data in a large prospective pooled European cohort.

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[a]Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Umeå, Sweden; [b]Department of Clinical Sciences in Malmö, Diabetes and Cardiovascular Diseases, Genetic Epidemiology, Lund University, Lund, Sweden; [c]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [d]Agency for Preventive and Social Medicine, Bregenz, Austria; [e]Department of Surgery, Skåne University Hospital, Lund University, Malmö, Sweden; [f]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [g]Norwegian Institute of Public Health, Oslo/Bergen, Norway; [h]Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden; [i]Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria; [j]Institute of Population-based Cancer Research, The Cancer Registry of Norway, Oslo, Norway; and [k]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden.

The authors report no conflicts of interest.

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Correspondence: Christel Häggström, Department of Surgical and Perioperative Sciences, Urology and Andrology Umeå University, 901 85 Umeå, Sweden. E-mail: christel.haggstrom@umu.se.

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The effect of age on the shape of the BMI-mortality relation and BMI associated with minimum all-cause mortality in a large Austrian cohort.

Peter RS[1], Mayer B[2], Concin H[3], Nagel G[1].

Author information

1 1] Agency for Preventive and Social Medicine, Bregenz, Austria [2] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany.

2 Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany.

3 Agency for Preventive and Social Medicine, Bregenz, Austria.

Abstract

BACKGROUND: It is unclear if the body mass index (BMI) associated with minimum all-cause mortality is constant throughout adult life or increasing with age.

METHODS: We applied multivariable fractional polynomials to the data of the Vorarlberg Health Monitoring and Prevention Program to quantify the BMI associated with minimum mortality over age. The analysis included data of 129,904 never-smoking women and men (mean age: 45.4 years) who were followed for a median of 18.6 years.

RESULTS: Optimum BMI in women increased with age, lying within the normal BMI category (according to the World Health Organization definition) from the age of 20 years (23.3 kg m (-2), 95% confidence interval (CI): 22.2-24.3) to the age of 54 years and in the lower half of the overweight category from the age of 55 years onwards, reaching 26.2 kg m(-2) (95% CI: 25.1-27.3) at the age of 69 years. In men, optimum BMI increased slightly from 23.7 kg m(-2) (95% CI: 22.1-25.2) at the age of 20 years until the age of 59 years, reaching a BMI of 25.4 kg m(-2) (95% CI: 24.8-26.0) and decreased afterwards to 22.7 kg m(-2) (95% CI: 20.9-24.6) at the age of 80 years.

CONCLUSIONS: Our results indicate that BMI associated with minimum all-cause mortality changes with age and that patterns differ by sex. Sex- and age-independent BMI recommendations might therefore be inappropriate. Further studies using flexible methods instead of predefined categories are necessary to revise BMI recommendations.

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Original article

Cancer

Metabolic risk score and cancer risk: pooled analysis of seven cohorts

Tanja Stocks,[1,2]* Tone Bjørge,[3,4] Hanno Ulmer,[5] Jonas Manjer,[6] Christel Häggström,[1] Gabriele Nagel,[7,8] Anders Engeland,[3,9] Dorthe Johansen,[6] Göran Hallmans,[10] Randi Selmer,[9] Hans Concin,[8] Steinar Tretli,[4] Håkan Jonsson[11] and Pär Stattin[1]

[1]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden, [2]Department of Clinical Sciences in Malmö, Diabetes and Cardiovascular Diseases, Genetic Epidemiology, Lund University, Lund, Sweden, [3]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, [4]Institute of Population-based Cancer Research, Cancer Registry of Norway, Oslo, Norway, [5]Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria, [6]Department of Surgery, Skåne University Hospital, Lund University, Malmö, Sweden, [7]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, [8]Agency for Preventive and Social Medicine, Bregenz, Austria, [9]Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, Norway, [10]Department of Public Health and Clinical Medicine, Nutritional Research, and [11]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

*Corresponding author. Department of Clinical Sciences in Malmö, Clinical Research Centre, Jan Waldenströms gata 35, 205 02 Malmö, Sweden. E-mail: tanja.stocks@med.lu.se

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Abstract

Background: There are few data on the joint influence of metabolic factors on risk of separate cancers.

Methods: We analysed data on body mass index, blood pressure and plasma levels of glucose, total cholesterol and triglycerides from seven European cohorts comprising 564 596 men and women with a mean age of 44 years. We weighted those factors equally into a standardized metabolic risk score [MRS, mean = 0, standard deviation (SD) = 1], with an individual's level indicated as SDs from the sex- and cohort-specific means. Cancer hazard ratios were calculated by Cox regression with age as timescale and with relevant adjustments including smoking status. All statistical tests were two-sided.

Results: During a mean follow-up of 12 years, 21 593 men and 14 348 women were diagnosed with cancer. MRS was linearly and positively associated with incident cancer in total and at sites ($P < 0.05$). In men, risk per SD MRS was increased by 43% (95% confidence interval: 27–61) for renal cell cancer, 43% (16–76) for liver cancer, 29% (20–38) for colon cancer, 27% (5–54) for oesophageal cancer, 20% (9–31) for rectal cancer, 19% (4–37) for leukaemias, 15% (1–30) for oral cancer and 10% (2–19) for bladder cancer. In

PLOS | ONE

RESEARCH ARTICLE

Long-Term Weight Change: Association with Impaired Glucose Metabolism in Young Austrian Adults

Katharina Wirth[1☯], Raphael S. Peter[1☯], Christoph H. Saely[2,3,4], Hans Concin[5], Gabriele Nagel[1,5]*

1 Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **2** Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria, **3** Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, **4** Private University of the Principality of Liechtenstein, Triesen, Liechtenstein, **5** Agency for Preventive and Social Medicine, Bregenz, Austria

☯ These authors contributed equally to this work.
* gabriele.nagel@uni-ulm.de

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

Abstract

Little is known about the associations between long-term weight change and the natural history of impaired fasting glucose (IFG) in young adults. We investigated the association between long-term body mass index (BMI) change and the risk of IFG using data of 24,930 20- to 40-year-old participants from the Vorarlberg Health Monitoring and Promotion Program (VHM&PP) cohort. Poisson models were applied to estimate the 10-year risk for new development of IFG (≥5.6 mmol/L), and persistence of IFG. Over 10 years, most men (68.2%) and women (70.0%) stayed within their initial BMI category. The risk for incident IFG was highest for men and women with persisting obesity (37.4% and 24.1%) and lowest with persisting normal weight (15.7% and 9.3%). Men transitioning from normal to overweight increased their risk of incident IFG by factor 1.45 (95%-CI: 1.31, 1.62), women by 1.70 (95%-CI: 1.50, 1.93), whereas transitioning from overweight to normal weight decreased the risk in men by 0.69 (95%-CI: 0.53, 0.90) and 0.94 (95%-CI: 0.66, 1.33) in women. Relative risks for men and women transitioning from obesity to overweight were 0.58 and 0.44, respectively. In conclusion, 10 year weight increase was associated with an increased IFG risk, weight decrease with a decreased risk of IFG in young adults.

Introduction

In Austria the prevalence of overweight or obesity among adults is high (male: 50.0%, female: 39.6%) and has been increasing during the past decades [1]. A recent publication of the Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study revealed that subjects were lean until the age of 18 years, but gained considerable weight until the age of 50 years [2]. Recent reports showed an increase of adiposity prevalence in young adults in Germany and Austria [3,4]. In the Vorarlberg Health Monitoring and Promotion Program (VHM&PP) cohort strongest weight gain was observed in men aged 20 to 40 years

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Review

Natural-Cause Mortality and Long-Term Exposure to Particle Components: An Analysis of 19 European Cohorts within the Multi-Center ESCAPE Project

Rob Beelen,[1] Gerard Hoek,[1] Ole Raaschou-Nielsen,[2] Massimo Stafoggia,[3] Zorana Jovanovic Andersen,[2,4] Gudrun Weinmayr,[5,6] Barbara Hoffmann,[6,7] Kathrin Wolf,[8] Evangelia Samoli,[9] Paul H. Fischer,[10] Mark J. Nieuwenhuijsen,[11,12] Wei W. Xun,[13,14] Klea Katsouyanni,[9] Konstantina Dimakopoulou,[9] Alessandro Marcon,[15] Erkki Vartiainen,[16] Timo Lanki,[17] Tarja Yli-Tuomi,[17] Bente Oftedal,[18] Per E. Schwarze,[18] Per Nafstad,[18,19] Ulf De Faire,[20] Nancy L. Pedersen,[21] Claes-Göran Östenson,[22] Laura Fratiglioni,[23] Johanna Penell,[20] Michal Korek,[20] Göran Pershagen,[20] Kirsten Thorup Eriksen,[2] Kim Overvad,[24,25] Mette Sørensen,[2] Marloes Eeftens,[1] Petra H. Peeters,[26,27] Kees Meliefste,[1] Meng Wang,[1] H. Bas Bueno-de-Mesquita,[10, 27, 28] Dorothea Sugiri,[6,7] Ursula Krämer,[6,7] Joachim Heinrich,[29] Kees de Hoogh,[13] Timothy Key,[30] Annette Peters,[8] Regina Hampel,[8] Hans Concin,[31] Gabriele Nagel,[5,31] Andrea Jaensch,[5] Alex Ineichen,[32,33] Ming-Yi Tsai,[32,33,34] Emmanuel Schaffner,[32,33] Nicole M. Probst-Hensch,[32,33] Christian Schindler,[32,33] Martina S. Ragettli,[32,33] Alice Vilier,[35,36,37] Françoise Clavel-Chapelon,[35,36,37] Christophe Declercq,[38] Fulvio Ricceri,[39] Carlotta Sacerdote,[40] Claudia Galassi,[40] Enrica Migliore,[40] Andrea Ranzi,[41] Giulia Cesaroni,[3] Chiara Badaloni,[3] Francesco Forastiere,[3] Michail Katsoulis,[42] Antonia Trichopoulou,[42] Menno Keuken,[43] Aleksandra Jedynska,[43] Ingeborg M. Kooter,[43] Jaakko Kukkonen,[44] Ranjeet S. Sokhi,[45] Paolo Vineis,[13] and Bert Brunekreef[1,26]

[1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands; [2]Danish Cancer Society Research Center, Copenhagen, Denmark; [3]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [4]Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [5]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [6]IUF–Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, and [7]Medical Faculty, University of Düsseldorf, Germany; [8]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [9]Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens, Athens, Greece; [10]National Institute for Public Health and the Environment, Bilthoven, the Netherlands; [11]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; [12]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), Madrid, Spain; [13]MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom; [14]University College London, CeLSIUS, London, United Kingdom; [15]Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy; [16]Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; [17]Department of Environmental Health, National Institute for Health and Welfare, Kuopio, Finland; [18]Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway; [19]Institute of Health and Society, University of Oslo, Oslo, Norway; [20]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [21]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [22]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [23]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden; [24]Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark; [25]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [26]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [27]Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College, London, United Kingdom; [28]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, the Netherlands; [29]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center of Environmental Health, Neuherberg, Germany; [30]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; [31]Agency for Preventive and Social Medicine, Bregenz, Austria; [32]Swiss Tropical and Public Health Institute, Basel, Switzerland; [33]University of Basel, Basel, Switzerland; [34]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA; [35]Inserm, Centre for research in Epidemiology and Population Health (CESP), Nutrition, Hormones and Women's Health team, Villejuif, France; [36]University Paris Sud, Villejuif, France; [37]IGR, Villejuif, France; [38]French Institute for Public Health Surveillance (InVS), Saint-Maurice, France; [39]Human Genetics Foundation-HuGeF, Turin, Italy; [40]Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza-University of Turin and Center for Cancer Prevention, Turin, Italy; [41]Environmental Health Reference Centre-Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy; [42]Hellenic Health Foundation, Athens, Greece; [43]TNO, Netherlands Organisation for Applied Scientific Research, Utrecht, the Netherlands; [44]Finnish Meteorological Institute, Helsinki, Finland; [45]Centre for Atmospheric and Instrumentation Research (CAIR), University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom

Background: Studies have shown associations between mortality and long-term exposure to particulate matter air pollution. Few cohort studies have estimated the effects of the elemental composition of particulate matter on mortality.

Objectives: Our aim was to study the association between natural-cause mortality and long-term exposure to elemental components of particulate matter.

Methods: Mortality and confounder data from 19 European cohort studies were used. Residential exposure to eight *a priori*–selected components of particulate matter (PM) was characterized following a strictly standardized protocol. Annual average concentrations of copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc within PM size fractions ≤ 2.5 μm ($PM_{2.5}$) and ≤ 10 μm (PM_{10}) were estimated using land-use regression models. Cohort-specific statistical analyses of the associations between mortality and air pollution were conducted using Cox proportional hazards models using a common protocol followed by meta-analysis.

Results: The total study population consisted of 291,816 participants, of whom 25,466 died from a natural cause during follow-up (average time of follow-up, 14.3 years). Hazard ratios were positive for almost all elements and statistically significant for $PM_{2.5}$ sulfur (1.14; 95% CI: 1.06, 1.23 per 200 ng/m^3). In a two-pollutant model, the association with $PM_{2.5}$ sulfur was robust to adjustment for $PM_{2.5}$ mass, whereas the association with $PM_{2.5}$ mass was reduced.

Conclusions: Long-term exposure to $PM_{2.5}$ sulfur was associated with natural-cause mortality. This association was robust to adjustment for other pollutants and $PM_{2.5}$.

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Introduction

Studies have shown associations between long-term exposure to particulate matter air pollution and mortality, with exposure characterized as the mass concentration of particles ≤ 10 μm (PM_{10}) or ≤ 2.5 μm ($PM_{2.5}$) (Brook et al. 2010; Brunekreef and Holgate 2002). Although these studies have identified associations between exposure to particulate matter mass and mortality, there is still uncertainty as to which particle components are the most harmful. In addition, particulate matter effect estimates for long-term studies on mortality have differed among studies, and an explanation for this might be differences in the chemical composition of particulate matter (Hoek et al. 2013).

Particulate matter is a heterogeneous mixture varying spatially and temporally in chemical composition related to the sources from which it originates (Kelly and Fussell 2012; Stanek et al. 2011). Components for which associations with a range of health end points have been reported in epidemiological and/or toxicological studies include (transition) metals, elemental carbon, inorganic secondary aerosols (sulfate, nitrate), and organic components, but the evidence is not

Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331 288 participants

*NCD Risk Factor Collaboration (NCD-RisC)**

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See Online for podcast interview with Majid Ezzati

*Members listed at end of Article

Correspondence to: Prof Majid Ezzati, Imperial College London, London W2 1PG, UK
majid.ezzati@imperial.ac.uk

Summary

Background Diabetes has been defined on the basis of different biomarkers, including fasting plasma glucose (FPG), 2-h plasma glucose in an oral glucose tolerance test (2hOGTT), and HbA_{1c}. We assessed the effect of different diagnostic definitions on both the population prevalence of diabetes and the classification of previously undiagnosed individuals as having diabetes versus not having diabetes in a pooled analysis of data from population-based health examination surveys in different regions.

Methods We used data from 96 population-based health examination surveys that had measured at least two of the biomarkers used for defining diabetes. Diabetes was defined using HbA_{1c} (HbA_{1c} ≥6·5% or history of diabetes diagnosis or using insulin or oral hypoglycaemic drugs) compared with either FPG only or FPG-or-2hOGTT definitions (FPG ≥7·0 mmol/L or 2hOGTT ≥11·1 mmol/L or history of diabetes or using insulin or oral hypoglycaemic drugs). We calculated diabetes prevalence, taking into account complex survey design and survey sample weights. We compared the prevalences of diabetes using different definitions graphically and by regression analyses. We calculated sensitivity and specificity of diabetes diagnosis based on HbA_{1c} compared with diagnosis based on glucose among previously undiagnosed individuals (ie, excluding those with history of diabetes or using insulin or oral hypoglycaemic drugs). We calculated sensitivity and specificity in each survey, and then pooled results using a random-effects model. We assessed the sources of heterogeneity of sensitivity by meta-regressions for study characteristics selected a priori.

Findings Population prevalence of diabetes based on FPG-or-2hOGTT was correlated with prevalence based on FPG alone (r=0·98), but was higher by 2–6 percentage points at different prevalence levels. Prevalence based on HbA_{1c} was lower than prevalence based on FPG in 42·8% of age–sex–survey groups and higher in another 41·6%; in the other 15·6%, the two definitions provided similar prevalence estimates. The variation across studies in the relation between glucose-based and HbA_{1c}-based prevalences was partly related to participants' age, followed by natural logarithm of per person gross domestic product, the year of survey, mean BMI, and whether the survey population was national, subnational, or from specific communities. Diabetes defined as HbA_{1c} 6·5% or more had a pooled sensitivity of 52·8% (95% CI 51·3–54·3%) and a pooled specificity of 99·74% (99·71–99·78%) compared with FPG 7·0 mmol/L or more for diagnosing previously undiagnosed participants; sensitivity compared with diabetes defined based on FPG-or-2hOGTT was 30·5% (28·7–32·3%). None of the preselected study-level characteristics explained the heterogeneity in the sensitivity of HbA_{1c} versus FPG.

Interpretation Different biomarkers and definitions for diabetes can provide different estimates of population prevalence of diabetes, and differentially identify people without previous diagnosis as having diabetes. Using an HbA_{1c}-based definition alone in health surveys will not identify a substantial proportion of previously undiagnosed people who would be considered as having diabetes using a glucose-based test.

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Introduction

Diabetes prevalence and diabetes-related deaths are rising in most parts of the world, at least partly fuelled by the worldwide increase in excess weight and adiposity.[1–5] This trend has created concerns about the health and functional consequences for patients, and costs for health systems.[6–8] Tracking the epidemic and the progress of programmes aimed at reducing diabetes and its complications requires consistent and comparable measurement of the prevalence of diabetes and the coverage of drug and lifestyle interventions that slow diabetes progression and decrease the risk of complications.

Different biomarkers have been used to define diabetes, including fasting plasma glucose (FPG), 2-h plasma glucose in an oral glucose tolerance test (2hOGTT), and, more recently, HbA_{1c}.[9–15] Population-based health surveys in different countries and at

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years (SD 2.0 years), 944 subjects had suffered a first CHD or stroke events, respectively 260, 218, 249 and 217 at 2, 4, 7 and 10 years of follow-up, and 1700 had died. After adjustment for socio-demographic variables, vascular risk factors, impairment in daily life activities and antidepressant use, the presence of DS was associated with a significant 31% increased risk of mortality (HR=1.31;95% CI: 1.15–1.48), while occurrence of a vascular event was related to a three-fold increased risk (HR=2.97; 95% CI: 2.56–3.44). There was no interaction between the presence of DS at study visits and occurrence of vascular event for the risk of mortality (p=0.50).
Conclusion: In older participants, the relative increased risk of all cause mortality associated with the presence of DS is independent of the occurrence of incident vascular events.
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Temporal trends in the treatment and outcomes of septua-, octo-, and nonagenarians with acute coronary syndrome

D. Radovanovic[1], A.W. Schoenenberger[2], S. Windecker[3], J.F. Iglesias[4], G. Pedrazzini[5], A.E. Stuck[2], P. Erne[6]. *[1]UZH - Institute of Social and Preventive Medicine, AMIS Plus Data Center, Epidemiology, Biostatistics and Prevention Institute, Zurich; [2]Bern University Hospital, Department of Geriatrics, Bern; [3]Bern University Hospital, Department of Cardiology, Bern; [4]University Hospital Centre Vaudois (CHUV), Service de Cardiologie, Lausanne; [5]Cardiocentro Ticino, Division of Cardiology, Lugano; [6]Klinik St Anna Hirslanden, Division of Cardiology, Luzern, Switzerland*

Background: Old patients with acute coronary syndrome (ACS) are a growing demographic with higher risk of worse outcomes than younger patients.
Purpose: To determine whether treatment and outcomes of old ACS patients changed over time.
Methods: We analyzed 13,662 ACS patients ≥70 years enrolled in the Acute Myocardial Infarction in Switzerland (AMIS) cohort between 2001 and 2012. Use of guideline-recommended therapies and in-hospital outcomes were analyzed according to three 4-year periods (2001–2004, 2005–2008, 2009–2012). To determine associations between use of percutaneous coronary interventions (PCI) and in-hospital mortality, logistic regression providing odds ratios (ORs) and 95% confidence intervals (CIs) was used.
Results: Between first and last 4-year period, PCI use increased from 43.8% to 69.6% of older ACS patients (P<0.001). The highest relative increase was found for primary PCI use among nonagenarians with ST-elevation myocardial infarction (3.6-fold increase between first and last 4-year period, P<0.001). Use of guideline-recommended drugs as well increased. At the same time, in-hospital mortality of the overall population decreased from 11.6% in the first to 10.0% in the last 4-year period (P=0.020), and in-hospital major adverse cardiac and cerebrovascular events from 14.4% to 11.3% (P<0.001). The highest relative decrease of in-hospital mortality (22.7%) between first and last 4-year period was observed among octogenarians (P=0.005). In the overall population, PCI use was associated with lower odds of in-hospital mortality and ORs did not markedly change between first and last 4-year period (adjusted OR for PCI use vs. no PCI use 0.29, 95% CI 0.22–0.40, in 2001–2004; and, adjusted OR for PCI use vs. no use 0.26, 95% CI 0.20–0.35, in 2009–2012).
Conclusions: Use of guideline-recommended therapies for ACS increased and in-hospital outcomes improved over the observed 12-year period. PCI use was associated with lower odds of in-hospital mortality with similar ORs between first and last 4-year period. This study suggests that better guideline adherence improves in-hospital outcomes of older ACS patients.

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Do risk factors explain the sex/gender gap in mortality from coronary heart disease?

J. Fritz[1], M. Edlinger[1], C.C. Kelleher[2], S. Strohmaier[3], G. Nagel[4], H. Concin[5], M. Hochleitner[1], E. Ruttmann[1], H. Ulmer[1]. *[1]Innsbruck Medical University, Innsbruck, Austria; [2]University College Dublin, Dublin, Ireland; [3]University of Oslo, Oslo, Norway; [4]University of Ulm, Ulm, Germany; [5]Agency for Preventive and Social Medicine, Bregenz, Austria*

Background: In Europe, per year, approximately 253,000 men, but only 77,000 women die prematurely from coronary heart disease (CHD) before the age of 65, while, when considering all ages, slightly more women do so than men. CHD rates increase with age, however to a varying extent between men and women. At younger ages, incidence and mortality are markedly lower in women, whereas with increasing age this gap narrows. However, little is known regarding the contribution of cardiovascular risk factors to this sex/gender effect.
Purpose: While there have been studies investigating the possible different role of cardiovascular risk factors in men and women, there have not yet been, to our knowledge, any attempts to explore how much of the sex/gender effect is mediated through risk factors. Presumably, since no appropriate statistical modelling approach for survival data was available. Recently, a new approach for mediation analysis was developed that allows to assess the specific contribution of risk factors explaining the difference between men and women regarding CHD outcomes.
Methods: The sex-specific CHD mortality was examined in prospective cohort data from Austria, consisting of 117,264 individuals younger than 50 years (as a proxy for menopausal status) and 54,998 older ones, with 3,892 deaths from CHD during a median follow-up of 14.6 years. Mediation analysis was used to decompose the sex/gender effect into a direct and an indirect component that is mediated by the four major cardiovascular risk factors systolic blood pressure, total cholesterol, fasting blood glucose, and smoking status.
Results: The total effect of sex/gender on CHD mortality decreased with age. While the age-adjusted hazard ratio (men versus women) was 4.7 (95% CI: 3.5 to 6.1) in individuals younger than 50 years, it was only 1.9 (95% CI: 1.7 to 2.1) in the ≥50 years age group.
In the <50 years age group, the four major cardiovascular risk factors were able to explain 40.9% of this difference. The strongest factor was systolic blood pressure explaining 21.7% of the total sex/gender effect.
In the ≥50 years age group, the contribution of the risk factors was small amounting to only 8.2%. Single risk factors contributed less than 5%, with total cholesterol even showing a significant "negative" effect, i.e. mediation in favour of men.
Conclusions: The extent to which risk factors contribute to the gap between men and women regarding CHD mortality decreases strongly with age. Over the ages of 50 years, the persisting survival advantage of women can be explained only in small part through the pathways of major risk factors.

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Quitting smoke 'hits a late break' in acceleration of vascular aging

D. Terentes-Printzios, C. Vlachopoulos, P. Xaplanteris, N. Ioakeimidis, P. Pietri, D. Tousoulis. *Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece*

Purpose: Vascular aging, as assessed by structural and functional properties of the arteries, is an independent indicator of cardiovascular risk. Smoking has a detrimental effect on arterial properties. We sought to investigate the effect of quitting smoke on the progression of vascular aging.
Methods: One hundred and forty-two subjects (mean age 51.9±10.8 years, 94 men, 61 hypertensives) with no established cardiovascular disease were investigated in two examinations over a 2-year period (mean follow-up visit 1.84 years). Subjects were categorized in current smokers, non-smokers and ex-smokers. Ex-smokers were further categorized according to the time elapsed since smoking (<5 years, 5–15 years and >15 years). Subjects had at the beginning and end of the study determinations of carotid-femoral pulse wave velocity (PWV). Based on these measurements the annual absolute changes were calculated.
Results: Smoking at baseline was not associated with statistically significant differences in PWV. However, the annual change was statistically different between the groups of smokers, non-smokers and the 3 groups of ex-smokers (p=0.041) after adjustment for relevant confounders. Specifically, smokers had 0.23m/s/year (95% CI: 0.10 to 0.35), non-smokers 0.17m/s/year (95% CI: 0.08 to 0.25), quitters (<5 years) had 0.28m/s/year (95% CI: 0.07 to 0.49), quitters (5–15 years) had 0.35m/s/year (95% CI: 0.11 to 0.59) and quitters (>15 years) –0.07m/s/year (95% CI: –0.26 to 0.13).
Conclusions: Quitting smoke seems to slow down progression of vascular aging after many years probably in an effort to compensate for former deleterious changes of smoking.

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Beta-blocker therapy optimization in elderly patients with left ventricular systolic dysfunction

M. Cortes Garcia[1], A.M. Romero[1], J.A. Franco[1], J.A. Palfy[1], A. Garcia[1], M.L. Martin[1], M. Lopez[1], P. Avila[1], E. De La Cruz[2], J. Farre[1]. *[1]Foundation Jimenez Diaz, Madrid, Spain; [2]University Hospital Príncipe de Asturias, Alcala de Henares, Spain*

Introduction: The elderly population with left ventricle systolic dysfunction (LVSD) has been underrepresented in clinical trials of beta-blockers (BB) and maybe this is the reason why theses drugs are used less commonly and in lower doses in this group of population. The objective of this study is to evaluate the importance of the optimization of the medical treatment with BB in elderly population with LVSD.
Methods: We included all patients (pts) ≥75 years old, with LVEF ≤35%, studied in our center between January 2008 and April 2012. Clinical variables of interest were collected and clinical follow-up was performed. In each pt was collected information about treatment with BB and the dose reached. With this data we created a variable that determined the percent dose of BB (BB%) compared to the target level established in clinical guidelines (50 mg/d for carvedilol and 10 mg/d for bisoprolol). To analyze the effect of BB% on mortality and cardiovascular events (death, hospitalization for heart failure or ventricular arrhythmia), we used a Cox model adjusting for confounding and interaction with relevant clinical variables. In addition, to show the survival curves, the variable %BB was categorized into 3 groups (not BB, doses <50% and ≥50% doses).
Results: 556 pts were included. The mean age was 81.9 years, mean LVEF was 28% and there 34% of women. 143 pts (25.7%) did not take BB, 268 (48.2%) took low doses BB and 145 (26.1%) achieved high doses. During follow 223 pts died (40.2%), 92 in the untreated group, 97 in the low dose and 34 at the high dose. After adjusting the Cox model with confounding and interaction variables, we found

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RESEARCH ARTICLE

Sex- and Time-Dependent Patterns in Risk Factors of End-Stage Renal Disease: A Large Austrian Cohort with up to 20 Years of Follow-Up

Constanze Pscheidt[1,2], Gabriele Nagel[1,2], Emanuel Zitt[3,4], Reinhard Kramar[5], Hans Concin[1], Karl Lhotta[3,4]*

1 Agency for Preventive and Social Medicine, Bregenz, Austria, **2** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **3** Department of Nephrology and Dialysis, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, **4** Vorarlberg Institute for Vascular Investigation and Treatment, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, **5** Austrian Dialysis and Transplant Registry, Rohr im Kremstal, Austria

* karl.lhotta@lkhf.at

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Abstract

Objective

We investigated the association between metabolic factors and End-Stage Renal Disease (ESRD) and quantified the magnitude of their influence dependent on sex and time of exposure up to 20 years.

Material and Methods

A prospective cohort study was conducted to determine risk factors for the development of ESRD. From 1988 to 2005 185,341 persons (53.9% women) participated in the "Vorarlberg Health Monitoring and Promotion Programme" (VHM&PP). Data on body mass index (BMI), fasting blood glucose (FBG), systolic (BPsys) and diastolic (BPdia) blood pressure, total cholesterol (TC), triglycerides (TG), gamma-glutamyltransferase (GGT) and smoking status were collected. Data of the population-based VHM&PP were merged with the Austrian Dialysis and Transplant Registry. Cox proportional hazards models were applied to calculate hazard ratios (HRs) for ESRD, stratified by sex and 5-year time intervals.

Results

During a mean follow-up of 17.5 years 403 patients (39.1% women) developed ESRD. Significant risk factors were: BMI (per 1 kg/m^2) HR 1.04 (95% CI 1.01–1.06), FBG (per 1 mmol/L) HR 1.09 (1.05–1.12), BPsys (per 5 mmHg) HR 1.10 (1.07–1.14), BPdia (per 5 mmHg) HR 1.09 (1.03–1.15), TG (per 1 mmol/L) HR 1.07 (1.02–1.13), TC (per 1 mmol/L) HR 1.22 (1.13–1.32). We observed a sex-specific risk pattern with an increased ESRD risk for men for increasing TG and smoking, and for women for increasing BMI and GGT. In time

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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, *]

[a] Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria
[b] School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland
[c] Oslo Centre for Biostatistics and Epidemiology, University of Oslo, Oslo, Norway
[d] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[e] Agency for Preventive and Social Medicine, Bregenz, Austria
[f] Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria
[g] Women's Health Centre, Medical University of Innsbruck, Innsbruck, Austria

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ABSTRACT

Background: In Europe, annually about 77,000 women, but 253,000 men die prematurely from coronary heart disease (CHD) before the age of 65 years. This gap narrows with increasing age and disappears after the eighth life decade. However, little is known regarding the contribution of cardiovascular risk factors to this sex difference.
Objective: We investigated to what extent men's higher risk of dying from CHD is explained through a different risk factor profile, as compared to women.
Methods: Mediation analysis technique was used to assess the specific contributions of blood pressure, cholesterol, glucose, and smoking to the difference between men and women regarding CHD mortality in a large Austrian cohort consisting of 117,264 individuals younger than 50 years (as a proxy for pre-menopausal status) and 54,998 older ones, with 3892 deaths due to CHD during a median follow-up of 14.6 years.
Results: Adjusting for age and year of examination, we observed a male versus female CHD mortality hazard ratio (HR) of 4.7 (95% CI: 3.4–5.9) in individuals younger than 50 years, of which 40.9% (95% CI: 27.1%–54.7%) was explained through risk factor pathways, mainly through blood pressure. In older participants, there was a HR of 1.9 (95% CI: 1.8–2.0) of which 8.2% (95% CI: 4.6%–11.7%) was mediated through the risk factors.
Conclusion: The extent to which major risk factors contribute to the sex difference regarding CHD mortality decreases with age. The female survival advantage was explained to a substantial part through the pathways of major risk factors only in younger individuals.

1. Introduction

Coronary heart disease (CHD) is the leading cause of death in most industrialized countries [1]. CHD incidence rates increase with age, however to a varying extent in males and females. At younger ages, incidence and mortality rates are markedly lower in women, whereas with increasing age the gap narrows. There is a lag effect of approximately ten years, i.e. the incidence rate of 65 year old women is comparable to that of 55 year old men [2]. By the eighth decade, the difference between both sexes is nearly absent [3,4]. In Europe, per year approximately 77,000 women (corresponding to 1.8% of all deaths), but 253,000 men (corresponding to 5.7% of all deaths) die prematurely from CHD before the age of 65,

* Corresponding author. Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Schoepfstrasse 41, 6020 Innsbruck, Austria.
E-mail address: hanno.ulmer@i-med.ac.at (H. Ulmer).

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ORIGINAL PAPER

Associations of pre-diagnostic body mass index with overall and cancer-specific mortality in a large Austrian cohort

Katharina Reichle[1,2] · Raphael S. Peter[1] · Hans Concin[2] · Gabriele Nagel[1,2]

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Abstract

Purpose Although obesity is a well-known risk factor for several cancers, its role on cancer survival is poorly understood.

Methods Within the VHM&PP cohort, 8,673 cancer patients (42.2 % women) were followed over a median time of 11.9 years. Cox proportional hazard models were used to estimate the association of pre-diagnostic overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI $\geq$ 30.0 kg/m^2) with all-cause and cancer-specific mortality. Cubic restricted splines were additionally modeled.

Results During 71,126 person-years, 4,571 deaths were observed. Compared to normal weight, overweight was associated with statistically significantly decreased all-cause mortality (HR 0.93; 95 % CI 0.87–0.997) and cancer-specific mortality (HR 0.91; 95 % CI 0.84–0.99). Underweight was statistically significantly associated with 28 % increased overall mortality, in particular in men [HR 2.02 (95 % CI 1.43–2.83) vs. HR 0.96 (95 % CI 0.71–1.30) in women]. J-shaped associations were found between BMI and mortality with the nadir around a BMI of 25 kg/m^2. Analysis by cancer site showed though not statistically significantly that overweight was associated with reduced mortality, while obesity was associated with increased cancer-specific mortality except cancers of the upper digestive tract. In patients with local stage colorectal cancers, obesity was associated with increased all-cause (vs. normal weight HR 1.90; 95 % CI 1.03–3.52) and cancer-specific mortality (HR 3.17; 95 % CI 1.29–7.81).

Conclusion Overweight patients have a better overall prognosis, while for obesity no association and for underweight worse prognosis were found. Our results on common cancers indicate that there are tumor- and stage-specific differences.

Keywords Weight · Body mass index · Cancer · Mortality · Prognosis · Survival · Epidemiology · VHM&PP

Background

Overweight and obesity are an increasing health problem in Western countries. In 2008, about 50 % of inhabitants in the WHO European Region were overweight, and roughly 23 % of women and 20 % of men were obese. The association between overweight and cancer incidence and mortality is well established [1–3]. Various cohort studies have been published, with a main focus on prostate cancer [4–6], postmenopausal breast cancer [7–9], and on colorectal cancer [7, 10–12]. Although there is evidence that obesity is a risk factor for several cancers, the impact of obesity on cancer survival is still poorly understood.

Approximately nine million cancer survivors are living in Europe. Worldwide, the number has been estimated to be almost 30 million, and this number is expected to grow [13]. Hence, there is an increasing interest in factors influencing survival time. Furthermore, the target after

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✉ Gabriele Nagel
gabriele.nagel@uni-ulm.de

[1] Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, 89081 Ulm, Germany

[2] Agency for Preventive and Social Medicine, Rheinstraße 61, 6900 Bregenz, Austria

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Evaluation of a mammography screening program within the population-based Vorarlberg Health Monitoring & Prevention Program (VHM&PP)

Gabriele Nagel[a,b,*], Willi Oberaigner[c], Raphael S. Peter[b], Hanno Ulmer[d], Hans Concin[a]

[a] Agency for Preventive and Social Medicine, Bregenz, Austria
[b] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[c] Department of Clinical Epidemiology of the Tyrolean State Hospitals Ltd., Cancer Registry of Tyrol, TILAK GmbH, Innsbruck, Austria
[d] Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Austria

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ABSTRACT

Objectives: To describe the mammography screening program from 1989 to 2005 within a population-based prevention program in Austria and to appraise it according to recommended quality indicators.
Material and method: From 01.01.1989 all women aged 40 years or older participating in the Vorarlberg Health Monitoring & Prevention Program (VHM&PP) was offered to undergo additionally a "screening mammography". Passive follow-up has been performed by record linkages with the Vorarlberg cancer registry and mortality statistics for information on outcome variables. Interval cancer rates have been estimated and the survival after breast cancer has been calculated by life table technique by examination period and age groups (40–49 years, 50–69 years).
Results: Between 1989 and 2005 50,100 women aged 40 to 69 years participated in the program, of which 123,652 mammogram results have been collected. In the target population the participation rate was 65.1%. During median follow-up time 13.5 years and 633,342 person-years overall 665 invasive cancer and 87 ductal carcinoma in situ (11.6%) cases have been identified. Between 1996 and 2004 the detection rates were 239.9 per 100.000 among women aged 40–49 years and 543.2 per 100,000 among women aged 50–69 years. The rates for interval cancers were 160.4 and 277.4 per 100 000 negative screens, respectively. During median follow-up of 13.5 years 165 deaths occurred with no difference in survival between patients with interval and screen detected cancers.
Conclusion: A mammography screening program has been performed between 1989 and 2005 in Vorarlberg. Till 2005 most quality indicators improved and met the EU-recommendations suggesting that alternative approaches to organized mammography screening based on routine data should be explored.

1. Introduction

Breast cancer (BC) is the most common cancer diagnosed in women worldwide and the leading cause of cancer death among women, accounting for 23% of the total cancer cases and 14% of cancer deaths [1]. During the following decades increasing breast cancer incidence in Austria is predicted to increase [2]. Therefore, the prevention and management of breast cancer in order to provide high quality health care is an important public health issue.

Mammography is the predominantly applied diagnostic and screening method for breast cancer [3]. Screening aims to achieve early detection of disease in order to change an incurable to a curable status. In the nineties, randomized clinical trials showed that mammography screening can reduce breast cancer mortality [4]. Overall, randomized clinical trials of mammography screening among women aged 50 to 70 years have shown a 15% reduction of breast cancer mortality after 10 years of follow-up [5]. During the past years, the publications of the Cochrane Collaboration fostered discussion about the benefit and harms of mammographic screening [6,7,5]. Mammography screening is also associated with harm, such as false positive results, overdiagnosis and overtreatment [8].

* Corresponding author at: Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr.22, 89081 Ulm, Germany. Fax: +49 731 50 12 31073.
E-mail address: gabriele.nagel@uni-ulm.de (G. Nagel).

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Particulate matter air pollution components and risk for lung cancer

O. Raaschou-Nielsen [a,b,*], R. Beelen [c], M. Wang [c], G. Hoek [c], Z.J. Andersen [a,d], B. Hoffmann [e,f], M. Stafoggia [g], E. Samoli [h], G. Weinmayr [e,f,i], K. Dimakopoulou [h], M. Nieuwenhuijsen [j], W.W. Xun [k], P. Fischer [l], K.T. Eriksen [a], M. Sørensen [a], A. Tjønneland [a], F. Ricceri [m], K. de Hoogh [k,n,o], T. Key [p], M. Eeftens [c,n,o], P.H. Peeters [q,r], H.B. Bueno-de-Mesquita [s,t,u,v], K. Meliefste [c], B. Oftedal [w], P.E. Schwarze [w], P. Nafstad [w,x], C. Galassi [m], E. Migliore [m], A. Ranzi [y], G. Cesaroni [g], C. Badaloni [g], F. Forastiere [g], J. Penell [z], U. De Faire [z], M. Korek [z], N. Pedersen [aa], C.-G. Östenson [ab], G. Pershagen [z], L. Fratiglioni [ac], H. Concin [ad], G. Nagel [i,ad], A. Jaensch [i], A. Ineichen [ae], A. Naccarati [ae], M. Katsoulis [af], A. Trichpoulou [af], M. Keuken [ag], A. Jedynska [ag], I.M. Kooter [ag], J. Kukkonen [ah], B. Brunekreef [c,q], R.S. Sokhi [ai], K. Katsouyanni [h,aj], P. Vineis [k]

[a] Danish Cancer Society Research Center, Copenhagen, Denmark
[b] Department of Environmental Science, Aarhus University, Roskilde, Denmark
[c] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[d] Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[e] IUF–Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[f] University of Düsseldorf, Düsseldorf, Germany
[g] Department of Epidemiology, Lazio Regional Health Service, Local Health Unit ASL RME, Rome, Italy
[h] Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[i] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[j] Center for Research in Environmental Epidemiology, Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain
[k] MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom
[l] National Institute for Public Health and the Environment, Center for Sustainability and Environmental Health, Bilthoven, The Netherlands
[m] Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza, University of Turin and Center for Cancer Prevention, Turin, Italy
[n] Swiss Tropical and Public Health Institute, Basel, Switzerland
[o] University of Basel, Basel, Switzerland
[p] Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[q] Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands
[r] School of Public Health, Imperial College London, London, United Kingdom
[s] Department for Determinants of Chronic Diseases, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[t] Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands
[u] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[v] Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[w] Norwegian Institute of Public Health, Oslo, Norway
[x] Institute of Health and Society, University of Oslo, Oslo, Norway
[y] Environmental Health Reference Centre, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy
[z] Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
[aa] Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[ab] Department of Molecular Medicine and Surgery, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden
[ac] Aging Research Centre, Department of Neurobiology, Care Sciences and Society, Karolinska Institute and Stockholm University, Stockholm, Sweden
[ad] Agency for Preventive and Social Medicine, Bregenz, Austria
[ae] Human Genetics Foundation, Molecular and Genetic Epidemiology Unit, Turin, Italy
[af] Hellenic Health Foundation, Athens, Greece
[ag] Netherlands Organisation for Applied Scientific Research, Utrecht, The Netherlands
[ah] Finnish Meteorological Institute, Helsinki, Finland
[ai] Centre for Atmospheric and Instrumentation Research, University of Hertfordshire, College Lane, Hatfield, United Kingdom
[aj] Department of Primary Care and Public Health Sciences and Environmental Research Group, King's College London, United Kingdom

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ABSTRACT

Background: Particulate matter (PM) air pollution is a human lung carcinogen; however, the components responsible have not been identified. We assessed the associations between PM components and lung cancer incidence. *Methods:* We used data from 14 cohort studies in eight European countries. We geocoded baseline addresses and

* Corresponding author at: Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark.
E-mail address: ole@cancer.dk (O. Raaschou-Nielsen).

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RESEARCH ARTICLE

γ-Glutamyltransferase and Breast Cancer Risk Beyond Alcohol Consumption and Other Life Style Factors – A Pooled Cohort Analysis

Oliver Preyer[1], Dorthe Johansen[2], Jessica Holly[3], Tanja Stocks[4], Alfonso Pompella[5], Gabriele Nagel[1,6], Hans Concin[1], Hanno Ulmer[7], Nicole Concin[3]*

1 Agency for Preventive and Social Medicine, Bregenz, Vorarlberg, Austria, **2** Surgery Research Unit, Lund University, Malmoe, Sweden, **3** Department of Obstetrics and Gynaecology, Innsbruck Medical University, Innsbruck, Austria, **4** Lund University Diabetes Centre, Diabetes and Cardiovascular Disease—Genetic Epidemiology Department of Clinical Sciences Malmö, CRC, Malmoe, Sweden, **5** Department of Experimental Pathology, University of Pisa, Medical School, Pisa, Italy, **6** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **7** Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria

* nicole.concin@i-med.ac.at

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

Abstract

Objective

Elevated γ-Glutamyltransferase serum levels are associated with increased risk of overall cancer incidence and several site-specific malignancies. In the present prospective study we report on the associations of serum γ-Glutamyltransferase with the risk of breast cancer in a pooled population-based cohort considering established life style risk factors.

Methods

Two cohorts were included in the present study, i.e. the Vorarlberg (n = 97,268) and the Malmoe cohort (n = 9,790). Cox proportional hazards regression models were fitted to estimate HRs for risk of breast cancer.

Results

In multivariate analysis adjusted for age, body mass index and smoking status, women with γ-Glutamyltransferase levels in the top quartile were at significantly higher risk for breast cancer compared to women in the lowest quartile (HR 1.21, 95% CI 1.09 to 1.35; p = 0.005). In the subgroup analysis of the Malmoe cohort, γ-Glutamyltransferase remained an independent risk factor for breast cancer when additionally considering alcohol intake. A statistically significant increase in risk was seen in women with γ-Glutamyltransferase-levels in the top versus lowest quartile in a multivariate model adjusted for age, body mass index, smoking status, physical activity, parity, oral contraceptive-use and alcohol consumption (HR 1.37, 95% CI 1.11–1.69, p = 0.006).

Conclusion

Our findings identified γ-Glutamyltransferase as an independent risk factor for breast cancer beyond the consumption of alcohol and other life style risk factors.

We are thus heartened by the agreement on the part of Schmidt et al.[1] that the ultimate question is empirical and not theoretical. The suggestion to shun the RD has been made in the belief that it is usually much more heterogeneous than ratio measures such as the OR in empirical research settings. Although there are more heterogeneous possibilities for the RD than for the OR, it would be difficult to defend the assumption that each of those possibilities has the same probability, within or across the many studies that are actually conducted. As noted in our article,[3] further evidence is therefore required before concluding that the risk difference is in fact a more heterogeneous measure.

Charles Poole
Department of Epidemiology
Gillings School of Global Public Health
University of North Carolina
Chapel Hill, NC

Ian Shrier
Centre for Clinical Epidemiology
Lady Davis Institute for Medical Research
Jewish General Hospital
McGill University
Montreal, QC, Canada

Peng Ding
Departments of Epidemiology and Statistics
Harvard University
Cambridge, MA

Tyler VanderWeele
Departments of Epidemiology and Biostatistics
Harvard T.H. Chan School of Public Health
Harvard University
Boston, MA
tvanderw@hsph.harvard.edu

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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]

[a]Bootstrapping with 5,000 samples was used to calculate the uncertainty of the estimates.
[b]On ln(HR) scale.
[c]Percentages as proportion of the total effect are not given. Estimates were numerically instable and therefore meaningless due to division by numbers close to zero.
[d]The 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.

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, we appreciate the studies of Lu et al.[1,2] where this topic has been addressed. Major strengths of the study in *The Lancet*[1] are the large number of cohorts included, of the study in EPIDEMIOLOGY[2] the sophisticated methodology. However, we think that the results deserve further discussion.

Since it is well established that the effects of the major metabolic risk factors, including BMI, on cardiovascular diseases decrease with age,[3] we wonder why this interaction effect was not considered in either study. Analyzing data of the Vorarlberg Health Monitoring & Promotion Programme (VHM&PP)[4] which is also part of the earlier study,[1] the interaction term BMI*age suggested a submultiplicative effect of the continuous variables BMI and age on the outcome death from coronary heart disease (CHD, defined via ICD-10 codes I20 to I25). Consequently, we performed mediation analyses assessing

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A century of trends in adult human height

NCD Risk Factor Collaboration (NCD-RisC)*

Eduardo Franco, Reviewing editor
Eduardo Franco, McGill University, Canada;

Email: majid.ezzati@imperial.ac.uk

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Abstract

Being taller is associated with enhanced longevity, and higher education and earnings. We reanalysed 1472 population-based studies, with measurement of height on more than 18.6 million participants to estimate mean height for people born between 1896 and 1996 in 200 countries. The largest gain in adult height over the past century has occurred in South Korean women and Iranian men, who became 20.2 cm (95% credible interval 17.5–22.7) and 16.5 cm (13.3–19.7) taller, respectively. In contrast, there was little change in adult height in some sub-Saharan African countries and in South Asia over the century of analysis. The tallest people over these 100 years are men born in the Netherlands in the last quarter of 20th century, whose average heights surpassed 182.5 cm, and the shortest were women born in Guatemala in 1896 (140.3 cm; 135.8–144.8). The height differential between the tallest and shortest populations was 19-20 cm a century ago, and has remained the same for women and increased for men a century later despite substantial changes in the ranking of countries.

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eLife digest

People from different countries grow to different heights. This may be partly due to genetics, but most differences in height between countries have other causes. For example, children and adolescents who are malnourished, or who suffer from serious diseases, will generally be shorter as adults. This is important because taller people generally live longer, are less likely to suffer from heart disease and stroke, and taller women and their children are less likely to have complications during and after birth. Taller people may also earn more and be more successful at school. However, they are also more likely to develop some cancers.

The NCD Risk Factor Collaboration set out to find out how tall people are, on average, in every country in the world at the moment, and how this has changed over the past 100 years. The analysis revealed large differences in height between countries. The tallest men were born in the last part of the 20th century in the Netherlands, and were nearly 183 cm tall on average. The shortest women were born in 1896 in Guatemala, and were on average 140 cm tall. The difference between the shortest and tallest countries is about 20 cm for both men and women. This means there are large differences between countries in terms of nutrition and the risk of developing some diseases.

The way in which height has changed over the past 100 years also varies from country to country. Iranian men born in 1996 were around 17 cm taller than those born in 1896, and South Korean women were 20 cm taller. In other parts of the world, particularly in South Asia and parts of Africa, people are only slightly taller than 100 years ago, and in some countries people are shorter than they were 50 years ago.

There is a need to better understand why height has changed in different countries by different amounts, and use this information to improve nutrition and health across the world. It would also be valuable to understand how much becoming taller has been responsible for improved health and longevity throughout the world.

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Introduction

Being taller is associated with enhanced longevity, lower risk of adverse pregnancy outcomes and cardiovascular and respiratory diseases, and higher risk of some cancers (Paajanen et al., 2010; Emerging Risk Factors Collaboration, 2012; Green et al., 2011; Nelson et al., 2015; Batty et al., 2010; World Cancer Research Fund / American Institute for Cancer Research, 2007; 2010; 2011; 2012; 2014a; 2014b; Nüesch et al., 2015; Davies et al., 2015; Zhang et al., 2015; Kozuki et al., 2015; Black et al., 2008). There is also evidence that taller people on average have higher education, earnings, and possibly even social position (Adair et al., 2013; Stulp et al., 2015; Barker et al., 2005; Strauss and Thomas, 1998; Chen and Zhou, 2007; Case and Paxson, 2008).

Although height is one of the most heritable human traits (Fisher, 1919; Lettre, 2011), cross-population differences are believed to be related to non-genetic, environmental factors. Of these, foetal growth (itself related to maternal size, nutrition and environmental exposures), and nutrition and infections during childhood and adolescence are particularly important determinants of height during adulthood (Cole, 2000; Silventoinen et al., 2000; Dubois et al., 2012; Haeffner et al., 2002; Sørensen et al., 1999; Victora et al., 2008; Eveleth and Tanner, 1990; Tanner, 1962; Tanner, 1992; Bogin, 2013). Information on height, and its trends, can therefore help understand the health impacts of childhood and adolescent nutrition and environment, and of their social, economic, and political determinants, on both non-communicable diseases (NCDs) and on neonatal health and survival in the next generation (Cole, 2000; Tanner, 1992; Tanner, 1987).

Trends in men's height have been analysed in Europe, the USA, and Japan for up to 250 years, using data on conscripts, voluntary military

PLOS ONE

RESEARCH ARTICLE

Anthropometric and Metabolic Risk Factors for ESRD Are Disease-Specific: Results from a Large Population-Based Cohort Study in Austria

Emanuel Zitt[1,2], Constanze Pscheidt[3,4], Hans Concin[3], Reinhard Kramar[5], Karl Lhotta[1,2], Gabriele Nagel[3,4]*

1 Department of Nephrology and Dialysis, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, **2** Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Academic Teaching Hospital Feldkirch, Feldkirch, Austria, **3** Agency for Preventive and Social Medicine, Bregenz, Austria, **4** Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, **5** Austrian Dialysis and Transplant Registry, Rohr im Kremstal, Austria

* gabriele.nagel@uni-ulm.de

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Abstract

Background

Anthropometric and metabolic risk factors for all-cause end-stage renal disease (ESRD) may vary in their impact depending on the specific primary renal disease.

Methods

In this Austrian population-based prospective cohort study (n = 185,341; 53.9% women) the following data were collected between 1985 and 2005: age, sex, body mass index (BMI), fasting blood glucose (FBG) from 1988, blood pressure, total cholesterol (TC), triglycerides (TG), gamma-glutamyl transferase (GGT) and smoking status. These data were merged with the Austrian Dialysis and Transplant Registry to identify ESRD patients. Cox proportional hazards models were applied to calculate hazard ratios (HR) for all-cause ESRD as well as for cause-specific ESRD due to the following primary renal diseases: autosomal dominant polycystic kidney disease (ADPKD), vascular nephropathy (VN), diabetic nephropathy (DN) and other diseases (OD).

Results

During a mean follow-up of 17.5 years 403 participants developed ESRD (ADPKD 36, VN 97, DN 86, and OD 184). All parameters except TG and GGT were significantly associated with all-cause ESRD risk. Particular cause-specific ESRD risk factor patterns were found: for ADPKD increased risk from hypertension (HR 11.55); for VN from smoking (HR 1.81), hypertension (HR 2.37), TG (≥5.70 vs. <1.17 mmol/L: HR 9.27); for DN from smoking (HR 1.77), BMI (≥30 vs. 18.5–24.9 kg/m^2: HR 7.55), FBG (≥6.94 vs. <5.55 mmol/L: HR 7.67), hypertension (HR 1.08), TG (≥5.70 vs. <1.17 mmol/L: HR 2.02), GGT (HR 2.14); and for

Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents

*The Global BMI Mortality Collaboration**

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See Comment page 734

*Members of the writing committee are listed at the end of the paper and a full list of investigators is provided in the appendix

Correspondence to: Prof John Danesh, Department of Public Health and Primary Care, University of Cambridge, Cambridge CB1 8RN, England, UK
gbmc@phpc.cam.ac.uk

See Online for appendix

Summary

Background Overweight and obesity are increasing worldwide. To help assess their relevance to mortality in different populations we conducted individual-participant data meta-analyses of prospective studies of body-mass index (BMI), limiting confounding and reverse causality by restricting analyses to never-smokers and excluding pre-existing disease and the first 5 years of follow-up.

Methods Of 10 625 411 participants in Asia, Australia and New Zealand, Europe, and North America from 239 prospective studies (median follow-up 13·7 years, IQR 11·4–14·7), 3 951 455 people in 189 studies were never-smokers without chronic diseases at recruitment who survived 5 years, of whom 385 879 died. The primary analyses are of these deaths, and study, age, and sex adjusted hazard ratios (HRs), relative to BMI 22·5–<25·0 kg/m².

Findings All-cause mortality was minimal at 20·0–25·0 kg/m² (HR 1·00, 95% CI 0·98–1·02 for BMI 20·0–<22·5 kg/m²; 1·00, 0·99–1·01 for BMI 22·5–<25·0 kg/m²), and increased significantly both just below this range (1·13, 1·09–1·17 for BMI 18·5–<20·0 kg/m²; 1·51, 1·43–1·59 for BMI 15·0–<18·5) and throughout the overweight range (1·07, 1·07–1·08 for BMI 25·0–<27·5 kg/m²; 1·20, 1·18–1·22 for BMI 27·5–<30·0 kg/m²). The HR for obesity grade 1 (BMI 30·0–<35·0 kg/m²) was 1·45, 95% CI 1·41–1·48; the HR for obesity grade 2 (35·0–<40·0 kg/m²) was 1·94, 1·87–2·01; and the HR for obesity grade 3 (40·0–<60·0 kg/m²) was 2·76, 2·60–2·92. For BMI over 25·0 kg/m², mortality increased approximately log-linearly with BMI; the HR per 5 kg/m² units higher BMI was 1·39 (1·34–1·43) in Europe, 1·29 (1·26–1·32) in North America, 1·39 (1·34–1·44) in east Asia, and 1·31 (1·27–1·35) in Australia and New Zealand. This HR per 5 kg/m² units higher BMI (for BMI over 25 kg/m²) was greater in younger than older people (1·52, 95% CI 1·47–1·56, for BMI measured at 35–49 years *vs* 1·21, 1·17–1·25, for BMI measured at 70–89 years; $p_{heterogeneity}$<0·0001), greater in men than women (1·51, 1·46–1·56, *vs* 1·30, 1·26–1·33; $p_{heterogeneity}$<0·0001), but similar in studies with self-reported and measured BMI.

Interpretation The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents. This finding supports strategies to combat the entire spectrum of excess adiposity in many populations.

Funding UK Medical Research Council, British Heart Foundation, National Institute for Health Research, US National Institutes of Health.

Introduction

The worldwide prevalence of overweight and obesity is high and is increasing.[1,2] WHO estimates that more than 1·3 billion adults worldwide are overweight, defined by WHO as a body-mass index (BMI) of 25–<30 kg/m², and a further 600 million are obese (BMI ≥30 kg/m²).[3] Appropriate analyses of large-scale prospective studies with prolonged follow-up generally indicate that both overweight and obesity are associated with increased mortality, as is underweight (defined conservatively by WHO as BMI <18·5 kg/m²). However, it is not known how such associations vary across major global regions, an uncertainty relevant to international strategies for overweight and obesity.[4] Most previous analyses have focused on people living in one particular country or continent,[5–12] even though associations with overweight and underweight might differ from one population to another.

Estimation of the relationships between BMI and mortality in various populations can help to assess the adverse physiological effects of excessive adiposity (and the adverse physiological effects of various determinants of low BMI). However, reliable estimates of the causal relevance of BMI to mortality need to limit the effects of reverse causality, because chronic disease and smoking can themselves affect BMI. To help achieve more valid estimates, prospective studies of BMI and mortality should, when possible, exclude: smokers, participants who already have some chronic disease at recruitment that could affect BMI, and those dying within 5 years of recruitment.[13–16]

The Global BMI Mortality Collaboration was established to provide a standardised comparison of

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ORIGINAL ARTICLE

Hip fracture incidence 2003–2013 and projected cases until 2050 in Austria: a population-based study

Hans Concin · Wolfgang Brozek · Karl-Peter Benedetto · Hartmut Häfele · Joachim Kopf · Thomas Bärenzung · Richard Schnetzer · Christian Schenk · Elmar Stimpfl · Ursula Waheed-Hutter · Hanno Ulmer · Kilian Rapp · Elisabeth Zwettler · Gabriele Nagel

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Abstract
Objectives Elevated hip fracture incidence is a major public health problem looming to aggravate in industrialized countries due to demographic developments. We report hip fracture incidence and expected future cases from Vorarlberg, the westernmost province of Austria, results potentially representative of Central European populations.
Methods Crude and standardized hip fracture incidence rates in Vorarlberg 2003–2013 are reported. Based on the age-specific incidence in 2013 or trends 2003–2013, we predict hip fractures till 2050.
Results Female age-standardized hip fracture incidence decreased 2005–2013, whereas for men, the trend was rather unclear. Uncorrected forecasts indicate that by 2050, female and male cases will each have more than doubled from 2015 in all demographic core scenarios. Corrected by incidence trends before 2013, cases are expected to drop among women but rise among men.
Conclusions We anticipate rising hip fracture numbers in Vorarlberg within the next decades, unless prevention programs that presumably account for decreasing incidence rates, particularly among women since 2005, take further effect to counteract the predicted steady increase due to demographic changes. Concomitantly, augmented endeavors to target the male population by these programs are needed.

Electronic supplementary material The online version of this article (doi:10.1007/s00038-016-0878-9) contains supplementary material, which is available to authorized users.

H. Concin · E. Stimpfl · U. Waheed-Hutter · G. Nagel
Agency for Preventive and Social Medicine, Bregenz, Austria

W. Brozek (✉) · E. Zwettler
Ludwig Boltzmann Institute of Osteology at the Hanusch Hospital of the Vienna Health Insurance Fund (WGKK) and Trauma Center Meidling of the Austrian Workers' Compensation Board (AUVA), 1st Medical Department, Hanusch Hospital, Vienna, Austria
e-mail: wolfgang.brozek@osteologie.at

K.-P. Benedetto
Department of Trauma Surgery, Landeskrankenhaus Feldkirch, Feldkirch, Austria

H. Häfele · J. Kopf
Department of Trauma Surgery, Landeskrankenhaus Bregenz, Bregenz, Austria

H. Häfele
Department of Trauma Surgery, Landeskrankenhaus Hohenems, Hohenems, Austria

T. Bärenzung
Department of Trauma Surgery, Landeskrankenhaus Bludenz, Bludenz, Austria

R. Schnetzer
Department of Trauma Surgery, Krankenhaus Dornbirn, Dornbirn, Austria

C. Schenk
Sanatorium Schruns, Schruns, Austria

H. Ulmer
Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria

K. Rapp
Department of Clinical Gerontology, Robert-Bosch-Hospital, Stuttgart, Germany

K. Rapp · G. Nagel
Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

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Epidemiology

Is There an Association Between Ambient Air Pollution and Bladder Cancer Incidence? Analysis of 15 European Cohorts

Marie Pedersen [a,b,], Massimo Stafoggia [c,d], Gudrun Weinmayr [e], Zorana J. Andersen [b], Claudia Galassi [f], Johan Sommar [g], Bertil Forsberg [g], David Olsson [g], Bente Oftedal [h], Norun H. Krog [h], Geir Aamodt [i], Andrei Pyko [d], Göran Pershagen [d], Michal Korek [d], Ulf De Faire [d], Nancy L. Pedersen [j], Claes-Göran Östenson [k], Laura Fratiglioni [l], Mette Sørensen [a], Kirsten T. Eriksen [a], Anne Tjønneland [a], Petra H. Peeters [m,n], Bas Bueno-de-Mesquita [n,o,p], Roel Vermeulen [n,q,r], Marloes Eeftens [q,s,t], Michelle Plusquin [n], Timothy J. Key [u], Andrea Jaensch [d], Gabriele Nagel [d,v], Hans Concin [v], Meng Wang [w], Ming-Yi Tsai [s,t,w], Sara Grioni [x], Alessandro Marcon [y], Vittorio Krogh [x], Fulvio Ricceri [e,z], Carlotta Sacerdote [e], Andrea Ranzi [aa], Giulia Cesaroni [c], Francesco Forastiere [c], Ibon Tamayo [bb,cc,dd], Pilar Amiano [ee,ff], Miren Dorronsoro [ee,ff], Leslie T. Stayner [gg], Manolis Kogevinas [bb,cc], Mark J. Nieuwenhuijsen [bb,cc], Ranjeet Sokhi [hh], Kees de Hoogh [s,t], Rob Beelen [q,ii], Paolo Vineis [n,jj], Bert Brunekreef [q,r], Gerard Hoek [q], Ole Raaschou-Nielsen [a,kk]*

[a] *The Danish Cancer Society Research Center, Copenhagen, Denmark;* [b] *Centre for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark;* [c] *Department of Epidemiology, Lazio Regional Health Service, Rome, Italy;* [d] *Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden;* [e] *Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany;* [f] *Unit of Cancer Epidemiology, Città della Salute e della Scienza University Hospital and Center for Cancer Prevention, Turin, Italy;* [g] *Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umea University, Umea, Sweden;* [h] *Norwegian Institute of Public Health, Oslo, Norway;* [i] *Department of Landscape Architecture and Spatial Planning, Norwegian University of Life Sciences, Ås, Norway;* [j] *Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden;* [k] *Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden;* [l] *Aging Research Center, Department of Neurobiology Care Science and Society, Karolinska Institute, Stockholm, Sweden;* [m] *Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands;* [n] *MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK;* [o] *Department for Determinants of Chronic Diseases, National Institute for Public Health and the Environment, Bilthoven, The Netherlands;* [p] *Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia;* [q] *Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands;* [r] *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands;* [s] *Swiss Tropical and Public Health Institute, Basel, Switzerland;* [t] *University of Basel, Basel, Switzerland;* [u] *Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK;* [v] *Agency for Preventive and Social Medicine, Bregenz, Austria;* [w] *Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA;* [x] *Epidemiology and Prevention Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [y] *Unit of Epidemiology & Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy;* [z] *Unit of Epidemiology, Regional Health Service, Grugliasco, Italy;* [aa] *Environmental Health Reference Centre, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy;* [bb] *Institute de Salut Global Barcelona, Barcelona, Spain;* [cc] *CIBER Epidemiología y Salud Pública, Madrid, Spain;* [dd] *Universitat Pompeu Fabra, Barcelona, Spain;* [ee] *Public Health Department of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain;* [ff] *Consortium for Biomedical Research in Epidemiology and Public Health, Madrid, Spain;* [gg] *Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL, USA;* [hh] *Centre for Atmospheric and Instrumentation Research, University of Hertfordshire, Hatfield, UK;* [ii] *National Institute for Public Health (RIVM), Bilthoven, The Netherlands;* [jj] *Molecular and Epidemiology Unit, Human Genetics Foundation, Turin, Italy;* [kk] *Department of Environmental Science, Aarhus University, Roskilde, Denmark*

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Observational Study

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Body mass trajectories, diabetes mellitus, and mortality in a large cohort of Austrian adults

Raphael Simon Peter, MSc[a,*], Ferdinand Keller, PhD[b], Jochen Klenk, PhD[a,c], Hans Concin, MD[d], Gabriele Nagel, MD, PhD[a,d]

Abstract

There are only few studies on latent trajectories of body mass index (BMI) and their association with diabetes incidence and mortality in adults.

We used data of the Vorarlberg Health Monitoring & Prevention Program and included individuals (N=24,875) with BMI measurements over a 12-year period. Trajectory classes were identified using growth mixture modeling for predefined age groups (<50, 50–65, >65 years of age) and men, women separately. Poisson models were applied to estimate incidence and prevalence of diabetes for each trajectory class. Relative all-cause mortality and diabetes-related mortality was estimated using Cox proportional hazard regression.

We identified 4 trajectory classes for the age groups <50 years and 50 to 65 years, and 3 for age groups >65 years. For all age groups, a stable BMI trajectory class was the largest, with about 90% of men and 70% to 80% of women. For the low stable BMI classes, the corresponding fasting glucose levels were the lowest. The highest diabetes prevalences were observed for decreasing trajectories. During subsequent follow-up of mean 8.1 (SD 2.0) years, 2741 individuals died. For men <50 years, highest mortality was observed for steady weight gainers. For all other age-sex groups, mortality was the highest for decreasing trajectories.

We found considerably heterogeneity in BMI trajectories by sex and age. Stable weight, however, was the largest class over all age and sex groups, and was associated with the lowest diabetes incidence and mortality suggesting that maintaining weight at a moderate level is an important public health goal.

Abbreviations: BIC = Bayesian Information Criterion, BMI = body mass index, CI = confidence interval, FG = fasting plasma glucose, GMM = growth mixture modeling, SD = standard deviation, T2DM = type 2 diabetes mellitus, VHM&PP = Vorarlberg Health Monitoring & Prevention Program.

Keywords: body mass index, diabetes, GMM, mortality, trajectories

1. Introduction

Health consequences of obesity usually defined by a body mass index (BMI) $>30\,kg\,m^{-2}$ have been well established. Obesity substantially increases the risk for hypertension,[1] type 2 diabetes mellitus (T2DM),[2] distorted lipid metabolism, and consequentially of cardiovascular events and mortality.[3,4] Whereas low body mass might be the result of previous weight loss due to disease and is associated with increased mortality,[5] especially in older individuals.[6] Furthermore, there may be not 1 BMI value where mortality is lowest, but the BMI associated with lowest mortality may change with age.[7,8] Studies on weight change and mortality found weight stability to be associated with lowest mortality.[9,10] Obesity affects survival besides other mechanisms through disturbed glucose metabolism. Weight gain is associated with T2DM in middle aged adults (40–59 years of age),[11] and with impaired fasting glucose (a pre-diabetic state) in young adults (20–39 years of age).[12] On the contrary, weight loss may also be associated with T2DM risk,[13,14] which, however, might depend on the individuals' baseline BMI.

So far most studies rely on arbitrary chosen categories of weight change[15] and may not be able to give a clear picture of underlying trajectories. There are only few studies on latent trajectories and their association with diabetes incidence and mortality in adults.[16–18] One reason might be the need for multiple measurements in adequate time distance and a sufficiently long follow-up. By identification of different BMI trajectories, our understanding of underlying etiological processes over life time can be increased.

Thus, it might be a more sensible approach to identify individuals following an unfavorable BMI trajectory instead of stratifying individuals based on their current BMI or short-term weight changes into risk groups. The objectives of our study were to identify long-term BMI trajectories and to appraise them in different age groups regarding their impact on glucose impairment, diabetes related, and overall mortality.

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[a] Institute of Epidemiology and Medical Biometry, Ulm University, [b] Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Ulm, Ulm, [c] Department of Geriatrics and Geriatric Rehabilitation, Robert-Bosch-Hospital, Stuttgart, Germany, [d] Agency for Preventive and Social Medicine, Bregenz, Austria.

[*] Correspondence: Raphael Simon Peter, Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, 89081, Ulm, Germany (e-mail: raphael.peter@uni-ulm.de).

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Ambient air pollution and primary liver cancer incidence in four European cohorts within the ESCAPE project

Marie Pedersen[a,b,*], Zorana J. Andersen[b], Massimo Stafoggia[c,d], Gudrun Weinmayr[e], Claudia Galassi[f], Mette Sørensen[a], Kirsten T. Eriksen[a], Anne Tjønneland[a], Steffen Loft[g], Andrea Jaensch[e], Gabriele Nagel[e,h], Hans Concin[h], Ming-Yi Tsai[i,j,k], Sara Grioni[l], Alessandro Marcon[m], Vittorio Krogh[l], Fulvio Ricceri[n,f], Carlotta Sacerdote[f], Andrea Ranzi[o], Ranjeet Sokhi[p], Roel Vermeulen[q,r,s], Kees de Hoogh[i,j], Meng Wang[k], Rob Beelen[q,t], Paolo Vineis[s,u], Bert Brunekreef[q,r], Gerard Hoek[q], Ole Raaschou-Nielsen[a,v]

[a] The Danish Cancer Society Research Center, Copenhagen, Denmark
[b] Centre for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[c] Department of Epidemiology, Lazio Regional Health Service, Local Health Unit ASL RM1, Rome, Italy
[d] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[e] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[f] Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy
[g] Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[h] Agency for Preventive and Social Medicine, Bregenz, Austria
[i] Swiss Tropical and Public Health Institute, Basel, Switzerland
[j] University of Basel, Basel, Switzerland
[k] Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[l] Epidemiology and Prevention Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[m] Unit of Epidemiology & Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[n] Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco, Italy
[o] Environmental Health Reference Centre, Regional Agency for Prevention, Environment and Energy of Emilia-Romagna, Modena, Italy
[p] Centre for Atmospheric and Instrumentation Research, University of Hertfordshire, College Lane, Hatfield, United Kingdom
[q] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[r] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[s] School of Public Health, Imperial College, London, United Kingdom
[t] National Institute for Public Health (RIVM), Bilthoven, The Netherlands
[u] Molecular end Epidemiology Unit, HuGeF, Human Genetics Foundation, Torino, Italy
[v] Department of Environmental Science, Aarhus University, Roskilde, Denmark

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ABSTRACT

Background: Tobacco smoke exposure increases the risk of cancer in the liver, but little is known about the possible risk associated with exposure to ambient air pollution.
Objectives: We evaluated the association between residential exposure to air pollution and primary liver cancer incidence.
Methods: We obtained data from four cohorts with enrolment during 1985–2005 in Denmark, Austria and Italy. Exposure to nitrogen oxides (NO_2 and NO_X), particulate matter (PM) with diameter of less than 10 μm (PM_{10}), less than 2.5 μm ($PM_{2.5}$), between 2.5 and 10 μm ($PM_{2.5-10}$) and $PM_{2.5\ absorbance}$ (soot) at baseline home addresses were estimated using land-use regression models from the ESCAPE project. We also investigated traffic density on the nearest road. We used Cox proportional-hazards models with adjustment for potential confounders for cohort-specific analyses and random-effects meta-analyses to estimate summary hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: Out of 174,770 included participants, 279 liver cancer cases were diagnosed during a mean follow-up of 17 years. In each cohort, HRs above one were observed for all exposures with exception of $PM_{2.5\ absorbance}$ and traffic density. In the meta-analysis, all exposures were associated with elevated HRs, but none of the associations reached statistical significance. The summary HR associated with a 10-μg/m^3 increase in NO_2 was

* Corresponding author at: Centre for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 København K, Denmark,.
E-mail address: mp@sund.ku.dk (M. Pedersen).

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Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants

*NCD Risk Factor Collaboration (NCD-RisC)**

Summary

Background One of the global targets for non-communicable diseases is to halt, by 2025, the rise in the age-standardised adult prevalence of diabetes at its 2010 levels. We aimed to estimate worldwide trends in diabetes, how likely it is for countries to achieve the global target, and how changes in prevalence, together with population growth and ageing, are affecting the number of adults with diabetes.

Methods We pooled data from population-based studies that had collected data on diabetes through measurement of its biomarkers. We used a Bayesian hierarchical model to estimate trends in diabetes prevalence—defined as fasting plasma glucose of 7·0 mmol/L or higher, or history of diagnosis with diabetes, or use of insulin or oral hypoglycaemic drugs—in 200 countries and territories in 21 regions, by sex and from 1980 to 2014. We also calculated the posterior probability of meeting the global diabetes target if post-2000 trends continue.

Findings We used data from 751 studies including 4 372 000 adults from 146 of the 200 countries we make estimates for. Global age-standardised diabetes prevalence increased from 4·3% (95% credible interval 2·4–7·0) in 1980 to 9·0% (7·2–11·1) in 2014 in men, and from 5·0% (2·9–7·9) to 7·9% (6·4–9·7) in women. The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 (28·5% due to the rise in prevalence, 39·7% due to population growth and ageing, and 31·8% due to interaction of these two factors). Age-standardised adult diabetes prevalence in 2014 was lowest in northwestern Europe, and highest in Polynesia and Micronesia, at nearly 25%, followed by Melanesia and the Middle East and north Africa. Between 1980 and 2014 there was little change in age-standardised diabetes prevalence in adult women in continental western Europe, although crude prevalence rose because of ageing of the population. By contrast, age-standardised adult prevalence rose by 15 percentage points in men and women in Polynesia and Micronesia. In 2014, American Samoa had the highest national prevalence of diabetes (>30% in both sexes), with age-standardised adult prevalence also higher than 25% in some other islands in Polynesia and Micronesia. If post-2000 trends continue, the probability of meeting the global target of halting the rise in the prevalence of diabetes by 2025 at the 2010 level worldwide is lower than 1% for men and is 1% for women. Only nine countries for men and 29 countries for women, mostly in western Europe, have a 50% or higher probability of meeting the global target.

Interpretation Since 1980, age-standardised diabetes prevalence in adults has increased, or at best remained unchanged, in every country. Together with population growth and ageing, this rise has led to a near quadrupling of the number of adults with diabetes worldwide. The burden of diabetes, both in terms of prevalence and number of adults affected, has increased faster in low-income and middle-income countries than in high-income countries.

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*NCD Risk Factor Collaboration members are listed at the end of the paper

Correspondence to:
Prof Majid Ezzati, School of Public Health, Imperial College London, London W2 1PG, UK
majid.ezzati@imperial.ac.uk

Introduction

Diabetes is an important cause of mortality, morbidity, and health-system costs in the world.[1,2] Therefore, there is an urgent need to implement population-based interventions that prevent diabetes, enhance its early detection, and use lifestyle and pharmacological interventions to prevent or delay its progression to complications. To motivate such actions, one of the global targets set after the 2011 UN High-Level Meeting on Non-Communicable Diseases (NCDs) is to halt, by 2025, the rise in the age-standardised adult prevalence of diabetes at its 2010 levels.[3] Valid and consistent estimates of diabetes prevalence over time are needed to evaluate the effect of interventions, compare trends in different countries, and measure progress towards the agreed target.

A previous study estimated trends in mean fasting plasma glucose from 1980 to 2008 and reported diabetes prevalence, but only as a secondary outcome and estimated based on mean fasting plasma glucose.[4] The International Diabetes Federation (IDF) periodically reports diabetes prevalence,[5,6] but does not analyse trends; uses some sources that are based solely on self-reported diabetes; and does not fully account for differences in diabetes definitions in different data sources,[7] even though diabetes prevalence varies depending on whether it is defined based on fasting plasma glucose, 2 h plasma glucose in an oral glucose tolerance test (2hOGTT), or haemoglobin A1c (HbA_{1c}).[8] Furthermore, it is not known how trends in prevalence, together with population growth and ageing, have affected the number of adults with diabetes. Our aim

Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants

*NCD Risk Factor Collaboration (NCD-RisC)**

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*NCD Risk Factor Collaboration members are listed at the end of the paper

Correspondence to:
Prof Majid Ezzati,
Imperial College London,
London W2 1PG, UK
majid.ezzati@imperial.ac.uk

Summary

Background Raised blood pressure is an important risk factor for cardiovascular diseases and chronic kidney disease. We estimated worldwide trends in mean systolic and mean diastolic blood pressure, and the prevalence of, and number of people with, raised blood pressure, defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher.

Methods For this analysis, we pooled national, subnational, or community population-based studies that had measured blood pressure in adults aged 18 years and older. We used a Bayesian hierarchical model to estimate trends from 1975 to 2015 in mean systolic and mean diastolic blood pressure, and the prevalence of raised blood pressure for 200 countries. We calculated the contributions of changes in prevalence versus population growth and ageing to the increase in the number of adults with raised blood pressure.

Findings We pooled 1479 studies that had measured the blood pressures of 19·1 million adults. Global age-standardised mean systolic blood pressure in 2015 was 127·0 mm Hg (95% credible interval 125·7–128·3) in men and 122·3 mm Hg (121·0–123·6) in women; age-standardised mean diastolic blood pressure was 78·7 mm Hg (77·9–79·5) for men and 76·7 mm Hg (75·9–77·6) for women. Global age-standardised prevalence of raised blood pressure was 24·1% (21·4–27·1) in men and 20·1% (17·8–22·5) in women in 2015. Mean systolic and mean diastolic blood pressure decreased substantially from 1975 to 2015 in high-income western and Asia Pacific countries, moving these countries from having some of the highest worldwide blood pressure in 1975 to the lowest in 2015. Mean blood pressure also decreased in women in central and eastern Europe, Latin America and the Caribbean, and, more recently, central Asia, Middle East, and north Africa, but the estimated trends in these super-regions had larger uncertainty than in high-income super-regions. By contrast, mean blood pressure might have increased in east and southeast Asia, south Asia, Oceania, and sub-Saharan Africa. In 2015, central and eastern Europe, sub-Saharan Africa, and south Asia had the highest blood pressure levels. Prevalence of raised blood pressure decreased in high-income and some middle-income countries; it remained unchanged elsewhere. The number of adults with raised blood pressure increased from 594 million in 1975 to 1·13 billion in 2015, with the increase largely in low-income and middle-income countries. The global increase in the number of adults with raised blood pressure is a net effect of increase due to population growth and ageing, and decrease due to declining age-specific prevalence.

Interpretation During the past four decades, the highest worldwide blood pressure levels have shifted from high-income countries to low-income countries in south Asia and sub-Saharan Africa due to opposite trends, while blood pressure has been persistently high in central and eastern Europe.

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Introduction

Raised blood pressure is the leading global risk factor for cardiovascular diseases and chronic kidney disease.[1] One of the global non-communicable disease (NCD) targets adopted by the World Health Assembly in 2013 is to lower the prevalence of raised blood pressure, defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher, by 25% compared with its 2010 level by 2025.[2] Consistent global information is needed to understand how countries compare on blood pressure levels and trends, and where interventions to curtail the rise in blood pressure are most needed.

The prevalence of raised blood pressure measures the number of high-risk people irrespective of treatment status, and is the indicator used in the global NCD target. However, blood pressure has a log-linear association with cardiovascular diseases and chronic kidney disease that continues well below the threshold for raised blood pressure, and treatment provides similar proportional risk reductions irrespective of pretreatment blood pressure.[3,4] Trends in mean population blood pressure measure how blood pressure distribution has shifted over time.

We pooled population-based data to estimate national, regional, and global trends from 1975 to 2015 in mean

aks gesundheit
im ländle vor ort

aks gesundheit GmbH
Ein Unternehmen der aks Gruppe

Rheinstraße 61
6900 Bregenz

T 055 74/202-0
F 055 74/202-9

gesundheit@aks.or.at
www.aks.or.at