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Modern Prevention Research in Vorarlberg

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Vorwort

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Vorwort für das Kompendium zur Präventionsforschung in Vorarlberg der aks Gesundheit GmbH

Die wissenschaftlichen Veröffentlichungen des aks sind eine wichtige Quelle für regionale, nationale und internationale Auswertungen. Das anhaltende Interesse und die weitreichende Anerkennung auch durch Platzierungen in renommierten Fachzeitschriften bestätigen die hervorragenden Leistungen Vorarlbergs im Bereich der Präventionsforschung. Der vorliegende Bericht gewährt FachexpertInnen und Interessierten spannende Einblicke in aktuelle Forschungsergebnisse. Unser Dank gilt den Autorinnen und Autoren, insbesondere Dr. Hans Concin, der maßgeblich an diesem Projekt beteiligt war. Das Land Vorarlberg wird die aks (Forschung und Wissenschaft) auch in Zukunft tatkräftig unterstützen, um gemeinsam die Präventionsforschung weltweit voranzutreiben.



Landeshauptmann Mag. Markus Wallner
Landesstatthalterin Dr. Barbara Schöbi-Fink
Landesrätin Martina Rüscher, MBA MSc

Menschen - Daten - Wissenschaft: Gesundheitsforschung in Vorarlberg

Gesundheit ist zweifellos eines der wertvollsten Güter im Leben eines jeden Menschen. Doch wie wird Gesundheit geschaffen und erhalten? In Vorarlberg begegnen wir dieser Frage mit einer beeindruckenden Antwort: dem Vorarlberger Gesundheitsmonitoring & Präventionsprogramm (VHM&PP) der aks-Wissenschaft. Seit den 1960er Jahren werden im Rahmen von Vorsorgeuntersuchungen in Vorarlberg Gesundheitsdaten gesammelt, die im Laufe der Jahrzehnte zu einem wahren Datenschatz angewachsen sind. Diese umfassende Datenbank gehört zu den größten weltweit und ist heute von unschätzbarem Wert für die Wissenschaft. Vor 20 Jahren wurde die erste wegweisende Studie aus diesem Fundus veröffentlicht, die in der globalen Forschungsgemeinschaft für Aufsehen sorgte. Im Jahr 2003 wurde die Publikation „Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system“ veröffentlicht. Diese Studie legte den Grundstein für die intensive Erforschung von Risikofaktoren für Herz- und Kreislauferkrankungen. Sie trug maßgeblich dazu bei, das Bewusstsein für die Prävention von Herz- und Kreislauferkrankungen zu schärfen und Risikofaktoren ins Rampenlicht zu rücken. Die Qualität und der Umfang des VHM&PP haben zu internationalen Kooperationen mit renommierten Institutionen geführt, die wissenschaftliche Studien in den angesehensten Fachzeitschriften, darunter „The Lancet“ und das „New England Journal of Medicine“, veröffentlichten. Doch wie schafft Wissenschaft in diesem Fall konkret Gesundheit? Einerseits durch die schiere Größe der Gesundheitsdatenbank, andererseits durch die einzigartige Fähigkeit des VHM&PP, verschiedene Datensätze miteinander zu verknüpfen. Dies ermöglicht aussagekräftige Studienergebnisse, die für die Gesundheitsvorsorge von entscheidender Bedeu

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tung sind. Ein Beispiel hierfür ist die Verknüpfung von Daten von Menschen mit Adipositas (Body-Mass-Index über 30) und einer Diabetesvorstufe (Insulinresistenz). Diese Verknüpfung zeigt, dass das Risiko für Krebserkrankungen, dialysepflichtige Nierenerkrankungen und Herz-Kreislauf-Erkrankungen bei dieser Gruppe signifikant erhöht ist. Das macht deutlich, wie wichtig gesunde Ernährung und Bewegung in der Gesundheitsförderung sind, um diesen schwerwiegenden Erkrankungen präventiv entgegenzuwirken. Das Vorarlberger Gesundheitsmonitoring &

Präventionsprogramm (VHM&PP) ist nicht nur ein regionales Vorzeigeprojekt, sondern ein leuchtendes Beispiel dafür, wie Wissenschaft Gesundheit schafft, Bewusstsein schafft und international Anerkennung findet. Diese Erkenntnisse aus Vorarlberg haben das Potenzial, das Leben von Menschen auf der ganzen Welt zu verbessern und zeigen, dass Wissenschaft und Gesundheit untrennbar miteinander verbunden sind. Unser herzlicher Dank gilt der Vorarlberger Landesregierung für die finanzielle Unterstützung, der Vorarlberger Bevölkerung, sowie dem Umweltinstitut Vorarlberg für die fruchtbare Kooperation in der ELAPSE Studie. Ihr Beitrag ist unverzichtbar für den Erfolg und die Fortsetzung dieser wegweisenden Gesundheitsforschung im Land.



Prim. Priv.-Doz. Dr. Emanuel Zitt, ESENeph, FASN
Prim. a. D. Dr. Hans Concin
Mag. Georg Posch

Tanja Stocks, PhD

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In 2006, I was a PhD student under Pär Stattin at Umeå University, Sweden, when the Metabolic syndrome and Cancer project (Me-Can) was launched with Pär as chair. Cohorts in our collaboration from Sweden and Norway, and the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), included almost 600,000 individuals with information from health examinations of anthropometrics and metabolic risk factors, and around 35,000 incident cancers during follow-up. Between 2009 and 2015 our collaboration resulted in 27 publications in peer-reviewed international journals (see www.me-can.se). Our studies on a metabolic risk score and its individual risk factors were often the largest in the field and it is fair to say that we made a great impact in the field. The success factor? A collaboration of easy-going, generous researchers with various expertise and a genuine interest in the collaboration because the studies were not only led from one centre, but by researchers from all the involved contributing cohorts/centres. I sometimes hear that conventional epidemiology based on dry data (i.e. no biological samples) belongs to the past. But what did we do? In 2016, we updated our data, now including around 800,000 individuals with 80,000 incident cancers during follow-up, and published another seven (soon eight) studies in journals of similar dignity as before. These covered new questions on certain cancers or modelling obesity and metabolic risk factors in a new way, for example, we utilized the many repeated health examinations, especially from the VHM&PP, to investigate weight changes and cancer risk. This 2nd round of Me-Can (2.0), I have operated as chair, so essentially, I have grown up as researcher with Me-Can and will always use this collaboration as a positive reference hard to beat. After these 17(!) years of collaboration, I would like to take the opportunity to thank all my VHM&PP collaborators throughout the years: Hanno Ulmer (co-PI), Gabriele Nagel (co-PI), Kilian Rapp (co-PI in Me-Can 1.0), Hans Concin, Josef Fritz, Michael Edlinger, Emanuel Zitt, Andrea Jaensch, Alois Lang, Susanne Strohmaier, Wegene Borena, Guenter Diem, Andrea Kleiner, Daniela Späth, Richard Schlenk, and Alexander Strasak. I am sure that the VHM&PP will continue to thrive and contribute to great research, stand alone or in collaborations!

Bert Brunekreef, PhD

Emeritus Professor of Environmental Epidemiology, University of Utrecht, The Netherlands.

Air pollution research and VHM&PP

In the past 15 years, VHM&PP has been actively involved in Europe-wide research on the health effects of air pollution. In the first project, the European Study of Cohorts for Air Pollution Effects (ESCAPE), over 30 cohort studies in Europe were involved, investigating effects of air pollution throughout the lifespan. Effects

studied ranged from low birthweight to mortality. The VHM&PP cohort was one of the largest cohorts in this collaboration, and unique in its semi-rural and alpine setting. This study lasted from 2008-2014 and it produced a large number of high quality papers. The second study wavs the study on Effects of Low-level Air Pollution: a Study from Europe (ELAPSE). Again, the VHM&PP contributed to many analyses, and was instrumental in showing that effects of air pollution on health in Europe were occurring at levels well below EU standards. The ELAPSE study ran from 2015 to 2022 and is still producing high quality papers.

Final project meeting of the ESCAPE collaboration.

Übersicht über Wissenschaftliche Arbeiten

Inhalt in chronologischer Reihenfolge

Preventing overdiagnosis in mammography screening – a public health perspective

Hans Concin ✉ und Gabriele Nagel

Aus der Zeitschrift Hormone Molecular Biology and Clinical Investigation
https://doi.org/10.1515/hmbci-2017-0040

Abstract

Prevention and management of breast cancer in order to provide high quality health care is an important public health issue. The existence of overdiagnosis for breast-cancer was controversial for a long time but is now broadly accepted. Overdiagnosis is defined as the diagnosis of "disease" that will never cause symptoms or death during a patient's ordinarily expected lifetime. Estimates of the overdiagnosis rate for breast cancer range up to 54% of screen-detected localized tumors. New approaches, such as the identification of high risk groups or primary prevention approaches could be more relevant from the public health perspective.

Keywords: breast cancer; overdiagnosis; public health; screening

Author Statement

Research funding: Authors state no funding involved.

Conflict of interest: Authors state no conflict of interest.

Informed consent: Informed consent is not applicable.

Ethical approval: The conducted research is not related to either human or animals use.

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PubMed (https://pubmed.ncbi.nlm.nih.gov/23737396/)

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

Marie Pedersen • Massimo Stafoggia • Gudrun Weinmayr • ... Bert Brunekreef • Gerard Hoek • Ole Raaschou-Nielsen • Show all authors Published: November 26, 2016 • DOI: https://doi.org/10.1016/j.euf.2016.11.008

Abstract

Background

Ambient air pollution contains low concentrations of carcinogens implicated in the etiology of urinary bladder cancer (BC). Little is known about whether exposure to air pollution influences BC in the general population.

Objective

To evaluate the association between long-term exposure to ambient air pollution and BC incidence.

Design, setting, and participants

We obtained data from 15 population-based cohorts enrolled between 1985 and 2005 in eight European countries (N = 303 431; mean follow-up 14.1 yr). We estimated exposure to nitrogen oxides (NO_2 and NO_x), particulate matter (PM) with diameter <10 μm (PM_{10}), <2.5 μm ($PM_{2.5}$), between 2.5 and 10 μm ($PM_{2.5–10}$), $PM_{2.5\ absorbance}$ (soot), elemental constituents of PM, organic carbon, and traffic density at baseline home addresses using standardized land-use regression models from the European Study of Cohorts for Air Pollution Effects project.

Outcome measurements and statistical analysis

We used Cox proportional-hazards models with adjustment for potential confounders for cohort-specific analyses and meta-analyses to estimate summary hazard ratios (HRs) for BC incidence.

Results and limitations

During follow-up, 943 incident BC cases were diagnosed. In the meta-analysis, none of the exposures were associated with BC risk. The summary HRs associated with a 10-μg/m^3 increase in NO_2 and 5-μg/m^3 increase in $PM_{2.5}$ were 0.98 (95% confidence interval [CI] 0.89–1.08) and 0.86 (95% CI 0.63–1.18), respectively. Limitations include the lack of information about lifetime exposure.

Conclusions

There was no evidence of an association between exposure to outdoor air pollution levels at place of residence and risk of BC.

Patient summary

We assessed the link between outdoor air pollution at place of residence and bladder cancer using the largest study population to date and extensive assessment of exposure and comprehensive data on personal risk factors such as smoking. We found no association between the levels of outdoor air pollution at place of residence and bladder cancer risk.

Keywords

Air pollution • Bladder cancer • Environment • Prevention

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Neuro-Oncology

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Long-term exposure to ambient air pollution and incidence of brain tumor: the European Study of Cohorts for Air Pollution Effects (ESCAPE)

Zorana J. Andersen, Marie Pedersen, Gudrun Weinmayr, Massimo Stafoggia, Claudia Galassi, Jeanette T. Jørgensen, Johan N. Sommar, Bertil Forsberg, David Olsson, Bente Oftedal, Gunn Marit Aasvang, Per Schwarze, Andrei Pyko, Göran Pershagen, Michal Korek, Ulf De Faire, Claes-Göran Östenson, Laura Fratiglioni, Kirsten T. Eriksen, Aslak H. Poulsen, Anne Tjønneland, Elvira Vaclavik Bräuner, Petra H. Peeters, Bas Bueno-de-Mesquita, Andrea Jaensch, Gabriele Nagel, Alois Lang, Meng Wang, Ming-Yi Tsai, Sara Grioni, Alessandro Marcon, Vittorio Krogh, Fulvio Ricceri, Carlotta Sacerdote, Enrica Migliore, Roel Vermeulen, Ranjeet Sokhi, Menno Keuken, Kees de Hoogh, Rob Beelen, Paolo Vineis, Giulia Cesaroni, Bert Brunekreef, Gerard Hoek, and Ole Raaschou-Nielsen

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PLOS ONE

RESEARCH ARTICLE

Longitudinal study of body mass index, dyslipidemia, hyperglycemia, and hypertension in 60,000 men and women in Sweden and Austria

Mieke Van Hemelrijck[1], Hanno Ulmer[2], Gabriele Nagel[3,4], Raphael Simon Peter[3], Josef Fritz[2], Robin Myte[5], Bethany van Guelpen[5], Bernhard Föger[4], Hans Concin[4], Christel Häggström[6,7,8], Pär Stattin[7], Tanja Stocks[9]*

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Data Availability Statement: All relevant aggregated data are presented in the article. Requests for the individual-level data of the Västerbotten Intervention Project can be made to the Department of Biobank Research, Umeå University (http://www.biobank.umu.se/biobank/nshds/), and will be subject to ethical review and assessment by a panel of scientists. Individual-level data cannot be made publically available due to legal restrictions imposed by the Swedish Data Protection Authority. Individual-level data of the

Abstract

Background

Obesity is suggested to underlie development of other metabolic aberrations, but longitudinal relationships between metabolic factors at various ages has not been studied in detail.

Methods

Data from 27,379 men and 32,275 women with in total 122,940 health examinations in the Västerbotten Intervention Project, Sweden and the Vorarlberg Health Monitoring and Prevention Programme, Austria were used to investigate body mass index (BMI), mid-blood pressure, and fasting levels of glucose, triglycerides, and total cholesterol at baseline in relation to 10-year changes of these factors and weight. We included paired examinations performed 10±2 years apart and used them for longitudinal analysis with linear regression of changes between the ages 30 and 40, 40 and 50, or 50 and 60 years.

Results

Higher levels of BMI were associated with increases in glucose and mid-blood pressure as well as triglycerides levels, and, to a lesser extent, decreases in cholesterol levels. For instance, per 5 kg/m^2 higher BMI at age 40, glucose at age 50 increased by 0.24 mmol/l (95%CI: 0.22–0.26) and mid-blood pressure increased by 1.54 mm Hg (95%CI: 1.35–1.74). The strongest association observed was between BMI at age 30 and mid-blood pressure, which was 2.12 mm Hg (95% CI: 1.79–2.45) increase over ten years per 5 kg/m^2 higher BMI level. This association was observed at an age when blood pressure levels on average

SCIENTIFIC REPORTS

OPEN

Long-term risk for end-stage kidney disease and death in a large population-based cohort

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Emanuel Zitt[1,2], Constanze Pscheidt[3,4], Hans Concin[3], Reinhard Kramar[5], Raphael S. Peter[4], Jan Beyersmann[6], Karl Lhotta[1,2] & Gabriele Nagel[3,4]

Knowledge of metabolic risk factors for end-stage kidney disease (ESKD) in the general population is limited when considering the competing event death in risk analysis. The aim of our prospective observational study was to investigate how blood pressure and metabolic factors might influence the risks for ESKD and death before ESKD in a large Austrian population-based cohort with long-term follow-up. 177,255 participants (53.8% women; mean age 42.5 years) were recruited between 1988 and 2005 and linked to the Austrian Dialysis and Transplant Registry and the National Mortality Registry. Over a mean follow-up of 16 years 358 participants reached ESKD and 19,512 participants died. Applying fully adjusted cause-specific Cox proportional hazards models elevated fasting blood glucose, hypertension, hypertrigylceridemia and hypercholesterolemia were associated with a higher relative risk for ESKD than for death before ESKD, whereas elevated γ-glutamyltransferase was associated with an increased relative risk of death but not ESKD. Results were similar using continuous or categorical exposure variable measures in the general cohort but differed in selected high-risk populations. These findings might help improve the design of renal risk factor modification trials and kidney disease awareness and prevention programs in the general population, which may ultimately decrease the burden of ESKD.

Epidemiological studies indicate that the metabolic syndrome and its components (elevated blood pressure, elevated triglycerides, low HDL cholesterol, impaired fasting blood glucose and central obesity) are associated with increased cardiovascular morbidity and all-cause mortality in the general population[1]. Furthermore, the metabolic syndrome is linked to the development and progression of chronic kidney disease (CKD)[2–4]. A meta-analysis of 31 studies clearly showed an association between the metabolic syndrome and cardiovascular disease, as well as kidney disease[5]. CKD itself is associated with a large burden of morbidity and mortality[6,7], exceeding the mortality risk of the general population by 10- to 20-fold[8].

Approximately one in 40 middle-aged men and one in 60 women will develop end-stage kidney disease (ESKD) during their lifetime[9]. There is some evidence to suggest that the presence of the metabolic syndrome and its components is associated with an increased risk for ESKD rather than an increased risk for death[10]. However, estimating the ESKD risk requires a careful approach that considers the competing event death before ESKD. As shown by Turin *et al.* the lifetime risk for ESKD in the general population is significantly attenuated with the competing risk death before ESKD (relative risk reduction in men by 36%, in women by 23%). In contrast, adjusting for the competing risk of death does not affect ESKD risk in people with impaired kidney function[9]. Evaluation of the influence of known risk factors on the long-term risk for these two competing events might provide new insights to strengthen risk reduction efforts in the general population to prevent ESKD-associated burden of morbidity and treatment costs.

Such studies applying cause-specific risk models in the general population are limited. Previous studies were performed in populations at high risk for ESKD, with either preexisting CKD[10], hypertension[11], diabetes mellitus[12] or cardiovascular disease[13], but not in a large general population-based cohort without a priori predefined

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Original article

Blood Pressure Patterns

Contributions of mean and shape of blood pressure distribution to worldwide trends and variations in raised blood pressure: a pooled analysis of 1018 population-based measurement studies with 88.6 million participants

NCD Risk Factor Collaboration (NCD-RisC)
Members are listed at the end of the paper.

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Abstract

Background: Change in the prevalence of raised blood pressure could be due to both shifts in the entire distribution of blood pressure (representing the combined effects of public health interventions and secular trends) and changes in its high-blood-pressure tail (representing successful clinical interventions to control blood pressure in the hypertensive population). Our aim was to quantify the contributions of these two phenomena to the worldwide trends in the prevalence of raised blood pressure.

Methods: We pooled 1018 population-based studies with blood pressure measurements on 88.6 million participants from 1985 to 2016. We first calculated mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP) and prevalence of raised blood pressure by sex and 10-year age group from 20–29 years to 70–79 years in each study, taking into account complex survey design and survey sample weights, where relevant. We used a linear mixed effect model to quantify the association between (probit-transformed) prevalence of raised blood pressure and age-group- and sex-specific mean blood pressure. We calculated the contributions of change in mean SBP and DBP, and of change in the prevalence-mean association, to the change in prevalence of raised blood pressure.

Results: In 2005–16, at the same level of population mean SBP and DBP, men and women in South Asia and in Central Asia, the Middle East and North Africa would have the highest prevalence of raised blood pressure, and men and women in the high-income Asia Pacific and high-income Western regions would have the lowest. In most region-sex-age groups where the prevalence of raised blood pressure declined, one half or more of the decline was due to the decline in mean blood pressure. Where prevalence of raised blood pressure has increased, the change was entirely driven by increasing mean blood pressure, offset partly by the change in the prevalence-mean association.

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Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE) ☆

Gudrun Weinmayr [a], Marie Pedersen [b c], Massimo Stafoggia [d e], Zorana J. Andersen [b], Claudia Galassi [f], Jule Munkenast [a], Andrea Jaensch [a], Bente Oftedal [g], Norun H. Krog [g], Geir Aamodt [h], Andrei Pyko [e], Göran Pershagen [e], Michal Korek [e], Ulf De Faire [e], Nancy L. Pedersen [i], Claes-Göran Östenson [j], Debora Rizzuto [k], Mette Sørensen [c], Anne Tjønneland [c], Bas Bueno-de-Mesquita [l]...Gabriele Nagel [a r]

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https://doi.org/10.1016/j.envint.2018.07.030

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Abstract

Introduction

Previous analysis from the large European multicentre ESCAPE study showed an association of ambient particulate matter <2.5 μm ($PM_{2.5}$) air pollution exposure at residence with the incidence of gastric cancer. It is unclear which components of PM are most relevant for gastric and also upper aerodigestive tract (UADT) cancer and some of them may not be strongly correlated with PM mass. We evaluated the association between long-term exposure to elemental components of $PM_{2.5}$ and PM_{10} and gastric and UADT cancer incidence in European adults.

Methods

Baseline addresses of individuals were geocoded and exposure was assessed by land-use regression models for copper (Cu), iron (Fe) and zinc (Zn) representing non-tailpipe traffic emissions; sulphur (S) indicating long-range transport; nickel (Ni) and vanadium (V) for mixed oil-burning and industry; silicon (Si) for crustal material and potassium (K) for biomass burning. Cox regression models with adjustment for potential confounders were used for cohort-specific analyses. Combined estimates were determined with random effects meta-analyses.

Results

Ten cohorts in six countries contributed data on 227,044 individuals with an average follow-up of 14.9 years with 633 incident cases of gastric cancer and 763 of UADT cancer.

The combined hazard ratio (HR) for an increase of 200 ng/m^3 of $PM_{2.5}$_S was 1.92 (95%-confidence interval (95%-CI) 1.13;3.27) for gastric cancer, with no indication of heterogeneity between cohorts (I^2 = 0%), and 1.63 (95%-CI 0.88;3.01) for $PM_{2.5}$_Zn (I^2 = 70%). For the other elements in $PM_{2.5}$ and all elements in PM_{10} including PM_{10}_S, non-significant HRs between 0.78 and 1.21 with mostly wide CIs were seen. No association was found between any of the elements and UADT cancer. The HR for $PM_{2.5}$_S and gastric cancer was robust to adjustment for additional factors, including diet, and restriction to study participants with stable addresses over follow-up resulted in slightly higher effect estimates with a decrease in precision. In a two-pollutant model, the effect estimate for total $PM_{2.5}$ decreased whereas that for $PM_{2.5}$_S was robust.

Conclusion

This large multicentre cohort study shows a robust association between gastric cancer and long-term exposure to $PM_{2.5}$_S but not PM_{10}_S, suggesting that S in $PM_{2.5}$ or correlated air pollutants may contribute to the risk of gastric cancer.

Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter

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Exposure to ambient fine particulate matter ($PM_{2.5}$) is a major global health concern. Quantitative estimates of attributable mortality are based on disease-specific hazard ratio models that incorporate risk information from multiple $PM_{2.5}$ sources (outdoor and indoor air pollution from use of solid fuels and secondhand and active smoking), requiring assumptions about equivalent exposure and toxicity. We relax these contentious assumptions by constructing a $PM_{2.5}$-mortality hazard ratio function based only on cohort studies of outdoor air pollution that covers the global exposure range. We modeled the shape of the association between $PM_{2.5}$ and nonaccidental mortality using data from 41 cohorts from 16 countries—the Global Exposure Mortality Model (GEMM). We then constructed GEMMs for five specific causes of death examined by the global burden of disease (GBD). The GEMM predicts 8.9 million [95% confidence interval (CI): 7.5–10.3] deaths in 2015, a figure 30% larger than that predicted by the sum of deaths among the five specific causes (6.9; 95% CI: 4.9–8.5) and 120% larger than the risk function used in the GBD (4.0; 95% CI: 3.3–4.8). Differences between the GEMM and GBD risk functions are larger for a 20% reduction in concentrations, with the GEMM predicting 220% higher excess deaths. These results suggest that $PM_{2.5}$ exposure may be related to additional causes of death than the five considered by the GBD and that incorporation of risk information from other, nonoutdoor, particle sources leads to underestimation of disease burden, especially at higher concentrations.

mortality | exposure | risk | concentration | fine particulate matter

Exposure to outdoor fine particulate matter ($PM_{2.5}$) is recognized as a major global health concern (1). In particular, both nonaccidental and cause-specific mortality have been associated with outdoor $PM_{2.5}$ concentrations. In cohort studies, where subjects provide information on major mortality risk factors such as cigarette smoking, obesity, and occupation, estimates of outdoor $PM_{2.5}$ exposure are assigned based on multiple year averages and followed over time to ascertain their date and underlying cause of death. The magnitude of the association between $PM_{2.5}$ exposure and the probability of death is described by the hazard ratio (2).

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Data deposition: Data and code related to this paper are available at https://github.com/mszyszkowicz/DataGEMM.

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Cancer Epidemiology

Air pollution and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE)

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Key words: gastric cancer, upper aerodigestive tract cancer, air pollution, epidemiology, ESCAPE

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

Rob Beleen, coordinating ESCAPE as a PostDoc at IRAS, Utrecht University, Utrecht, The Netherlands, died far too early in September 2017. He will live in our memories as a warm-hearted, friendly and always helpful human being and as a great scientist.

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Risk of bladder cancer by disease severity in relation to metabolic factors and smoking: A prospective pooled cohort study of 800,000 men and women

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Cancer Epidemiology

Previous studies on metabolic factors and bladder cancer (BC) risk have shown inconsistent results and have commonly not investigated associations separately by sex, smoking, and tumor invasiveness. Among 811,633 participants in six European cohorts, we investigated sex-specific associations between body mass index (BMI), mid-blood pressure (BP, [systolic + diastolic]/2), plasma glucose, triglycerides, total cholesterol and risk of BC overall, non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC). Among men, we additionally assessed additive interactions between metabolic factors and smoking on BC risk. During follow-up, 2,983 men and 754 women were diagnosed with BC. Among men, triglycerides and BP were positively associated with BC risk overall (hazard ratio [HR] per standard deviation [SD]: 1.17 [95% confidence interval (CI) 1.06–1.27] and 1.09 [1.02–1.17], respectively), and among women, BMI was inversely associated with risk (HR: 0.90 [0.82–0.99]). The associations for BMI and BP differed between men and women ($p_{interaction} \leq 0.005$). Among men, BMI, cholesterol and triglycerides were positively associated with risk for NMIBC (HRs: 1.09 [95% CI 1.01–1.18], 1.14 [1.02–1.25], and 1.30 [1.12–1.48] respectively), and BP was positively associated with MIBC (HR: 1.23 [1.02–1.49]). Among women, glucose was positively associated with MIBC (HR: 1.99 [1.04–3.81]). Apart from cholesterol, HRs for metabolic factors did not significantly differ between MIBC and NMIBC, and there were no interactions between smoking and metabolic factors on BC. Our study supports an involvement of metabolic aberrations in BC risk. Whilst some associations were significant only in certain sub-groups, there were generally no significant differences in associations by smoking or tumor invasiveness.

Key words: bladder cancer, metabolic factors, smoking, non-muscle invasive bladder cancer, muscle-invasive bladder cancer
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Bone Mineral Density and Breast Cancer Incidence and Mortality in Postmenopausal Women: A Long-Term Follow-Up Study

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View Article

Abstract

Purpose: To examine whether bone mineral density (BMD) is predictive of breast cancer risk and mortality in a population of early postmenopausal women participating in a medical prevention program in western Austria.

Patients and Methods: Between May 1991 and February 1999, lumbar spine BMD was measured by dual-energy X-ray absorptiometry (*N* = 1163, mean age 56.9 ± 5.7 years) or quantitative computed tomography (*N* = 2283, mean age 56.8 ± 5.4 years) in 3446 women aged ≥50 years. Data on medication and lifestyle factors were collected by questionnaire. Participants were prospectively followed up for breast cancer incidence, and breast cancer patients were followed up for mortality. To calculate risk of breast cancer and mortality, Cox proportional hazards models were applied.

Results: During median follow-up of 20.7 years, 185 invasive breast cancer cases and 22 deaths due to breast cancer occurred. Risk of breast cancer in the highest versus the lowest BMD quartile was nonsignificantly reduced, in particular when follow-up was restricted to 10 years (hazard ratio 0.53, 95% confidence interval 0.25–1.12). There was no risk reduction when follow-up began 10 years after BMD measurement. There was no association between BMD and all-cause or breast cancer-specific mortality among breast cancer patients, but a trend toward reduced mortality risk in the highest BMD quartile.

Conclusions: We hypothesize that BMD is not reflective of estrogen exposure and not predictive of breast cancer risk, at least in young postmenopausal women. Confounders such as vitamin D might underlie low breast cancer risk at high BMD, thus mirroring better health status.

LETTER

OPEN

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Rising rural body-mass index is the main driver of the global obesity epidemic in adults

NCD Risk Factor Collaboration (NCD-RisC)*

Body-mass index (BMI) has increased steadily in most countries in parallel with a rise in the proportion of the population who live in cities[1,2]. This has led to a widely reported view that urbanization is one of the most important drivers of the global rise in obesity[3–6]. Here we use 2,009 population-based studies, with measurements of height and weight in more than 112 million adults, to report national, regional and global trends in mean BMI segregated by place of residence (a rural or urban area) from 1985 to 2017. We show that, contrary to the dominant paradigm, more than 55% of the global rise in mean BMI from 1985 to 2017—and more than 80% in some low- and middle-income regions—was due to increases in BMI in rural areas. This large contribution stems from the fact that, with the exception of women in sub-Saharan Africa, BMI is increasing at the same rate or faster in rural areas than in cities in low- and middle-income regions. These trends have in turn resulted in a closing—and in some countries reversal—of the gap in BMI between urban and rural areas in low- and middle-income countries, especially for women. In high-income and industrialized countries, we noted a persistently higher rural BMI, especially for women. There is an urgent need for an integrated approach to rural nutrition that enhances financial and physical access to healthy foods, to avoid replacing the rural undernutrition disadvantage in poor countries with a more general malnutrition disadvantage that entails excessive consumption of low-quality calories.

Being underweight or overweight can lead to adverse health outcomes. BMI—a measure of underweight and overweight—is rising in most countries[2]. It is commonly stated that urbanization is one of the most important drivers of the worldwide rise in BMI because diet and lifestyle in cities lead to adiposity[3–6]. However, such statements are typically based on cross-sectional comparisons in one or a small number of countries. Only a few studies have analysed how BMI is changing over time in rural and urban areas. The majority have been in one country, over short durations, and/or in one sex and narrow age groups. The few studies that covered more than one country[7–12] used at most a few dozen data sources and hence could not systematically estimate trends, and focused primarily on women of child-bearing age.

Data on how BMI in rural and urban populations is changing are needed to plan interventions that address underweight and overweight. Here, we report on mean BMI in rural and urban areas of 200 countries and territories from 1985 to 2017. We used 2,009 population-based studies of human anthropometry conducted in 190 countries (Extended Data Fig. 1), with measurements of height and weight in more than 112 million adults aged 18 years and older. We excluded data based on self-reported height and weight because they are subject to bias. For each sex, we used a Bayesian hierarchical model to estimate mean BMI by year, country and rural or urban place of residence. As described in the Methods, the estimated trends in population mean BMI represent a combination of (1) the change in the health of individuals due to change in their economic status and environment, and (2) the change in the composition of individuals that make up the population (and their economic status and environment).

From 1985 to 2017, the proportion of the world's population who lived in urban areas[1] increased from 41% to 55%. Over the same period, global age-standardized mean BMI increased from 22.6 kg m^{-2} (95% credible interval 22.4–22.9) to 24.7 kg m^{-2} (24.5–24.9) in women, and from 22.2 kg m^{-2} (22.0–22.4) to 24.4 kg m^{-2} (24.2–24.5) in men. The increase in mean BMI was 2.09 kg m^{-2} (1.73–2.44) and 2.10 kg m^{-2} (1.79–2.41) among rural women and men, respectively, compared to 1.35 kg m^{-2} (1.05–1.65) and 1.59 kg m^{-2} (1.33–1.84) in urban women and men. Nationally, change in mean BMI ranged from small decreases among women in 12 countries in Europe and Asia Pacific, to a rise of >5 kg m^{-2} among women in Egypt and Honduras. The lowest observed sex-specific mean BMI over these 33 years was that of rural women in Bangladesh of 17.7 kg m^{-2} (16.3–19.2) and rural men in

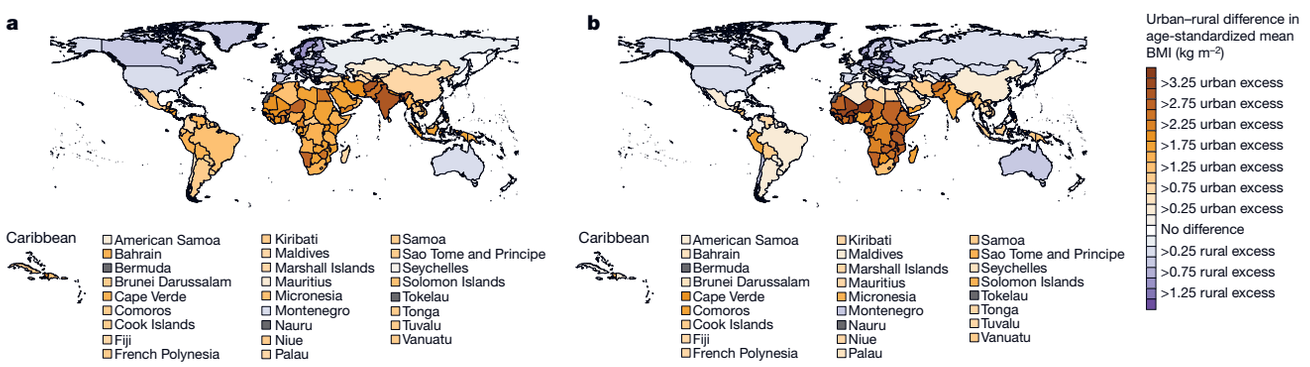

Fig. 1 | The difference between rural and urban age-standardized mean BMI in women. a, Difference in age-standardized mean BMI in 1985. **b**, Difference in age-standardized mean BMI in 2017. We did not estimate the difference between rural and urban areas for countries and territories in which the entire population live in areas classified as urban (Singapore, Hong Kong, Bermuda and Nauru) or rural (Tokelau)—shown in grey. See Extended Data Fig. 2 for mean BMI at the national level and in rural and urban populations in 1985 and 2017. See Extended Data Fig. 6 for comparisons of the results between women and men.

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Height and body-mass index trajectories of school-aged children and adolescents from 1985 to 2019 in 200 countries and territories: a pooled analysis of 2181 population-based studies with 65 million participants

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

Summary

Background Comparable global data on health and nutrition of school-aged children and adolescents are scarce. We aimed to estimate age trajectories and time trends in mean height and mean body-mass index (BMI), which measures weight gain beyond what is expected from height gain, for school-aged children and adolescents.

Methods For this pooled analysis, we used a database of cardiometabolic risk factors collated by the Non-Communicable Disease Risk Factor Collaboration. We applied a Bayesian hierarchical model to estimate trends from 1985 to 2019 in mean height and mean BMI in 1-year age groups for ages 5–19 years. The model allowed for non-linear changes over time in mean height and mean BMI and for non-linear changes with age of children and adolescents, including periods of rapid growth during adolescence.

Findings We pooled data from 2181 population-based studies, with measurements of height and weight in 65 million participants in 200 countries and territories. In 2019, we estimated a difference of 20 cm or higher in mean height of 19-year-old adolescents between countries with the tallest populations (the Netherlands, Montenegro, Estonia, and Bosnia and Herzegovina for boys; and the Netherlands, Montenegro, Denmark, and Iceland for girls) and those with the shortest populations (Timor-Leste, Laos, Solomon Islands, and Papua New Guinea for boys; and Guatemala, Bangladesh, Nepal, and Timor-Leste for girls). In the same year, the difference between the highest mean BMI (in Pacific island countries, Kuwait, Bahrain, The Bahamas, Chile, the USA, and New Zealand for both boys and girls and in South Africa for girls) and lowest mean BMI (in India, Bangladesh, Timor-Leste, Ethiopia, and Chad for boys and girls; and in Japan and Romania for girls) was approximately 9–10 kg/m². In some countries, children aged 5 years started with healthier height or BMI than the global median and, in some cases, as healthy as the best performing countries, but they became progressively less healthy compared with their comparators as they grew older by not growing as tall (eg, boys in Austria and Barbados, and girls in Belgium and Puerto Rico) or gaining too much weight for their height (eg, girls and boys in Kuwait, Bahrain, Fiji, Jamaica, and Mexico; and girls in South Africa and New Zealand). In other countries, growing children overtook the height of their comparators (eg, Latvia, Czech Republic, Morocco, and Iran) or curbed their weight gain (eg, Italy, France, and Croatia) in late childhood and adolescence. When changes in both height and BMI were considered, girls in South Korea, Vietnam, Saudi Arabia, Turkey, and some central Asian countries (eg, Armenia and Azerbaijan), and boys in central and western Europe (eg, Portugal, Denmark, Poland, and Montenegro) had the healthiest changes in anthropometric status over the past 3·5 decades because, compared with children and adolescents in other countries, they had a much larger gain in height than they did in BMI. The unhealthiest changes—gaining too little height, too much weight for their height compared with children in other countries, or both—occurred in many countries in sub-Saharan Africa, New Zealand, and the USA for boys and girls; in Malaysia and some Pacific island nations for boys; and in Mexico for girls.

Interpretation The height and BMI trajectories over age and time of school-aged children and adolescents are highly variable across countries, which indicates heterogeneous nutritional quality and lifelong health advantages and risks.

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See Online for appendix

Introduction

Growth and development through childhood and adolescence are affected by social, nutritional, and environmental factors at home, at school, and in the community. During school ages (typically 5–19 years), these factors amplify or mitigate adversity in infancy and early childhood and, if healthy, can help consolidate gains from early childhood and correct some nutritional

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Cancer

BMI and weight changes and risk of obesity-related cancers: a pooled European cohort study

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Abstract

Background: Obesity is an established risk factor for several cancers. Adult weight gain has been associated with increased cancer risk, but studies on timing and duration of adult weight gain are relatively scarce. We examined the impact of BMI (body mass index) and weight changes over time, as well as the timing and duration of excess weight, on obesity- and non-obesity-related cancers.

Methods: We pooled health data from six European cohorts and included 221 274 individuals with two or more height and weight measurements during 1972–2014. Several BMI and weight measures were constructed. Cancer cases were identified through linkage with national cancer registries. Hazard ratios (HRs) of cancer with 95% confidence intervals (CIs) were derived from time-dependent Cox-regression models.

Results: During follow-up, 27 881 cancer cases were diagnosed; 9761 were obesity-related. The HR of all obesity-related cancers increased with increasing BMI at first and last measurement, maximum BMI and longer duration of overweight (men only) and

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Metabolic factors and hip fracture risk in a large Austrian cohort study

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ABSTRACT

To explore the association of incident hip fractures with metabolic syndrome (MetS) and its single components, we designed a prospective cohort study of hip fracture incidence among 117,053 participants of a population-based health surveillance program in Vorarlberg, the westernmost Austrian province. Incident hip fractures were recorded between 5 and 10 years after inclusion at baseline from 2003 to 2009. Applying Cox proportional hazard models for each MetS component and for a composite z-score for MetS, hazards for fracture were estimated in quintiles, as continuous z-score variables, and as pathological cut off values. Mean age was 50.1 ± 15.6 years at baseline, 5–10 years after which 947 incident hip fractures occurred. An association of a higher composite MetS score with decreased hip fracture risk was observed in women (HR 0.80, 95%-CI 0.88–0.96, $p < 0.01$) which disappeared upon adjustment for BMI. BMI was inversely associated with hip fracture risk in women and men (HR for the highest compared with the lowest quintile: 0.83 (95%-CI: 0.63–1.10, $p_{trend} < 0.05$) and 0.55 (95%-CI: 0.38–0.79, $p_{trend} < 0.001$), respectively). Only in women, hip fracture risk was reduced at high cholesterol levels (HR for the highest relative to the lowest quintile: 0.64, 95%-CI: 0.48–0.84, $p_{trend} < 0.05$) and in hypercholesterolemic patients (HR 0.82, 95%-CI: 0.67–0.99, $p < 0.05$), but elevated in hyperglycemic patients (HR 1.33, 95%-CI: 1.05–1.70, $p < 0.05$). Hypertriglyceridemia was associated with increased male hip fracture risk (HR 1.33, 95%-CI: 1.03–1.72, $p < 0.05$). The inverse association between the MetS and hip fracture risk is mainly driven by one single component, namely BMI.

1. Introduction

As one consequence of osteoporosis, hip fracture is among the most prevalent and devastating injuries among the elderly (Morris and Zuckerman, 2002; Keen, 2003). It is associated with increased mortality, morbidity, disability and economic costs to both the patient and society (Johnell and Kanis, 2004, 2005; Dhanwal et al., 2011). Because of the growing proportion of the aging population after all in industrialized countries, in recent years hip fractures have emerged as a tremendous global public health concern (WHO Scientific Group on the Prevention and Management of Osteoporosis, 2003). 1.6 million annual cases worldwide were estimated for the year 2000 with a predicted threefold increase of this number by the year 2050 (Gullberg et al., 1997). In the European Union among the population aged ≥50 years, hip fracture incidence in 2010 ranged between 231 and 640/100,000 in Romania and Denmark, respectively (Hernlund et al., 2013). In Austria, the number of hip fractures was estimated to amount to well above 15,000 in 2008, yielding a fairly high incidence of 456/100,000 among those aged ≥50, however, a decreasing secular trend since 2006 was observed (Dimai et al., 2011).

Likewise, the metabolic syndrome (MetS) must be regarded as an eminent public health issue, given its considerable prevalence that was estimated to affect 20–30% of the adult population in most countries worldwide, rising with advanced age and economic prosperity (Grundy, 2008). MetS is a compound condition consisting of various pathologic factors including obesity, hypertension, hyperglycemia and dyslipidemia, and is associated with high risk for the development of cardiovascular diseases (CVD) and type II diabetes mellitus (Levesque and Lamarche, 2008). In view of numerous reports of an association of osteoporotic fractures, particularly hip fractures, with ischemic heart disease, heart failure, hypertension, and diabetes, a relation between MetS and bone health can be expected (Janghorbani et al., 2007;

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Cancer Epidemiology

Linear age-course effects on the associations between body mass index, triglycerides, and female breast and male liver cancer risk: An internal replication study of 800,000 individuals

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Apart from the consistently observed differential association between obesity and breast cancer risk by menopausal status, the associations between obesity and other metabolic imbalances with risks of cancers have not been systematically investigated across the age-course. We created two random 50–50% cohorts from six European cohorts comprising 813,927 individuals. In the "discovery cohort", we used Cox regression with attained age as time-scale and tested interactions between body mass index (BMI), blood pressure, plasma glucose, triglycerides and cholesterol, and attained age in relation to cancer risk. Results with a *p*-value below 0.05 were additionally tested in the "replication cohort" where a replicated result was considered evidence of a linear interaction with attained age. These findings were investigated by flexible parametric survival models for any age-plateaus in their shape of associations with cancer risk across age. Consistent with other studies, BMI was negatively related to breast cancer risk (*n* cases = 11,723) among younger (premenopausal) women. However, the association remained negative for several years after menopause and, although gradually weakening over age, the association became positive only at 62 years of age. This linear and positive age-interaction was also found for triglycerides and breast cancer, and for BMI and triglycerides in relation to liver cancer among men (*n* cases = 444). These findings are unlikely to be due to chance owing to the replication. The linear age-interactions in breast cancer may suggest an influence by other age-related factors than menopause; however, further investigation of age-related effect modifiers in both breast and liver cancer is needed.

Key words: survival analysis, cohort study, metabolic factors, cancer risk, age interaction

Abbreviations: 40-y: the 40-year programme; BMI: body mass index; HR: hazard ratio; ICD: International Classification of Diseases; Me-Can: Metabolic syndrome and Cancer project; MPP: Malmö Preventive Project; NCS: Norwegian Counties Study; PH: proportional hazards; SD: standard deviation; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme; VIP: Västerbotten Intervention Project; *Z* score: standardized exposures with a mean value of zero and a standard deviation of one

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

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Lipids

The triglyceride-glucose index as a measure of insulin resistance and risk of obesity-related cancers

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Abstract

Background: The role of insulin resistance as a mediator in the association of body mass index (BMI) with site-specific cancer risk has, to our knowledge, never been systematically quantified.

Methods: Altogether 510 471 individuals from six European cohorts, with a mean age of 43.1 years, were included. We used the triglyceride glucose product (TyG index) as a surrogate measure for insulin resistance. We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with 10 common obesity-related cancers, and quantified the proportion of the effect of BMI mediated through TyG index on the log-transformed hazard ratio (HR) scale.

Results: During a median follow-up of 17.2 years, 16 052 individuals developed obesity-related cancers. TyG index was associated with the risk of cancers of the kidney HR per one standard deviation increase 1.13, 95% confidence interval: 1.07 to 1.20], liver (1.13, 1.04 to 1.23), pancreas (1.12, 1.06 to 1.19), colon (1.07, 1.03 to 1.10) and rectum (1.09, 1.04 to 1.14). Substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas (42%), rectum (34%) and colon (20%); smaller proportions for kidney

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Sex- and age-specific variations, temporal trends and metabolic determinants of serum uric acid concentrations in a large population-based Austrian cohort

Emanuel Zitt[1,2,3], Anton Fischer[1,3], Karl Lhotta[1,2], Hans Concin[3] & Gabriele Nagel[3,4]✉

Little is known about sex- and age-specific variations and temporal trends in serum uric acid (SUA) concentrations, the prevalence of hyperuricemia and its association with metabolic risk factors in the general population. Between January 1, 1985 and June 30, 2005 146,873 participants (42% women) were recruited. Prevalence of hyperuricemia was estimated applying a common (SUA > 360 µmol/L) and sex-specific cut-off points (women > 340 µmol/L, men > 420 µmol/L). At baseline, mean age was 41.2 years in men and 51.5 years in women, mean SUA concentration was 314.8 µmol/L and 243.6 µmol/L, respectively. Applying a common cut-off point, the prevalence of hyperuricemia was 18.5% in men and 4.4% in women and by sex-specific cut-off points it was 15.1% and 13.8%, respectively. SUA levels increased by 6.7 µmol/L per decade in men, but remained constant in women until the age of 50 years with a sharp increase by approximately 22 µmol/L per decade thereafter. In men and women, hyperuricemia was associated with obesity, hypertriglyceridemia and elevated gamma-glutamyl transferase. With increasing age SUA levels and the prevalence of hyperuricemia rise in a sex-specific manner. Above the age of 65 years, the sex-specific prevalence of hyperuricemia in women outreaches that in men.

Uric acid (UA) is generated by the metabolic breakdown of purine nucleotides and nucleosides such as adenosine. In humans and great apes it is the final degradation product, whereas in other mammals UA is further oxidized to allantoin. Uricase, the enzyme catalyzing this process, has been silenced during human evolution by nonsense mutations[1]. Therefore, humans have three to ten times higher serum UA (SUA) levels than do other species. Urate is excreted by the kidney by free glomerular filtration with complex reabsorption and secretion in the proximal tubulus[2].

It is hypothesized that the powerful antioxidant capacity of UA may have caused a survival advantage during human evolution[3]. On the other hand, high UA levels have been shown to be associated with hypertension, cardiovascular disease, metabolic syndrome, diabetes and chronic kidney disease, making it a valuable biomarker for these conditions[4–9]. Furthermore, UA levels and prevalence of hyperuricemia seem to have increased during recent decades and years[10–13]. Therefore, from a public health perspective knowledge and surveillance of SUA levels in the general population are valuable goals.

The aim of the present study was to describe sex- and age-specific variations and temporal trends in SUA concentrations, the prevalence of hyperuricemia and its association with metabolic risk factors in a large population-based cohort over a follow-up of 20 years.

Herein, we present SUA levels obtained during a period of over 20 years for 146.873 persons with over 530.000 individual SUA measurements collected between 1985 and 2005 in Vorarlberg, the westernmost state of Austria.

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Article

Repositioning of the global epicentre of non-optimal cholesterol

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NCD Risk Factor Collaboration (NCD-RisC)*

High blood cholesterol is typically considered a feature of wealthy western countries[1,2]. However, dietary and behavioural determinants of blood cholesterol are changing rapidly throughout the world[3] and countries are using lipid-lowering medications at varying rates. These changes can have distinct effects on the levels of high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol, which have different effects on human health[4,5]. However, the trends of HDL and non-HDL cholesterol levels over time have not been previously reported in a global analysis. Here we pooled 1,127 population-based studies that measured blood lipids in 102.6 million individuals aged 18 years and older to estimate trends from 1980 to 2018 in mean total, non-HDL and HDL cholesterol levels for 200 countries. Globally, there was little change in total or non-HDL cholesterol from 1980 to 2018. This was a net effect of increases in low- and middle-income countries, especially in east and southeast Asia, and decreases in high-income western countries, especially those in northwestern Europe, and in central and eastern Europe. As a result, countries with the highest level of non-HDL cholesterol—which is a marker of cardiovascular risk—changed from those in western Europe such as Belgium, Finland, Greenland, Iceland, Norway, Sweden, Switzerland and Malta in 1980 to those in Asia and the Pacific, such as Tokelau, Malaysia, The Philippines and Thailand. In 2017, high non-HDL cholesterol was responsible for an estimated 3.9 million (95% credible interval 3.7 million–4.2 million) worldwide deaths, half of which occurred in east, southeast and south Asia. The global repositioning of lipid-related risk, with non-optimal cholesterol shifting from a distinct feature of high-income countries in northwestern Europe, north America and Australasia to one that affects countries in east and southeast Asia and Oceania should motivate the use of population-based policies and personal interventions to improve nutrition and enhance access to treatment throughout the world.

Blood cholesterol is one of the most important risk factors for ischaemic heart disease (IHD) and ischaemic stroke[4–6]. Consistent and comparable information on cholesterol levels and trends in different countries can help to benchmark national performance in addressing non-optimal cholesterol, investigate the reasons behind differential trends and identify countries in which interventions are needed the most.

A previous global analysis[7] reported trends in total cholesterol from 1980 to 2008, but did not analyse important lipid fractions—including HDL and non-HDL cholesterol—that are key to understanding the cardiovascular disease risk associated with non-optimal cholesterol. Dietary and behavioural determinants of cholesterol have changed throughout the world in the past decades, including a worldwide rise in adiposity[8,9], divergent global trends in alcohol use[10], a rise in the intake of animal-source foods in middle-income countries (especially in east Asia)[3,11], and a replacement of saturated fats and trans fats with unsaturated fats in some high-income countries[3,11,12]. There is also considerable variation in how much different countries have adopted lipid-lowering medications[13]. These changes are likely to have influenced cholesterol levels substantially in the decade since the last estimates were made. Furthermore, HDL and non-HDL cholesterol, which have opposite associations with cardiovascular diseases[4,5], respond differently to diet and treatment, and may therefore have different geographical patterns and trends over time[14]. Information on these major lipid fractions, which were not included in the previous global estimates, is essential for priority setting and intervention choice.

Here we pooled 1,127 population-based studies that measured blood lipids in 102.6 million individuals aged 18 years and older (Extended Data Figs. 1, 2 and Supplementary Table 1) and used a Bayesian hierarchical model to estimate trends from 1980 to 2018 in mean total, non-HDL and HDL cholesterol levels for 200 countries. We also estimated the number of deaths caused by IHD and ischaemic stroke that were attributable to high levels of non-HDL cholesterol using information on its hazards from epidemiological studies.

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Long-term exposure to fine particle elemental components and lung cancer incidence in the ELAPSE pooled cohort

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Long-term low-level ambient air pollution exposure and risk of lung cancer – A pooled analysis of 7 European cohorts

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Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: The ELAPSE project

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Effect of Secular Trend, Age, and Length of Follow-up on Optimum Body Mass Index From 1985 Through 2015 in a Large Austrian Cohort

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ABSTRACT

Background: Obesity and its health consequences will dominate health care systems in many countries during the next decades. However, the body mass index (BMI) optimum in relation to all-cause mortality is still a matter of debate.

Material and Methods: Data of the Vorarlberg Health Monitoring & Prevention Program (VHM&PP, 1985–2005) and data provided by the Main Association of Austrian Social Security Institutions (MAASSI, 2005–2015) were analyzed. Information was available on age, sex, smoking status, measured height and weight, and mortality. Generalized additive models were used to model mortality as a function of BMI, calendar time, age, and follow-up.

Results: In MAASSI ($N = 282{,}216$, 46.0% men), men and women were on average 2.7 years older than in VHM&PP ($N = 185{,}361$, 46.1% men). Average BMI was slightly higher in men (26.1 vs 25.7 kg/m^2) but not in women (24.6 vs 24.7 kg/m^2). We found an interactive effect of age and follow-up on the BMI optimum. Over age 35 years in men and 55 years in women, the BMI optimum decreased with length of follow-up. While keeping covariates fixed, BMI optimum increased slightly between 1985 and 2015 in men and women, 24.9 (95% CI, 23.9–25.9) to 26.4 (95% CI, 25.3–27.3), and 22.4 (95% CI, 21.7–23.1) to 23.3 (95% CI, 22.6–24.5) kg/m^2, respectively.

Conclusion: Age and length of follow-up have a pronounced effect on the BMI associated with the lowest all-cause mortality. After controlling for age and length of follow-up, the BMI optimum increased slightly over 30 years in this large study sample.

Key words: BMI; mortality; age; secular trend; length of follow-up

INTRODUCTION

Obesity has become an explicit public health concern in high income and some middle-income countries.[1] Recent studies indicate that obesity and its health consequences will dominate health care systems in many countries during the next decades.[1,2] In children and adolescents, the increasing body mass index (BMI) trends have plateaued in many high-income countries, albeit at high levels.[2] In Austria, the obesity prevalence is still rising, especially in men.[3] Also, globally the increase in BMI has not slowed down.[1]

The association between BMI and mortality is, therefore, a matter of public interest.[4–7] The relationship between BMI and mortality is U-shaped indication that low and high BMI is associated with higher mortality.[7,8] The BMI optimum in the BMI all-cause mortality relationship changes with age and its pattern differs by sex.[6] Heterogeneity in the association between BMI and mortality is attributable to ethnicity, age, and length of follow-up.[9] Thus, these factors need consideration in the investigation of the BMI all-cause mortality relationship.

While average BMI increased over time, it is unclear if the BMI optimum stayed constant or increased as well.[4] Afzal et al reported in 2016 that among three Danish cohorts, the BMI associated with the lowest mortality increased by 3.3 kg/m^2 from 1976–1978 to 2003–2013.[4] On the contrary, Wang et al found among Canadian adults that with fixed long-term follow-up duration, the BMI value associated with the lowest mortality remains relatively stable over time.[10]

While previous studies considered modifying factors like sex, age, length of follow-up,[9] or a secular trend,[4,10] there has not been an investigation into all these factors simultaneously. In this study, we, therefore, investigated the association of BMI with all-cause mortality in the general population over three decades considering a secular trend, sex, age, and length of follow-up as possible effect modifiers.

METHODS

The Vorarlberg Health Monitoring & Prevention Program (VHM&PP) was carried out by the Agency of Social and

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Modeling multi-level survival data in multi-center epidemiological cohort studies: Applications from the ELAPSE project

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ABSTRACT

Background: We evaluated methods for the analysis of multi-level survival data using a pooled dataset of 14 cohorts participating in the ELAPSE project investigating associations between residential exposure to low levels of air pollution ($PM_{2.5}$ and NO_2) and health (natural-cause mortality and cerebrovascular, coronary and lung cancer incidence).

Methods: We applied five approaches in a multivariable Cox model to account for the first level of clustering corresponding to cohort specification: (1) not accounting for the cohort or using (2) indicator variables, (3) strata, (4) a frailty term in frailty Cox models, (5) a random intercept under a mixed Cox, for cohort

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The Triglyceride-Glucose Index and Obesity-Related Risk of End-Stage Kidney Disease in Austrian Adults

Josef Fritz, PhD; Wolfgang Brozek, PhD; Hans Concin, MD; Gabriele Nagel, MD; Julia Kerschbaum, MD; Karl Lhotta, MD; Hanno Ulmer, PhD; Emanuel Zitt, MD

Abstract

IMPORTANCE It is unknown whether the triglyceride-glucose (TyG) index as a measure of insulin resistance is associated with the risk of developing end-stage kidney disease (ESKD). Because individuals who are overweight or obese often develop insulin resistance, mediation of the association between body mass index (BMI) and ESKD risk through the TyG index seems plausible but has not been investigated.

OBJECTIVE To evaluate whether the TyG index is associated with ESKD risk and, if so, to what extent the TyG index mediates the association between BMI and ESKD.

DESIGN, SETTING, AND PARTICIPANTS A total of 176 420 individuals were recruited during routine health examinations to participate in the Austrian Vorarlberg Health Monitoring and Promotion Program (VHM&PP), a prospective, population-based cohort study with participant enrollment between January 1, 1988, and June 30, 2005, and a mean follow-up of 22.7 years. Data analysis was conducted from March 1, 2020, to September 30, 2020.

EXPOSURES Body mass index and the logarithmized product of fasting triglyceride and glucose concentrations (TyG index), as determined during the baseline health examination.

MAIN OUTCOMES AND MEASURES End-stage kidney disease, as indicated by initiation of kidney replacement therapy, either dialysis or kidney transplantation.

RESULTS Of the 176 420 participants, 94 885 were women (53.8%); mean (SD) age was 42.5 (15.4) years. During a mean (SD) follow-up of 22.7 (6.9) years, 454 (0.3%) participants developed ESKD and 35 234 (20.0%) died. In multivariable-adjusted Cox proportional hazards models, the TyG index was significantly associated with the risk of ESKD, both with (hazard ratio [HR] per 1-SD increase, 1.68; 95% CI, 1.56-1.82) and without (HR per 1-SD increase, 1.79; 95% CI, 1.66-1.93) the inclusion of BMI as a covariate. Mediation analysis using a newly proposed 2-stage regression method for survival data showed that a 5-point increase in BMI increased the risk of ESKD by 58% (HR [total association], 1.58; 95% CI, 1.43-1.75), and that 41.7% of the total association (95% CI, 31.6%-51.8%) was mediated through the TyG index (HR [indirect association], 1.21; 95% CI, 1.18-1.25).

CONCLUSIONS AND RELEVANCE This study found that the TyG index appeared to be associated with ESKD risk and mediates nearly half of the total association between BMI and ESKD in the general population. Public health efforts aiming at the reduction of body weight might decrease the kidney sequelae of insulin resistance and the burden of ESKD.

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Key Points

Question To what extent does the triglyceride-glucose index, a novel measure of insulin resistance, explain the association between body mass index and end-stage kidney disease risk?

Findings In this population-based cohort study of 176 420 Austrian participants, the triglyceride-glucose index was significantly associated with incident end-stage kidney disease risk. Approximately 40% of the association between body mass index and end-stage kidney disease was mediated through the triglyceride-glucose index.

Meaning The findings of this study appear to support the hypothesis of insulin resistance being an important intermediate in the association between obesity and end-stage kidney disease.

+ Supplemental content

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Serum uric acid is associated with incident hip fractures in women and men – Results from a large Austrian population-based cohort study

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Highlights

- High serum levels of uric acid were associated with the risk of hip fractures occurring at age 50 years and over.
- The risk association was stronger in men than in women.
- Hyperuricemia was associated with greater hip fracture risk in men but not women.
- Among covariates, high total cholesterol was associated with lower fracture risk.

Abstract

Objectives

Serum markers that can be used to estimate the risk of bone fractures are rare, and findings for one candidate marker, uric acid, are heterogeneous. Our aim was to investigate the potential of serum uric acid (SUA) to predict hip fractures occurring in people aged 50 years and over.

Study design

During a medical prevention program over the period 1985–2005 in Vorarlberg, baseline data were collected on SUA levels and covariates (age, BMI, blood pressure, smoking status, diabetes, triglycerides and cholesterol) from 185,397 individuals, of whom 42,488 women and 35,908 men met the inclusion criteria of this population-based cohort study. Information on incident cancer and end-stage kidney disease was acquired from registries.

Main outcome measure

Incident hip fracture occurring in participants aged 50 years and over during the observation period 2003–2013.

Results

SUA was associated with a rise in female hip fracture risk by 6% per unit increase (HR 1.06, 95 %-CI 1.01−1.10), and risk in the highest vs. lowest SUA quartile was significantly increased (HR 1.17, 95 %-CI 1.01−1.35), but not at hyperuricemic (>5.7 mg/dl) vs. normouricemic (≤5.7 mg/dl) levels. In men, hip fracture risk rose by 15 % per unit increase (HR 1.15, 95 %-CI 1.08−1.22), and risk was significantly higher in the highest vs. lowest SUA quartile (HR 1.50, 95 %-CI 1.17−1.91) as well as at hyperuricemic (>7.0 mg/dl) vs. normouricemic (≤7.0 mg/dl) levels (HR 1.48, 95 %-CI 1.19−1.84).

Conclusions

Our results link SUA with increased risk of hip fractures, particularly in men.

Keywords

Serum uric acid • Hip fracture • Vorarlberg Health Monitoring and Promotion Program • Osteoporosis

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP8368.

Long-Term Exposure to Fine Particle Elemental Components and Natural and Cause-Specific Mortality—a Pooled Analysis of Eight European Cohorts within the ELAPSE Project

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Background: Inconsistent associations between long-term exposure to particles with an aerodynamic diameter ≤2.5 μm [fine particulate matter ($PM_{2.5}$)] components and mortality have been reported, partly related to challenges in exposure assessment.

Objectives: We investigated the associations between long-term exposure to $PM_{2.5}$ elemental components and mortality in a large pooled European cohort; to compare health effects of $PM_{2.5}$ components estimated with two exposure modeling approaches, namely, supervised linear regression (SLR) and random forest (RF) algorithms.

Methods: We pooled data from eight European cohorts with 323,782 participants, average age 49 y at baseline (1985–2005). Residential exposure to 2010 annual average concentration of eight $PM_{2.5}$ components [copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V), and zinc (Zn)] was estimated with Europe-wide SLR and RF models at a 100 × 100 m scale. We applied Cox proportional hazards models to

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RESEARCH ARTICLE

Heterogeneous contributions of change in population distribution of body mass index to change in obesity and underweight

NCD Risk Factor Collaboration (NCD-RisC)*

Abstract From 1985 to 2016, the prevalence of underweight decreased, and that of obesity and severe obesity increased, in most regions, with significant variation in the magnitude of these changes across regions. We investigated how much change in mean body mass index (BMI) explains changes in the prevalence of underweight, obesity, and severe obesity in different regions using data from 2896 population-based studies with 187 million participants. Changes in the prevalence of underweight and total obesity, and to a lesser extent severe obesity, are largely driven by shifts in the distribution of BMI, with smaller contributions from changes in the shape of the distribution. In East and Southeast Asia and sub-Saharan Africa, the underweight tail of the BMI distribution was left behind as the distribution shifted. There is a need for policies that address all forms of malnutrition by making healthy foods accessible and affordable, while restricting unhealthy foods through fiscal and regulatory restrictions.

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Introduction

Underweight as well as obesity can lead to adverse health outcomes (***Prospective Studies Collaboration et al., 2009***; ***Global BMI Mortality Collaboration, 2016***; ***Emerging Risk Factors Collaboration et al., 2011***). For at least four decades, the prevalence of underweight has decreased, and that of obesity has increased, in most countries with significant variation in the magnitude of these changes across regions of the world (***NCD Risk Factor Collaboration (NCD-RisC), 2017a***; ***NCD Risk Factor Collaboration (NCD-RisC), 2019***).

A shift in the whole distribution of body mass index (BMI) would simultaneously affect mean BMI as well as the prevalence of underweight and obesity (***Razak et al., 2018***; ***Rose and Day, 1990***). In contrast, changes in the shape of BMI distribution – for example, widening or narrowing of the BMI distribution, becoming more or less skewed, or having a thinner or thicker tail – would affect the prevalence of underweight and obesity with only small impacts on the population mean, as shown schematically in ***Figure 1***. Understanding these two mechanisms is essential as they may require different public health and clinical responses (***Penman and Johnson, 2006***). But it is unclear how much the two mechanisms have contributed to the observed decline in underweight and rise in obesity in different world regions.

Some studies have investigated whether the rise in obesity or the decrease of underweight over time, or differences across countries, were due to a shift in BMI distribution versus changes in the low- or high-BMI tails of the distribution (***Razak et al., 2018***; ***Wang et al., 2007***; ***Wagner et al., 2019***; ***Vaezghasemi et al., 2016***; ***Razak et al., 2013***; ***Popkin and Slining, 2013***; ***Popkin, 2010***; ***Peeters et al., 2015***; ***Ouyang et al., 2015***; ***Monteiro et al., 2002***; ***Midthjell et al., 2013***; ***Lebel et al., 2018***; ***Khang and Yun, 2010***; ***Helmchen and Henderson, 2004***; ***Hayes et al., 2015***; ***Green et al., 2016***; ***Flegal and Troiano, 2000***; ***Stenholm et al., 2015***; ***Hayes et al., 2017***; ***Flegal et al., 2012***; ***Bovet et al., 2008***). Most of these studies focused on a single or small number of countries over relatively short durations or covered only one sex, a narrow age group, or specific

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Research paper

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

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ABSTRACT

Background: Prognostic implications of blood cholesterol may differ at different stages of life. This cohort study compares the value of total cholesterol (TC) readings earlier versus later in life for the prediction of coronary atherosclerosis, cardiovascular events, and cardiovascular death.
Methods: In a cardiovascular observation study (CVOS) we performed coronary angiography and prospectively recorded cardiovascular events in 1090 patients over up to 19 years. These patients had participated in a health survey (HS) 15 years prior to the CVOS baseline. TC was measured twice, first at the earlier HS and then later at CVOS recruiting.
Findings: Patients in the highest versus the lowest TC-category of the HS had an OR of 4.30 [2.41−7.65] for significant CAD at angiography, a HR of 1.74 [1.10−2.76] for cardiovascular events, and a HR of 7.55 [1.05−54.49] for cardiovascular death after multivariate adjustment. In contrast, TC as measured at the baseline of the CVOS was neither significantly associated with significant CAD (OR= 0.75 [0.49−1.13]) nor with cardiovascular events or death during follow-up (HR= 0.86 [0.62−1.18] and 0.79 [0.41−1.53], respectively). Moreover, the ESC/EAS-SCORE was found to be more powerful in predicting cardiovascular mortality when using earlier instead of later TC, with a continuous net reclassification improvement of 0.301 ($p<0.001$).
Interpretation: Early measurement not only enables early intervention in keeping with the concept of lifelong exposure to atherogenic lipoproteins. These data also suggest that cardiovascular risk prediction is more accurate if using earlier in life TC readings.
Funding: The present study did not receive any particular funding

1. Introduction

Ever since the early reports from the Framingham study [1], total serum cholesterol (TC) has become a standard in risk factor evaluation in human epidemiology and clinical medicine and as such is embedded in the Systematic COronary Risk Estimation (SCORE) chart predicting the risk for fatal cardiovascular disease in European populations [2]. According to SCORE, the 10-year risk for fatal cardiovascular events increases by approximately a factor of 4 between the ages of 50 and 65, provided that the other risk factors including TC remain

Abbreviations: AUC, area under the curve; CAD, coronary artery disease; CVOS, cardiovascular observation study; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HS, health survey; ROC, receiver operating characteristics; SCORE, Systematic COronary Risk Estimation; TC, total cholesterol; TC_{CVOS}, total cholesterol at cardiovascular observation study; TC_{HS}, total cholesterol at health survey

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Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project

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Long-term exposure to air pollution, especially from fossil fuel combustion sources such as motorised traffic, is associated with the development of asthma in adults, even at levels below the current EU and US limit values and possibly WHO guidelines https://bit.ly/2QW5yA7

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ABSTRACT

Background: Long-term exposure to ambient air pollution has been linked to childhood-onset asthma, although evidence is still insufficient. Within the multicentre project Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), we examined the associations of long-term exposures to particulate matter with a diameter <2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2) and black carbon (BC) with asthma incidence in adults.

Methods: We pooled data from three cohorts in Denmark and Sweden with information on asthma hospital diagnoses. The average concentrations of air pollutants in 2010 were modelled by hybrid land-use regression models at participants' baseline residential addresses. Associations of air pollution exposures with asthma incidence were explored with Cox proportional hazard models, adjusting for potential confounders.

Results: Of 98 326 participants, 1965 developed asthma during a mean follow-up of 16.6 years. We observed associations in fully adjusted models with hazard ratios of 1.22 (95% CI 1.04–1.43) per 5 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, 1.17 (95% CI 1.10–1.25) per 10 $\mu g \cdot m^{-3}$ for NO_2 and 1.15 (95% CI 1.08–1.23) per 0.5×10^{-5} m^{-1} for BC. Hazard ratios were larger in cohort subsets with exposure levels below the European Union and US limit values and possibly World Health Organization guidelines for $PM_{2.5}$ and NO_2. NO_2 and BC estimates remained unchanged in two-pollutant models with $PM_{2.5}$, whereas $PM_{2.5}$ estimates were attenuated to unity. The concentration–response curves showed no evidence of a threshold.

Conclusions: Long-term exposure to air pollution, especially from fossil fuel combustion sources such as motorised traffic, was associated with adult-onset asthma, even at levels below the current limit values.

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CANCER EPIDEMIOLOGY

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Metabolic factors and the risk of small intestine cancers: Pooled study of 800 000 individuals in the metabolic syndrome and cancer project

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Abstract

To explore the largely unknown etiology of small intestine cancer, we examined metabolic factors and risk of small intestine cancer overall and by subtypes. Among 404 220 women and 403 265 men in six European cohorts, we applied Cox regression with adjustment for smoking and body mass index (BMI), to calculate sex-specific hazard ratios (HRs) of small intestine cancer by levels of BMI, mean arterial pressure (MAP) and plasma total cholesterol, triglycerides and glucose. We also calculated HRs for these factors combined (metabolic score; MetS) and used Wald test statistics to investigate pairwise interactions between metabolic factors on risk. We also performed analyses separately per subtype (neuroendocrine tumors [NETs] and adenocarcinomas). During a median follow-up of 16.9 years, 144 women and 195 men were diagnosed with small intestine cancer, including 184 NETs and 99 adenocarcinomas. Among men, no main associations or interactions between metabolic factors were observed in relation to the risk of small intestine cancer. Among women, triglycerides were positively and linearly associated with risk (HR per standard deviation [SD]: 1.23, 95% confidence interval [CI]: 1.04-1.46), and a positive association was also observed for the MetS (HR per SD: 1.25, 95% CI: 1.02-1.52). Positive interactions were observed among women between triglycerides and cholesterol (P = .0005), and between MAP and glucose (P = .009), on risk. Glucose was positively associated with adenocarcinomas among women. This large, prospective study suggests that elevated triglycerides, and metabolic factors in interaction, confer an increased risk of small intestine cancer among women, but not among men.

Abbreviations: 40-y, The Age 40-program; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases-Oncology; log, logarithms naturalis; MAP, mean arterial pressure; Me-Can, Metabolic syndrome and Cancer project; MetS, metabolic score; MPP, Malmö Preventive Project; NCS, The Norwegian County Study; Oslo, The Oslo study I cohort; siNETs, small intestine neuroendocrine tumors; VHM&PP, The Vorarlberg Health Monitoring and Prevention Program; VIP, The Västerbotten Intervention Project.

Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants

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

Summary

Background Hypertension can be detected at the primary health-care level and low-cost treatments can effectively control hypertension. We aimed to measure the prevalence of hypertension and progress in its detection, treatment, and control from 1990 to 2019 for 200 countries and territories.

Methods We used data from 1990 to 2019 on people aged 30–79 years from population-representative studies with measurement of blood pressure and data on blood pressure treatment. We defined hypertension as having systolic blood pressure 140 mm Hg or greater, diastolic blood pressure 90 mm Hg or greater, or taking medication for hypertension. We applied a Bayesian hierarchical model to estimate the prevalence of hypertension and the proportion of people with hypertension who had a previous diagnosis (detection), who were taking medication for hypertension (treatment), and whose hypertension was controlled to below 140/90 mm Hg (control). The model allowed for trends over time to be non-linear and to vary by age.

Findings The number of people aged 30–79 years with hypertension doubled from 1990 to 2019, from 331 (95% credible interval 306–359) million women and 317 (292–344) million men in 1990 to 626 (584–668) million women and 652 (604–698) million men in 2019, despite stable global age-standardised prevalence. In 2019, age-standardised hypertension prevalence was lowest in Canada and Peru for both men and women; in Taiwan, South Korea, Japan, and some countries in western Europe including Switzerland, Spain, and the UK for women; and in several low-income and middle-income countries such as Eritrea, Bangladesh, Ethiopia, and Solomon Islands for men. Hypertension prevalence surpassed 50% for women in two countries and men in nine countries, in central and eastern Europe, central Asia, Oceania, and Latin America. Globally, 59% (55–62) of women and 49% (46–52) of men with hypertension reported a previous diagnosis of hypertension in 2019, and 47% (43–51) of women and 38% (35–41) of men were treated. Control rates among people with hypertension in 2019 were 23% (20–27) for women and 18% (16–21) for men. In 2019, treatment and control rates were highest in South Korea, Canada, and Iceland (treatment >70%; control >50%), followed by the USA, Costa Rica, Germany, Portugal, and Taiwan. Treatment rates were less than 25% for women and less than 20% for men in Nepal, Indonesia, and some countries in sub-Saharan Africa and Oceania. Control rates were below 10% for women and men in these countries and for men in some countries in north Africa, central and south Asia, and eastern Europe. Treatment and control rates have improved in most countries since 1990, but we found little change in most countries in sub-Saharan Africa and Oceania. Improvements were largest in high-income countries, central Europe, and some upper-middle-income and recently high-income countries including Costa Rica, Taiwan, Kazakhstan, South Africa, Brazil, Chile, Turkey, and Iran.

Interpretation Improvements in the detection, treatment, and control of hypertension have varied substantially across countries, with some middle-income countries now outperforming most high-income nations. The dual approach of reducing hypertension prevalence through primary prevention and enhancing its treatment and control is achievable not only in high-income countries but also in low-income and middle-income settings.

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Introduction

Hypertension, along with pre-hypertension and other hazardously high blood pressure, is responsible for 8·5 million deaths from stroke, ischaemic heart disease, other vascular diseases, and renal disease worldwide.[1,2] Hypertension can be detected in the

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Long-term exposure to air pollution and liver cancer incidence in six European cohorts

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Abbreviations: BC, black carbon; CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm (cohort); CI, confidence interval; CPS-II, Cancer Prevention Study II; DCH, Diet, Cancer and Health (cohort); DNC, Danish Nurse Cohort; DEHM, Danish Eulerian Hemispheric Model; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (cohort); EEA, European Environment Agency; ELAPSE, Effects of Low-Level Air Pollution (project); EPIC-MORGEN, EPIC-Monitoring Project on Risk Factor (cohort); EPIC-NL, Dutch European Investigation into Cancer and Nutrition (cohort); EPIC-PROSPECT, EPIC-Chronic Diseases in the Netherlands; ESCAPE, European Study of Cohorts for Air Pollution Effects (project); HR, hazard ratio; ICD-10, International Classification of diseases 10th version; ICD-9, International Classification of diseases ninth version; MAPLE, Mortality-Air Pollution Associations in Low-Exposure Environments (project); NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NUTS-1, Nomenclature of territorial units for statistics; O_3, ozone; PM, particulate matter; $PM_{2.5}$, particulate matter with diameter <2.5 μm; SALT, Stockholm Screening Across the Lifespan Twin study (cohort); SDPP, Stockholm Diabetes Prevention Program (cohort); SES, socioeconomic status; Sixty, Stockholm cohort of 60-year-olds (cohort); SNAC-K, Swedish National Study on Aging and Care in Kungsholmen (cohort); VHM&PP, Vorarlberg Health Monitoring and Prevention Program (cohort).

The Inverse Association of Body Mass Index with Lung Cancer: Exploring Residual Confounding, Metabolic Aberrations and Within-Person Variability in Smoking

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ABSTRACT

Background: The inverse observational association between body mass index (BMI) and lung cancer risk remains unclear. We assessed whether the association is explained by metabolic aberrations, residual confounding, and within-person variability in smoking, and compared against other smoking-related cancers.

Methods: We investigated the association between BMI, and its combination with a metabolic score (MS) of mid-blood pressure, glucose, and triglycerides, with lung cancer and other smoking-related cancers in 778,828 individuals. We used Cox regression, adjusted and corrected for within-person variability in smoking (status/pack-years), calculated from 600,201 measurements in 221,958 participants.

Results: Over a median follow-up of 20 years, 20,242 smoking-related cancers (6,735 lung cancers) were recorded. Despite adjustment and correction for substantial within-person variability in smoking, BMI remained inversely associated with lung cancer [HR per standard deviation increase, 0.87 (95% confidence interval 0.85–0.89)]. Individuals with BMI less than 25 kg/m^2 and high MS had the highest risk [HR 1.52 (1.44–1.60) vs. BMI ≥25 with low MS]. These associations were weaker and nonsignificant among nonsmokers. Similar associations were observed for head and neck cancers and esophageal squamous cell carcinoma, whereas for other smoking-related cancers, we generally observed positive associations with BMI.

Conclusions: The increased lung cancer risk with low BMI and high MS is unlikely due to residual confounding and within-person variability in smoking. However, similar results for other cancers strongly related to smoking suggest a remaining, unknown, effect of smoking.

Impact: Extensive smoking-adjustments may not capture all the effects of smoking on the relationship between obesity-related factors and risk of smoking-related cancers.

Introduction

Body mass index (BMI), a surrogate measure of obesity, has been related to higher risks of many cancer forms with some of the strongest associations found for smoking-related cancers, especially esophageal (adenocarcinoma), renal cell, and liver cancer (1–3). In contrast, a consistent inverse association has been reported for lung cancer (1–5). As smoking is strongly related to both lung cancer and lower body weight (6, 7), the inverse association has been proposed to be caused by residual confounding by insufficient adjustment for smoking (3, 8). Mendelian randomization studies, which under certain assumptions estimate causal associations (9), have not supported the inverse association with lung cancer (10–12), and several large observational studies showed no association among nonsmokers (3, 5, 13). However, some studies did show an inverse association among nonsmokers (14), or among smokers even after accounting for detailed smoking information (4, 5). Therefore, as alternative explanation for the inverse relationship between BMI and lung cancer, Renehan and colleagues suggested larger measurement error of smoking than of BMI (8). To our knowledge, this has not yet been investigated.

In contrast to BMI, waist circumference has been positively related to lung cancer risk (4, 15). A large prospective study by Yu and colleagues showed the highest lung cancer risk for low BMI and high waist circumference combined (4). This phenotype was associated with heavy smoking, but it was suggested that central obesity with lower muscle mass, and therefore retained BMI, and more metabolic aberrations potentially associated with lung cancer, could underlie these findings (4, 15). Investigating BMI and metabolic aberrations jointly, with extensive control for smoking habits, could clarify whether the association between BMI and lung cancer is dependent on the presence of metabolic aberrations, and whether the increased lung cancer risk with low BMI could potentially be reflective of a sarcopenic phenotype with metabolic aberrations.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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

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ABSTRACT

OBJECTIVE

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

DESIGN

Pooled analysis of eight cohorts.

SETTING

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

PARTICIPANTS

325 367 adults from the general population recruited mostly in the 1990s or 2000s with detailed lifestyle data. Stratified Cox proportional hazard models were used to analyse the associations between air pollution and mortality. Western Europe-wide land use regression models were used to characterise residential air pollution concentrations of ambient fine particulate matter ($PM_{2.5}$), nitrogen dioxide, ozone, and black carbon.

MAIN OUTCOME MEASURES

Deaths due to natural causes and cause specific mortality.

RESULTS

Of 325 367 adults followed-up for an average of 19.5 years, 47 131 deaths were observed. Higher exposure to $PM_{2.5}$, nitrogen dioxide, and black carbon was associated with significantly increased risk of almost all outcomes. An increase of 5 μg/m^3 in $PM_{2.5}$ was associated with 13% (95% confidence interval 10.6% to 15.5%) increase in natural deaths; the corresponding figure for a 10 μg/m^3 increase in nitrogen dioxide was 8.6% (7% to 10.2%). Associations with $PM_{2.5}$, nitrogen dioxide, and black carbon remained significant at low concentrations. For participants with exposures below the US standard of 12 μg/m^3 an increase of 5 μg/m^3 in $PM_{2.5}$ was associated with 29.6% (14% to 47.4%) increase in natural deaths.

CONCLUSIONS

Our study contributes to the evidence that outdoor air pollution is associated with mortality even at low pollution levels below the current European and North American standards and WHO guideline values. These findings are therefore an important contribution to the debate about revision of air quality limits, guidelines, and standards, and future assessments by the Global Burden of Disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In the framework of the update of the World Health Organization air quality guidelines, systematic reviews of studies of the effect of long term exposure to major outdoor air pollutants (fine particles, nitrogen dioxide, and ozone) have been done

Findings showed that long term exposure to ambient air pollution was significantly associated with natural and cause specific mortality, but associations at concentrations below current limit values were not well understood

WHAT THIS STUDY ADDS

Long term exposure to outdoor air pollution was positively associated with mortality even at levels well below the EU limit values, US Environmental Protection Agency national ambient air quality standards, and WHO air quality guidelines for fine particles and nitrogen dioxide

This new evidence supports reconsideration of existing guideline values and standards

The finding of associations at low levels of air pollution and mortality also supports policies to reduce air pollution below current legal limit values

Introduction

Epidemiological cohort studies have consistently found associations between long term exposure to outdoor air pollution and a range of morbidity and mortality endpoints. Concentrations of health relevant regulated pollutants, including fine particles and nitrogen dioxide, have decreased in the past decades in developed countries. Recent evaluations

Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project

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Summary

Background Long-term exposure to outdoor air pollution increases the risk of cardiovascular disease, but evidence is unclear on the health effects of exposure to pollutant concentrations lower than current EU and US standards and WHO guideline limits. Within the multicentre study Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), we investigated the associations of long-term exposures to fine particulate matter ($PM_{2·5}$), nitrogen dioxide (NO_2), black carbon, and warm-season ozone (O_3) with the incidence of stroke and acute coronary heart disease.

Methods We did a pooled analysis of individual data from six population-based cohort studies within ELAPSE, from Sweden, Denmark, the Netherlands, and Germany (recruited 1992–2004), and harmonised individual and area-level variables between cohorts. Participants (all adults) were followed up until migration from the study area, death, or incident stroke or coronary heart disease, or end of follow-up (2011–15). Mean 2010 air pollution concentrations from centrally developed European-wide land use regression models were assigned to participants' baseline residential addresses. We used Cox proportional hazards models with increasing levels of covariate adjustment to investigate the association of air pollution exposure with incidence of stroke and coronary heart disease. We assessed the shape of the concentration-response function and did subset analyses of participants living at pollutant concentrations lower than predefined values.

Findings From the pooled ELAPSE cohorts, data on 137 148 participants were analysed in our fully adjusted model. During a median follow-up of 17·2 years (IQR 13·8–19·5), we observed 6950 incident events of stroke and 10 071 incident events of coronary heart disease. Incidence of stroke was associated with $PM_{2·5}$ (hazard ratio 1·10 [95% CI 1·01–1·21] per 5 µg/m³ increase), NO_2 (1·08 [1·04–1·12] per 10 µg/m³ increase), and black carbon (1·06 [1·02–1·10] per $0·5\ 10^{-5}$/m increase), whereas coronary heart disease incidence was only associated with NO_2 (1·04 [1·01–1·07]). Warm-season O_3 was not associated with an increase in either outcome. Concentration-response curves indicated no evidence of a threshold below which air pollutant concentrations are not harmful for cardiovascular health. Effect estimates for $PM_{2·5}$ and NO_2 remained elevated even when restricting analyses to participants exposed to pollutant concentrations lower than the EU limit values of 25 µg/m³ for $PM_{2·5}$ and 40 µg/m³ for NO_2.

Interpretation Long-term air pollution exposure was associated with incidence of stroke and coronary heart disease, even at pollutant concentrations lower than current limit values.

Funding Health Effects Institute.

Introduction

Ambient air pollution has decreased in recent decades in Europe and North America, but epidemiological studies in Australia, Canada, and the USA have suggested adverse health effects even at very low concentrations of pollution.[1–7] However, most of these studies investigated mortality and less evidence is available for incident disease.[8–12] According to WHO, cardiovascular disease is the leading cause of death worldwide and accountable for a large share of morbidity and health-care costs.[13] Thus, assessing the specific air pollution-related health burden of cardiovascular disease is crucial to inform policy makers. Such an assessment is especially important in view of upcoming revisions to the air quality directive in Europe,[14] the US national ambient air quality standard for particulate matter (PM)[15] and the WHO air quality guidelines.

Of all types of cardiovascular disease, coronary heart disease and stroke constitute the most frequent

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ORIGINAL ARTICLE

Thirty years of hip fracture incidence in Austria: is the worst over?

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Abstract

Summary Nationwide hip fracture incidence in the Austrian population was assessed over a period of 30 years (1989–2018), including 20 years data from a previous study and a recent 10 years follow-up. While absolute numbers in men continued to increase, absolute numbers in women and age-standardized incidences in both men and women decreased.

Purpose In the Austrian population ≥ 50 years, nationwide hip fracture incidences over a period of 20 years (1989–2008) have shown an initial steep increase, followed by a leveling-off during the last few years of observation. The purpose of the present study was to follow up on hip fracture incidences for another 10 years (2009–2018) and to analyze trends over the entire period of 30 years.

Methods ICD-10 code classes S72.0, S72.1, and S72.2 were applied. All data were retrieved from the Statistics Austria database and its hospital discharge register. Annual absolute numbers, crude and age-standardized incidences, and incidence rate ratios (IRR) were stratified by sex and 5-year age intervals, and calculated by using a correction factor for multiple registrations.

Results Total number of hip fracture cases increased from 13,984 (2009) to 14,640 (2015), and decreased thereafter to 14,457 (2018), despite a persistent increase in men. Age-standardized incidences peaked at 476/100,000 (2010), followed by a decrease to 408/100,000 (2018). The observed overall decrease was mainly driven by the female population. Incidence rate ratios (IRRs) yielded a statistically significant average annual decrease of age-standardized incidences in both women and men (ΔIRR 0.984; 0.981–0.987).

Conclusion While absolute numbers of hip fracture in women showed a slight decrease during the last 10 years of observation, numbers in men continued to increase. Age-standardized incidences nevertheless decreased in both men and women, which may be interpreted as a trend in the right direction. However, due to the rapid aging of the population, it cannot be precluded that this trend will be compromised during the next few decades.

Keywords Epidemiology · Hip fracture · Austria · Incidence trend

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1]. Among osteoporotic fractures, hip fracture has been recognized as the most serious one because of its consequences in regard to premature death, disability, chronic pain, and diminished quality of life [2].

Austria, located in the southern part of Central Europe, counted some 8.9 million inhabitants in 2019 [3]. Similar to other countries in the European Union, the present-day age pyramid shows a narrow base due to a reduction in birth

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Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project

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Summary

Background Long-term exposure to ambient air pollution has been associated with premature mortality, but associations at concentrations lower than current annual limit values are uncertain. We analysed associations between low-level air pollution and mortality within the multicentre study Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE).

Methods In this multicentre longitudinal study, we analysed seven population-based cohorts of adults (age ≥30 years) within ELAPSE, from Belgium, Denmark, England, the Netherlands, Norway, Rome (Italy), and Switzerland (enrolled in 2000–11; follow-up until 2011–17). Mortality registries were used to extract the underlying cause of death for deceased individuals. Annual average concentrations of fine particulate matter ($PM_{2·5}$), nitrogen dioxide (NO_2), black carbon, and tropospheric warm-season ozone (O_3) from Europe-wide land use regression models at 100 m spatial resolution were assigned to baseline residential addresses. We applied cohort-specific Cox proportional hazard models with adjustment for area-level and individual-level covariates to evaluate associations with non-accidental mortality, as the main outcome, and with cardiovascular, non-malignant respiratory, and lung cancer mortality. Subset analyses of participants living at low pollutant concentrations (as per predefined values) and natural splines were used to investigate the concentration-response function. Cohort-specific effect estimates were pooled in a random-effects meta-analysis.

Findings We analysed 28 153 138 participants contributing 257 859 621 person-years of observation, during which 3 593 741 deaths from non-accidental causes occurred. We found significant positive associations between non-accidental mortality and $PM_{2·5}$, NO_2, and black carbon, with a hazard ratio (HR) of 1·053 (95% CI 1·021–1·085) per 5 μg/m³ increment in $PM_{2·5}$, 1·044 (1·019–1·069) per 10 μg/m³ NO_2, and 1·039 (1·018–1·059) per $0·5\times10^{-5}$/m black carbon. Associations with $PM_{2·5}$, NO_2, and black carbon were slightly weaker for cardiovascular mortality, similar for non-malignant respiratory mortality, and stronger for lung cancer mortality. Warm-season O_3 was negatively associated with both non-accidental and cause-specific mortality. Associations were stronger at low concentrations: HRs for non-accidental mortality at concentrations lower than the WHO 2005 air quality guideline values for $PM_{2·5}$ (10 μg/m³) and NO_2 (40 μg/m³) were 1·078 (1·046–1·111) per 5 μg/m³ $PM_{2·5}$ and 1·049 (1·024–1·075) per 10 μg/m³ NO_2. Similarly, the association between black carbon and non-accidental mortality was highest at low concentrations, with a HR of 1·061 (1·032–1·092) for exposure lower than $1·5\times10^{-5}$/m, and 1·081 (0·966–1·210) for exposure lower than $1·0\times10^{-5}$/m.

Interpretation Long-term exposure to concentrations of $PM_{2·5}$ and NO_2 lower than current annual limit values was associated with non-accidental, cardiovascular, non-malignant respiratory, and lung cancer mortality in seven large European cohorts. Continuing research on the effects of low concentrations of air pollutants is expected to further inform the process of setting air quality standards in Europe and other global regions.

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ARTICLE

Long-term exposure to ambient air pollution and bladder cancer incidence in a pooled European cohort: the ELAPSE project

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BACKGROUND: The evidence linking ambient air pollution to bladder cancer is limited and mixed.
METHODS: We assessed the associations of bladder cancer incidence with residential exposure to fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), warm season ozone (O_3) and eight $PM_{2.5}$ elemental components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) in a pooled cohort ($N = 302{,}493$). Exposures were primarily assessed based on 2010 measurements and back-extrapolated to the baseline years. We applied Cox proportional hazard models adjusting for individual- and area-level potential confounders.
RESULTS: During an average of 18.2 years follow-up, 967 bladder cancer cases occurred. We observed a positive though statistically non-significant association between $PM_{2.5}$ and bladder cancer incidence. Hazard Ratios (HR) were 1.09 (95% confidence interval (CI): 0.93–1.27) per 5 μg/m^3 for 2010 exposure and 1.06 (95% CI: 0.99–1.14) for baseline exposure. Effect estimates for NO_2, BC and O_3 were close to unity. A positive association was observed with $PM_{2.5}$ zinc (HR 1.08; 95% CI: 1.00–1.16 per 10 ng/m^3).
CONCLUSIONS: We found suggestive evidence of an association between long-term $PM_{2.5}$ mass exposure and bladder cancer, strengthening the evidence from the few previous studies. The association with zinc in $PM_{2.5}$ suggests the importance of industrial emissions.

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

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ABSTRACT

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

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

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

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

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Excess body weight is associated with an increased risk of incident CKD, kidney function decline, and development of ESKD in the general population.[1–4] Despite this evident and strong epidemiologic link, the underlying biologic mechanisms still remain unclear. Metabolic factors linked to excess body weight, such as insulin resistance, hypertension, hyperuricemia, and dyslipidemia, may act as causal intermediates in the relationship between overweight/obesity and renal risk, but their relative contributions in this relationship are unknown.[5–9]

Insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia are established metabolic risk factors that have been associated with risk of various diseases, such as cardiovascular disease, CKD, and ESKD.[5,10–21] Overweight and obesity are

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

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Osteoporosis International **33**, 1295–1307 (2022)

Abstract

Summary

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

Introduction

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

Methods

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

Results

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

Conclusions

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

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Article

Long-Term Exposure to Source-Specific Fine Particles and Mortality—A Pooled Analysis of 14 European Cohorts within the ELAPSE Project

Jie Chen,* Gerard Hoek, Kees de Hoogh, Sophia Rodopoulou, Zorana J. Andersen, Tom Bellander, Jørgen Brandt, Daniela Fecht, Francesco Forastiere, John Gulliver, Ole Hertel, Barbara Hoffmann, Ulla Arthur Hvidtfeldt, W. M. Monique Verschuren, Karl-Heinz Jöckel, Jeanette T. Jørgensen, Klea Katsouyanni, Matthias Ketzel, Diego Yacamán Méndez, Karin Leander, Shuo Liu, Petter Ljungman, Elodie Faure, Patrik K. E. Magnusson, Gabriele Nagel, Göran Pershagen, Annette Peters, Ole Raaschou-Nielsen, Debora Rizzuto, Evangelia Samoli, Yvonne T. van der Schouw, Sara Schramm, Gianluca Severi, Massimo Stafoggia, Maciej Strak, Mette Sørensen, Anne Tjønneland, Gudrun Weinmayr, Kathrin Wolf, Emanuel Zitt, Bert Brunekreef, and George D. Thurston

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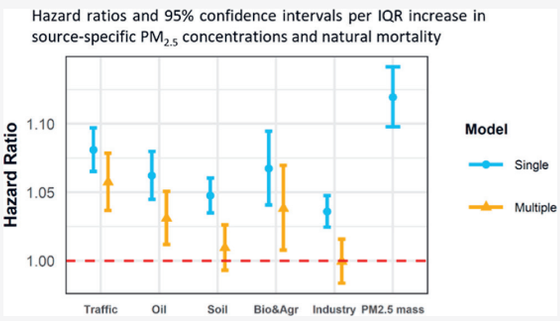
ABSTRACT: We assessed mortality risks associated with source-specific fine particles ($PM_{2.5}$) in a pooled European cohort of 323,782 participants. Cox proportional hazard models were applied to estimate mortality hazard ratios (HRs) for source-specific $PM_{2.5}$ identified through a source apportionment analysis. Exposure to 2010 annual average concentrations of source-specific $PM_{2.5}$ components was assessed at baseline residential addresses. The source apportionment resulted in the identification of five sources: traffic, residual oil combustion, soil, biomass and agriculture, and industry. In single-source analysis, all identified sources were significantly positively associated with increased natural mortality risks. In multisource analysis, associations with all sources attenuated but remained statistically significant with traffic, oil, and biomass and agriculture. The highest association per interquartile increase was observed for the traffic component (HR: 1.06; 95% CI: 1.04 and 1.08 per 2.86 $\mu g/m^3$ increase) across five identified sources. On a 1 $\mu g/m^3$ basis, the residual oil-related $PM_{2.5}$ had the strongest association (HR: 1.13; 95% CI: 1.05 and 1.22), which was substantially higher than that for generic $PM_{2.5}$ mass, suggesting that past estimates using the generic $PM_{2.5}$ exposure response function have underestimated the potential clean air health benefits of reducing fossil-fuel combustion. Source-specific associations with cause-specific mortality were in general consistent with findings of natural mortality.



KEYWORDS: *source apportionment, fine particulate matter ($PM_{2.5}$), absolute principal component analysis (APCA), mortality*

1. INTRODUCTION

Epidemiological studies around the world have generally reported associations between fine particle mass ($PM_{2.5}$) exposure and mortality and morbidity, with variations in the magnitude of effect estimates.[1] Part of these effect size fluctuations per unit mass may be related to the fact that the composition of $PM_{2.5}$ mass varies in time and space, depending on sources of emission and atmospheric chemistry, which may in turn result in differences in toxicity and risk to health of $PM_{2.5}$ mass.[2−5] Understanding which components of the PM mixture are of greater health impact than others would help inform targeted policies to control $PM_{2.5}$ from those sources that contribute most of the toxic components in the PM mixture as well as allow more accurate assessments of source-specific health impacts.

To date, many studies have reported associations between adverse health outcomes and long-term exposure to a series of $PM_{2.5}$ constituents, including secondary inorganic aerosols

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ORIGINAL ARTICLE

Long-term Air Pollution Exposure and Pneumonia-related Mortality in a Large Pooled European Cohort

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Abstract

Rationale: Ambient air pollution exposure has been linked to mortality from chronic cardiorespiratory diseases, while evidence on respiratory infections remains more limited.

Objectives: We examined the association between long-term exposure to air pollution and pneumonia-related mortality in adults in a pool of eight European cohorts.

Methods: Within the multicenter project ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe), we pooled data from eight cohorts among six European countries. Annual mean residential concentrations in 2010 for fine particulate matter, nitrogen dioxide (NO_2), black carbon (BC), and ozone were estimated using Europe-wide hybrid land-use regression models. We applied stratified Cox proportional hazard models to investigate the associations between air pollution and pneumonia, influenza, and acute lower respiratory infections (ALRI) mortality.

Measurements and Main Results: Of 325,367 participants, 712 died from pneumonia and influenza combined, 682 from pneumonia, and 695 from ALRI during a mean follow-up of 19.5 years. NO_2 and BC were associated with 10–12% increases in pneumonia and influenza combined mortality, but 95% confidence intervals included unity (hazard ratios, 1.12 [0.99–1.26] per 10 μg/m^3 for NO_2; 1.10 [0.97–1.24] per 0.5 10^{-5}m^{-1} for BC). Associations with pneumonia and ALRI mortality were almost identical. We detected effect modification suggesting stronger associations with NO_2 or BC in overweight, employed, or currently smoking participants compared with normal weight, unemployed, or nonsmoking participants.

Conclusions: Long-term exposure to combustion-related air pollutants NO_2 and BC may be associated with mortality from lower respiratory infections, but larger studies are needed to estimate these associations more precisely.

Keywords: air pollution; respiratory infections; long-term exposure; adults

Acute lower respiratory infections (ALRI), including pneumonia (infection of lung alveoli), as well as infections of the airways, such as bronchitis and influenza, are common respiratory diseases that pose a large burden and can be life-threatening, ranking as the fourth leading cause of death worldwide in 2017 (1). Pneumonia is the most common ALRI, caused by viruses, bacteria, or fungi. While there is a general decline in the pneumonia mortality rate in European countries (2), pneumonia remains the most frequent cause of death from infection, especially in children and older people (3, 4). Short-term exposure to air

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Full length article

Exposure to surrounding greenness and natural-cause and cause-specific mortality in the ELAPSE pooled cohort

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Long-term air pollution exposure and malignant intracranial tumours of the central nervous system: a pooled analysis of six European cohorts

Ulla Arthur Hvidtfeldt, Jie Chen, Sophia Rodopoulou, Maciej Strak, Kees de Hoogh, Zorana J. Andersen, Tom Bellander, Jørgen Brandt, Daniela Fecht, Francesco Forastiere, John Gulliver, Ole Hertel, Barbara Hoffmann, Klea Katsouyanni, Matthias Ketzel, Karin Leander, Patrik K. E. Magnusson, Gabriele Nagel, Göran Pershagen, Debora Rizzuto, Evangelia Samoli, Rina So, Massimo Stafoggia, Anne Tjønneland, … Ole Raaschou-Nielsen + Show authors

British Journal of Cancer **129**, 656–664 (2023)

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Abstract

Background

Risk factors for malignant tumours of the central nervous system (CNS) are largely unknown.

Methods

We pooled six European cohorts (*N* = 302,493) and assessed the association between residential exposure to nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), black carbon (BC), ozone (O_3) and eight elemental components of $PM_{2.5}$ (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) and malignant intracranial CNS tumours defined according to the International Classification of Diseases ICD-9/ICD-10 codes 192.1/C70.0, 191.0–191.9/C71.0–C71.9, 192.0/C72.2–C72.5. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results

During 5,497,514 person-years of follow-up (average 18.2 years), we observed 623 malignant CNS tumours. The results of the fully adjusted linear analyses showed a hazard ratio (95% confidence interval) of 1.07 (0.95, 1.21) per 10 $\mu g/m^3$ NO_2, 1.17 (0.96, 1.41) per 5 $\mu g/m^3$ $PM_{2.5}$, 1.10 (0.97, 1.25) per 0.5 $10^{-5}m^{-1}$ BC, and 0.99 (0.84, 1.17) per 10 $\mu g/m^3$ O_3.

Conclusions

We observed indications of an association between exposure to NO_2, $PM_{2.5}$, and BC and tumours of the CNS. The PM elements were not consistently associated with CNS tumour incidence.

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Full length article

Long-term exposure to air pollution and mortality from dementia, psychiatric disorders, and suicide in a large pooled European cohort: ELAPSE study

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Full length article

Long-term air pollution exposure and Parkinson's disease mortality in a large pooled European cohort: An ELAPSE study

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Breast Cancer Incidence in Relation to Long-Term Low-Level Exposure to Air Pollution in the ELAPSE Pooled Cohort

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Abstract

Background: Established risk factors for breast cancer include genetic disposition, reproductive factors, hormone therapy, and lifestyle-related factors such as alcohol consumption, physical inactivity, smoking, and obesity. More recently a role of environmental exposures, including air pollution, has also been suggested. The aim of this study, was to investigate the relationship between long-term air pollution exposure and breast cancer incidence.

Methods: We conducted a pooled analysis among six European cohorts (n = 199,719) on the association between long-term residential levels of ambient nitrogen dioxide (NO2), fine particles (PM2.5), black carbon (BC), and ozone in the warm season (O3) and breast cancer incidence in women. The selected cohorts represented the lower range of air pollutant concentrations in Europe. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results: During 3,592,885 person-years of follow-up, we observed a total of 9,659 incident breast cancer cases. The results of the fully adjusted linear analyses showed a HR (95% confidence interval) of 1.03 (1.00-1.06) per 10 µg/m^3 NO2, 1.06 (1.01-1.11) per 5 µg/m^3 PM2.5, 1.03 (0.99-1.06) per 0.5 10-5 m-1 BC, and 0.98 (0.94-1.01) per 10 µg/m^3 O3. The effect estimates were most pronounced in the group of middle-aged women (50-54 years) and among never smokers.

Conclusions: The results were in support of an association between especially PM2.5 and breast cancer.

Impact: The findings of this study suggest a role of exposure to NO2, PM2.5, and BC in development of breast cancer.

Originalarbeit

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Soziale Ungleichheit in der Zahngesundheit von Kindern

Behandlungsbedürftige Karies der 6- bis 12-jährigen Volksschulkinder in Vorarlberg (Österreich) in Bezug zu regionalen sozioökonomischen Determinanten und Migration

Hintergrund und Fragestellung

Sozioökonomische Determinanten wie Bildung, Einkommen und Beschäftigung sowie Migrationshintergrund sind Risikofaktoren in Bezug auf die Kariesentstehung bei Kindern [2, 4, 19]. Aufgrund der hohen Prävalenzen von behandlungsbedürftiger Karies, dem starken sozialen Gradienten sowie der schlechten Datenlage der Altersgruppe der Volksschulkinder wird in dieser Studie die gesundheitliche Ungleichheit in Bezug zu behandlungsbedürftiger Karies von Volksschulkindern in Vorarlberg untersucht.

Ziel der Arbeit war es, den Zusammenhang zwischen regionalen sozioökonomischen Determinanten, dem Migrationshintergrund der Kinder und behandlungsbedürftiger Karies bei Volksschulkindern in Vorarlberg im Schuljahr 2016/17 zu untersuchen.

Studiendesign und Untersuchungsmethoden

Zahnprophylaktische Gruppenuntersuchung

Zugrunde liegen die Daten der zahnprophylaktischen Gruppenuntersuchungen an Vorarlberger Kindergärten und Schulberg jährlich und kostenfrei von Zahnärzt*innen auf Karies und Zahnfehlstellungen untersucht werden. Die Gruppenuntersuchungen sind Teil des Präventionsprogramms „Max Prophylax", welches noch weitere zahnprophylaktische Maßnahmen umfasst [22]. Die Studie schließt dabei nur die Daten der 6- bis 12-jährigen Volksschulkinder ein. Die zahnärztliche Untersuchung wird mit Hilfe eines Spiegels und bei Bedarf unter Zuhilfenahme einer Sonde bzw. eines Luftpusters durchgeführt [21]. Altersspezifische Mittelwerte und Standardabweichungen (SD) bei der Bestimmung der Schwere der Karies werden mittels dt-Index (Anzahl der unbehandelten kariösen Milchzähne) und Dt-Index (Anzahl der unbehandelten kariösen bleibenden Zähne) nach WHO-Methodik [13] angegeben. Der Behandlungsbedarf beschreibt die aktuelle Kariesprävalenz, dabei gelten Kinder mit einem und mehr unbehandelten kariösen Zähnen als behandlungsbedürftig. Bei der Auswertung wurde nur Dentinkaries und nicht die Kariesvorstufen eingeschlossen. Demnach wird Karies erst im Stadium der Kavitation, d. h. wenn ein Hohlraum bereits im Zahnschmelz sichtbar ist, diagnostiziert [10]. Da die Untersuchung gesetzlich nicht verpflichtend ist, ist davon auszugehen, dass nicht fehlenden und unplausiblen Werten ausgeschlossen ($n = 56$). Wenn Kinder am Tag der Untersuchung nicht anwesend waren oder die Untersuchung verweigert haben, wurden diese nicht erfasst. Es wurde angenommen, dass diese Kinder zufällig fehlten.

Auswahl der regionalen Sozialindikatoren

Da bei den zahnprophylaktischen Gruppenuntersuchungen keine individuellen Indikatoren zum sozioökonomischen Status (SES) erhoben werden, wurden diese über regionale Indikatoren abgebildet. Die Auswahl der Indikatoren auf Gemeindeebene orientiert sich an dem deutschen regionalen sozioökonomischen Deprivationsindex, der sozioökonomische Ungleichheiten in Bezug zu Gesundheit auf regionaler Ebene abbildet [7]. Als regionale Indikatoren auf Gemeindeebene wurden das durchschnittliche Jahresbruttogehalt, die Arbeitslosenquote (in %) und der Anteil der Personen mit Tertiärabschluss herangezogen. Die Sozialindikatoren für das Jahr 2017 wurden den amtlichen Statistiken der Statistik Austria entnommen. Der Migrationshintergrund der Kinder wurde mittels des Anteils der

Article

Diminishing benefits of urban living for children and adolescents' growth and development

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NCD Risk Factor Collaboration (NCD-RisC)*

Optimal growth and development in childhood and adolescence is crucial for lifelong health and well-being[1–6]. Here we used data from 2,325 population-based studies, with measurements of height and weight from 71 million participants, to report the height and body-mass index (BMI) of children and adolescents aged 5–19 years on the basis of rural and urban place of residence in 200 countries and territories from 1990 to 2020. In 1990, children and adolescents residing in cities were taller than their rural counterparts in all but a few high-income countries. By 2020, the urban height advantage became smaller in most countries, and in many high-income western countries it reversed into a small urban-based disadvantage. The exception was for boys in most countries in sub-Saharan Africa and in some countries in Oceania, south Asia and the region of central Asia, Middle East and north Africa. In these countries, successive cohorts of boys from rural places either did not gain height or possibly became shorter, and hence fell further behind their urban peers. The difference between the age-standardized mean BMI of children in urban and rural areas was <1.1 kg m^{-2} in the vast majority of countries. Within this small range, BMI increased slightly more in cities than in rural areas, except in south Asia, sub-Saharan Africa and some countries in central and eastern Europe. Our results show that in much of the world, the growth and developmental advantages of living in cities have diminished in the twenty-first century, whereas in much of sub-Saharan Africa they have amplified.

The growth and development of school-aged children and adolescents (ages 5–19 years) are influenced by their nutrition and environment at home, in the community and at school. Healthy growth and development at these ages help consolidate gains and mitigate inadequacies from early childhood and vice versa[1], with lifelong implications for health and well-being[2–6]. Until recently, the growth and development of older children and adolescents received substantially less attention than in early childhood and adulthood[7]. Increasing attention on the importance of health and nutrition during school years has been accompanied by a presumption that differences in nutrition and the environment lead to distinct, and generally less healthy, patterns of growth and development at these ages in cities compared to rural areas[8–17]. This presumption is despite some empirical studies showing that food quality and nutrition are better in cities[18,19].

Data on growth and developmental outcomes during school ages are needed, alongside data on the efficacy of specific interventions and policies, to select and prioritize policies and programmes that promote health and health equity, both for the increasing urban population and for children who continue to grow up in rural areas. Consistent and comparable global data also help benchmark across countries and territories and draw lessons on good practice. Yet, globally, there are fewer data on growth trajectories in rural and urban areas in these formative ages than for children under 5 years of age[20] or for adults[21]. The available studies have been in one country, at one point in time and/or in one sex and narrow age groups. The few studies that covered more than one country[22–24] mostly focused on older girls and used at most a few dozen data sources and hence could not systematically measure long-term trends. Consequently, many policies and programmes that aim to enhance healthy growth and development in school ages focus narrowly and generically on specific features of nutrition or the environment in either cities or rural areas[10,13,25–28]. Little attention has been paid to the similarities and differences between relevant outcomes in these settings or to the heterogeneity of the urban–rural differences across countries.

Here we report on the mean height and BMI of school-aged children and adolescents residing in rural and urban areas of 200 countries and territories (referred to as countries hereafter) from 1990 to 2020. Height and BMI are anthropometric measures of growth and development that are influenced by the quality of nutrition and healthiness of the living environment and are highly predictive of health and well-being throughout life in observational and Mendelian randomization studies[2–6]. These studies have shown that having low height and excessively low BMI increases the risk of morbidity and mortality, and low height impairs cognitive development and reduces educational performance and work productivity in later life[2–4]. A high BMI in these

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Article

Metabolically (un)healthy obesity and risk of obesity-related cancers: a pooled study

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Abstract

Background: Studies of obesity with or without metabolic aberrations, commonly termed *metabolically unhealthy* or *healthy obesity*, in relation to cancer risk are scarce.

Methods: We investigated body mass index (normal weight, overweight, obesity) jointly and in interaction with metabolic health status in relation to obesity-related cancer risk (n = 23 630) among 797 193 European individuals. A metabolic score comprising mid-blood pressure, plasma glucose, and triglycerides was used to define metabolically healthy and unhealthy status. Hazard ratios (HRs) and multiplicative interactions were assessed using Cox regression, and additive interactions were assessed using the relative excess risk for interaction. All statistical tests were 2-sided.

Results: Metabolically unhealthy obesity, with a baseline prevalence of 7%, was, compared with metabolically healthy normal weight, associated with an increased relative risk of any obesity-related cancer and of colon, rectal, pancreas, endometrial, liver, gallbladder, and renal cell cancer ($P < .05$), with the highest risk estimates for endometrial, liver, and renal cell cancer (HR = 2.55-3.00). Metabolically healthy obesity showed a higher relative risk for any obesity-related cancer and colon (in men), endometrial, renal cell, liver, and gallbladder cancer, though the risk relationships were weaker. There were no multiplicative interactions, but there were additive, positive interactions between body mass index and metabolic health status on obesity-related and rectal cancer among men and on endometrial cancer ($P < .05$).

Conclusions: This study highlights that the type of metabolic obesity phenotype is important when assessing obesity-related cancer risk. In general, metabolic aberrations further increased the obesity-induced cancer risk, suggesting that obesity and metabolic aberrations are useful targets for prevention.

Obesity is an established risk factor for several cancers (1,2). It is often accompanied by metabolic aberrations, which have been a commonly proposed mechanism to link obesity with cancer (3,4). The metabolic syndrome, a cluster of conditions including obesity and metabolic aberrations, has been shown to be associated with an increased risk of some obesity-related cancers (5,6), such as pancreatic (5-9), postmenopausal breast (5,10), liver (5,6,11,12), colorectal (5,6,13,14), endometrial (5,6,15,16), and renal cell cancer (6,17).

During the last decade, obesity with or without metabolic aberrations, commonly termed *metabolically unhealthy* or *healthy obesity*, has been extensively investigated in the cardiovascular field (18-20); however, studies regarding cancer are limited. A meta-analysis published in 2020 showed an increased risk of cancer among metabolically healthy obese individuals, but it was based on only 7 studies of different cancer forms and did not summarize the findings for other combinations of body size and metabolic health status (21). A recent prospective study did this

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Exposure to ambient air pollution and elevated blood levels of gamma-glutamyl transferase in a large Austrian cohort

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Jan Wirsching, Gabriele Nagel, Ming-Yi Tsai, Kees de Hoogh, Andrea Jaensch, Bernhard Anwander, Ranjeet S. Sokhi, Hanno Ulmer, Emanuel Zitt, Hans Concin, Bert Brunekreef, Gerard Hoek, Gudrun Weinmayr

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Highlights

- Air pollution is affecting GGT, a marker of oxidative stress and liver disease.
- Relevant sources appear to be traffic, wood burning and long range transported PM.
- Associations with sulfur seem to be independent of metals (Cu, Fe, Ni, Zn).
- Associations below EU limits stress importance of revising air quality regulation.

Abstract

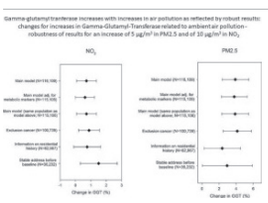
Gamma glutamyl transferase (GGT) is related to oxidative stress and an indicator for liver damage. We investigated the association between air pollution and GGT in a large Austrian cohort (*N* = 116,109) to better understand how air pollution affects human health.

Data come from voluntary prevention visits that were routinely collected within the Vorarlberg Health Monitoring and Prevention Program (VHM&PP). Recruitment was ongoing from 1985 to 2005. Blood was drawn and GGT measured centralized in two laboratories. Land use regression models were applied to estimate individuals' exposure at their home address for particulate matter (PM) with a diameter of <2.5 μm (PM2.5), <10 μm (PM10), fraction between 10 μm and 2.5 μm (PMcoarse), as well as PM2.5 absorbance (PM2.5abs), NO_2, NO_x and eight components of PM. Linear regression models, adjusting for relevant individual and community-level confounders were calculated.

The study population was 56% female with a mean age of 42 years and mean GGT was 19.0 units. Individual PM2.5 and NO_2 exposures were essentially below European limit values of 25 and 40 μg/m^3, respectively, with means of 13.58 μg/m^3 for PM2.5 and 19.93 μg/m^3 for NO_2. Positive associations were observed for PM2.5, PM10, PM2.5abs, NO_2, NO_x, and Cu, K, S in PM2.5 and PM10 fractions and Zn mainly in PM2.5 fraction. The strongest association per interquartile range observed was an increase of serum GGT concentration by 1.40% (95%-CI: 0.85%; 1.95%) per 45.7 ng/m^3 S in PM2.5. Associations were robust to adjustments for other biomarkers, in two-pollutant models and the subset with a stable residential history.

We found that long-term exposure to air pollution (PM2.5, PM10, PM2.5abs, NO_2, NO_x) as well as certain elements, were positively associated with baseline GGT levels. The elements associated suggest a role of traffic emissions, long range transport and wood burning.

Graphical abstract



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Keywords

GGT; Nitrogen oxides; Particulate matter; Long-term exposure; Sources; Chemical elements

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Long-term air pollution exposure and malignant intracranial tumours of the central nervous system: a pooled analysis of six European cohorts

Ulla Arthur Hvidtfeldt, Jie Chen, Sophia Rodopoulou, Maciej Strak, Kees de Hoogh, Zorana J. Andersen, Tom Bellander, Jørgen Brandt, Daniela Fecht, Francesco Forastiere, John Gulliver, Ole Hertel, Barbara Hoffmann, Klea Katsouyanni, Matthias Ketzel, Karin Leander, Patrik K. E. Magnusson, Gabriele Nagel, Göran Pershagen, Debora Rizzuto, Evangelia Samoli, Rina So, Massimo Stafoggia, Anne Tjønneland, ... Ole Raaschou-Nielsen + Show authors

British Journal of Cancer **129**, 656–664 (2023)

Abstract

Background

Risk factors for malignant tumours of the central nervous system (CNS) are largely unknown.

Methods

We pooled six European cohorts (*N* = 302,493) and assessed the association between residential exposure to nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), black carbon (BC), ozone (O_3) and eight elemental components of $PM_{2.5}$ (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) and malignant intracranial CNS tumours defined according to the International Classification of Diseases ICD-9/ICD-10 codes 192.1/C70.0, 191.0–191.9/C71.0–C71.9, 192.0/C72.2–C72.5. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results

During 5,497,514 person-years of follow-up (average 18.2 years), we observed 623 malignant CNS tumours. The results of the fully adjusted linear analyses showed a hazard ratio (95% confidence interval) of 1.07 (0.95, 1.21) per 10 $\mu g/m^3$ NO_2, 1.17 (0.96, 1.41) per 5 $\mu g/m^3$ $PM_{2.5}$, 1.10 (0.97, 1.25) per 0.5 $10^{-5}m^{-1}$ BC, and 0.99 (0.84, 1.17) per 10 $\mu g/m^3$ O_3.

Conclusions

We observed indications of an association between exposure to NO_2, $PM_{2.5}$, and BC and tumours of the CNS. The PM elements were not consistently associated with CNS tumour incidence.

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Multiple myeloma risk in relation to long-term air pollution exposure - A pooled analysis of four European cohorts

Ulla Arthur Hvidtfeldt [a], Jie Chen [b], Sophia Rodopoulou [c], Maciej Strak [b d], Kees de Hoogh [e f], Zorana J. Andersen [g], Tom Bellander [h], Jørgen Brandt [i j], Francesco Forastiere [k l], Boel Brynedal [m], Ole Hertel [n], Barbara Hoffmann [o], Klea Katsouyanni [c p], Matthias Ketzel [i q], Karin Leander [h], Patrik K.E. Magnusson [r], Gabriele Nagel [s], Göran Pershagen [h], Debora Rizzuto [t u], Evangelia Samoli [c]...Ole Raaschou-Nielsen [a i]

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Abstract

Background

Air pollution is a growing concern worldwide, with significant impacts on human health. Multiple myeloma is a type of blood cancer with increasing incidence. Studies have linked air pollution exposure to various types of cancer, including leukemia and lymphoma, however, the relationship with multiple myeloma incidence has not been extensively investigated.

Methods

We pooled four European cohorts (N=234,803) and assessed the association between residential exposure to nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), black carbon (BC), and ozone (O_3) and multiple myeloma. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results

During 4,415,817 person-years of follow-up (average 18.8 years), we observed 404 cases of multiple myeloma. The results of the fully adjusted linear analyses showed hazard ratios (95% confidence interval) of 0.99 (0.84, 1.16) per 10μg/m³ NO_2, 1.04 (0.82, 1.33) per 5μg/m³ $PM_{2.5}$, 0.99 (0.84, 1.18) per 0.5 $10^{-5}m^{-1}$ BCE, and 1.11 (0.87, 1.41) per 10μg/m³ O_3.

Conclusions

We did not observe an association between long-term ambient air pollution exposure and incidence of multiple myeloma.

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Global variation in diabetes diagnosis and prevalence based on fasting glucose and hemoglobin A1c

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NCD Risk Factor Collaboration (NCD-RisC)*

Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) are both used to diagnose diabetes, but these measurements can identify different people as having diabetes. We used data from 117 population-based studies and quantified, in different world regions, the prevalence of diagnosed diabetes, and whether those who were previously undiagnosed and detected as having diabetes in survey screening, had elevated FPG, HbA1c or both. We developed prediction equations for estimating the probability that a person without previously diagnosed diabetes, and at a specific level of FPG, had elevated HbA1c, and vice versa. The age-standardized proportion of diabetes that was previously undiagnosed and detected in survey screening ranged from 30% in the high-income western region to 66% in south Asia. Among those with screen-detected diabetes with either test, the age-standardized proportion who had elevated levels of both FPG and HbA1c was 29–39% across regions; the remainder had discordant elevation of FPG or HbA1c. In most low- and middle-income regions, isolated elevated HbA1c was more common than isolated elevated FPG. In these regions, the use of FPG alone may delay diabetes diagnosis and underestimate diabetes prevalence. Our prediction equations help allocate finite resources for measuring HbA1c to reduce the global shortfall in diabetes diagnosis and surveillance.

Diabetes is associated with debilitating complications such as amputation, vision loss and renal failure, and with increased risk of cardiovascular events, dementia, some cancers and infectious diseases such as severe COVID-19 and tuberculosis[1–6]. The diagnostic criteria for diabetes have evolved over time to incorporate hemoglobin A1c (HbA1c), which is a measure of long-term glycemic status and more convenient to measure for patients than fasting glucose or the 2-h oral glucose tolerance test (OGTT)[7–10]. In contemporary guidelines, any one or the combination of fasting plasma glucose (FPG), OGTT and HbA1c may be used to diagnose diabetes[10–14]. With the exception of diagnosis of gestational diabetes, OGTT is now rarely used in clinical practice or population surveillance because of the inconvenience related to the glucose load, 2-h time frame and the two blood draws required for the test[15,16]. FPG and HbA1c, which are both used in clinical practice and epidemiological research and surveillance, measure different glycemic features, namely basal glucose level (FPG) and average glucose level in the previous 2–3 months (HbA1c)[17]. Therefore, individuals may have elevated levels of one or both biomarkers, and FPG and HbA1c may classify different people as having diabetes[9,10]. Diabetes also has a long subclinical period defined by hyperglycemia and can remain undiagnosed without screening or other mechanisms for early identification[18].

Some studies have assessed sensitivity and specificity of diabetes diagnosis using either FPG or HbA1c relative to the OGTT or have compared diabetes prevalence based on these different glycemic biomarkers, but most did not provide a direct comparison of HbA1c and FPG[19–21]. Most population-based studies on the concordance and discordance

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