Aus dem Institut für Biometrie und Klinische Epidemiologie
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DISSERTATION

Application and discussion of advanced statistical methods in observational studies

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Content

Abstract

Background: Observational studies provide important information for evidence-based medicine, since not all research questions can be answered using randomized clinical trials. However, in the absence of randomization, observational studies can be challenging by their study designs and data structures, where appropriate statistical solutions are often not easily applicable. In this thesis (i) the association between guideline-based blood pressure regulation and mortality, (ii) social determinants of the risk of early care dependency onset or worsening, and (iii) time trends in rates of the sudden infant death syndrome in different countries were investigated.

Methods: Data from the Berlin Initiative Study (BIS), a cohort with 2,069 participants aged ≥ 70 years, just as an ecological study based on aggregated data on infant mortality from 52 countries from 1969 to 2012 were used. To answer the three research questions (i) a multiple Cox proportional-hazards model was fitted within BIS participants treated with antihypertensives. Second, (ii) a multiple multi-state model was applied to BIS data to simultaneously consider different onset and worsening times of the care levels. Finally, based on the country-level data, (iii) restricted cubic splines for smoothing were jointly used with cluster analysis to identify countries with similar trends.

Results: We found that participants with guideline-based regulated blood pressure had a higher risk of death compared to participants with non-regulated blood pressure (adjusted hazard ratio (95% confidence interval): 1.26 (1.04-1.54)). Older adults without a partner were in tendency at higher risk of early care dependency onset than persons with a partner (adjusted hazard ratio (95% confidence interval): 1.19 (0.79–1.79)). Moreover, we identified four clusters of countries with different time trends in rates of sudden infant death syndrome, where specific trends might be related to time points of large public campaigns such as campaigns on supine sleep position. These epidemiologic findings could only be derived after correctly merging and restructuring several datasets to make them applicable for the chosen analyses, where additionally some of the latter had to be technically implemented a priori. In all studies, careful sensitivity analyses were key to better understand estimated effects and their robustness.

Conclusion: Based on two fields of research, within elderly and on global infant mortality, we can see how important the contribution of observational studies to current evidence is. Many other fields greatly rely on observational data, where appropriate handling of design, data structure and specific data issues, just as sound statistical modeling are key.

Zusammenfassung

Hintergrund: Beobachtungsstudien liefern wichtige Informationen in evidenzbasierter Medizin, denn nicht alle Forschungsfragen können mit randomisierten klinischen Studien beantwortet werden. Aufgrund des Fehlens einer Randomisierung, können Beobachtungsstudien jedoch eine Herausforderung darstellen, ebenso wie durch die Vielzahl von Studiendesigns und komplexer Datenstrukturen. Geeignete statistische Lösungen sind daher oft nicht einfach anwendbar. In dieser Arbeit wurden (i) der Zusammenhang zwischen leitliniengerechter Blutdruckregulierung und Sterblichkeit, (ii) soziale Determinanten des Risikos für den Beginn oder die Verschlechterung von früher Pflegebedürftigkeit und (iii) zeitliche Trends in den Raten des plötzlichen Kindstodsyndroms verschiedener Länder untersucht.

Methoden: Es wurden Daten der Berlin Initiative Study (BIS) verwendet, einer Kohorte mit 2.069 Teilnehmern im Alter ≥ 70 Jahren, ebenso wie eine ökologische Studie, die auf aggregierten Daten zur Säuglingssterblichkeit aus 52 Ländern von 1969 bis 2012 basiert. Zur Beantwortung der drei Forschungsfragen wurde (i) ein multiples Cox-Proportional-Hazards-Modell innerhalb der mit Antihypertensiva behandelten BIS-Teilnehmer angewendet. Zweitens wurde (ii) ein multiples Multi-State-Modell auf die BIS-Daten angewendet, um gleichzeitig unterschiedliche Zeitpunkte des Beginns und der Verschlimmerung der Versorgungsstufen zu berücksichtigen. Auf der Grundlage der Daten auf Länderebene wurden schließlich (iii) kubische Splines zur Glättung der Daten, ebenso wie eine Clusteranalyse, um Länder mit ähnlichen Trends zu identifizieren verwendet.

Ergebnisse: Patienten mit leitliniengemäß eingestellten Blutdruck zeigten ein höheres Sterberisiko im Vergleich zu Patienten, deren Blutdruck nicht gemäß den Leitlinien eingestellt war (adjustierte Hazard Ratio (95% Konfidenzintervall): 1,26 (1,04-1,54)). Wir konnten zeigen, dass ältere Erwachsene ohne Partner tendenziell ein höheres Risiko für den frühen Eintritt der Pflegebedürftigkeit hatten als Personen mit Partner (adjustierte Hazard Ratio (95% Konfidenzintervall): 1,19 (0,79-1,79)). Außerdem identifizierten wir in Bezug auf die Raten des plötzlichen Kindstods vier Cluster mit unterschiedlichen zeitlichen Trends, wobei spezifische Trends innerhalb der Cluster mit den Zeitpunkten der Initiierung großer Kampagnen zusammenhängen könnten, wie z. B. Kampagnen zur Rückenlage im Schlaf. Diese epidemiologischen Erkenntnisse konnten nur nach korrekter Zusammenführung und Umstrukturierung mehrerer Datensätze abgeleitet werden, um sie für die gewählten Analysen verwenden zu können, wobei zusätzlich einige der letzteren vorab technisch umgesetzt werden

mussten. In allen Studien waren sorgfältige Sensitivitätsanalysen der Schlüssel zum besseren Verständnis der geschätzten Effekte und ihrer Robustheit.

Schlussfolgerung: Anhand von zwei Forschungsfeldern, innerhalb älterer Menschen und zur globalen Säuglingssterblichkeit, können wir sehen, wie wichtig der Beitrag von Beobachtungsstudien zur aktuellen Evidenz ist. Viele andere Bereiche stützen sich in hohem Maße auf Beobachtungsdaten, wobei ein angemessener Umgang mit Design, Datenstruktur und spezifischen Datenproblemen ebenso wie eine solide statistische Modellierung entscheidend sind.

1. Introduction

In evidence-based medicine research questions can be addressed by different study designs. Randomized controlled trials (RCT) are a powerful tool in clinical research to analyze treatment effects. Patients are randomly assigned to the treatment groups, to ensure equal distribution of characteristics affecting the study outcome between the groups. In contrast, the absence of randomization in observational studies can induce bias, as the observed study groups differ in their characteristics and differences seen in the outcome are possibly a result of these inequalities and cannot be attributed to the treatment or exposure of interest.

Apart from the advantages of RCTs, there are many research questions, which cannot be addressed by randomly assigning groups, for example the effect of smoking on lung cancer (1). Ligthelm et al. (2007) defined an observational study as "*a study that provides estimates and examines association of events in their natural settings without recourse to experimental intervention*" (2) and contrast advantages and disadvantages of observational studies and emphasize

- the advantage of a broader spectrum of patients in observational studies due to more relaxed inclusion and exclusion criteria,
- the advantage that in cohort studies long-term follow-up measures over decades are available, and
- the advantage that several outcomes can be studied in parallel.

Therefore, observational studies play an important role in current research and have been used increasingly in the last decades. Furthermore Barton (2000) shows two systematic reviews published in the New England Journal of Medicine (3) (4), which compared RCTs and observational studies in therapeutic areas and did not find major differences in treatment effect estimates between RCTs and observational studies. (5)

There is a wide variety of observational study designs (e.g. cohort studies, case-control studies, and cross sectional studies), a broad range of research questions, and analyses are often based on several data sources. The correct analysis of data in observational studies is therefore both challenging and complex. Due to the absence of randomization, the researcher has to be aware of numerous potential sources of bias (e.g. confounding bias, selection bias, information bias, and immortal time bias) and potential bias due to missing observations, especially in longitudinal studies. (6), (1), (7) Each of these challenges has to be considered in the preparation prior to the analysis (e.g. the set-up of the dataset), and/or by special, more sophisticated statistical and epidemiological methods like confounder adjustment, matching, or multiple imputation. There are guidelines like the STRATOS initiative "Strengthening analytical thinking for observational

studies" (7) and STROBE "The Strengthening the Reporting of Observational Studies in Epidemiology" (8), which help researchers to achieve high quality in analysing and reporting observational studies. STRATOS focuses on data analysis, with the following nine main topics: "study design", "initial data analysis", "causal inference", "measurement error and misclassification", "selection of variables and functional forms in multivariable analysis", "missing data", "survival analysis", "high-dimensional data", and "evaluation of diagnostic tests and prediction models". (7) (9)

The STROBE statement provides a checklist of 22 items with recommendations for reporting an observational study. The items distinguish between different study designs (cohort study, case-control study, and cross-sectional study) and provide guidance on what should be reported in each section of the paper.

This thesis describes and discusses the application of advanced statistical methods in answering three different research questions using data of two observational studies, which resulted in three publications[1]: Douros et al. (2019), Schneider et al. (2020) and Müller-Nordhorn et al. (2020). The first study is the Berlin Initiative Study (BIS), a longitudinal cohort study with 2,069 participants aged ≥ 70 years, recruited in 2009/2010 and followed until December 2016. All participants are members of one of the largest statutory health insurance companies in Germany, AOK-Nordost. Study data of individuals of this age observed over a longer period are rare. The second study deals with international time trends in sudden unexpected infant death. Aggregated data of 52 countries from 1969 to 2012 of infant mortality and the ICD-code that provides information about the cause of death were analysed.

Publication 1: Douros et al. (2019) focuses on participants treated with antihypertensives in the BIS and their risk of all-cause mortality. Arterial hypertension is a prevalent disease in the elderly population which is treated with these drugs and the discussion on the target blood pressure values is ongoing, where different recommendations between a systolic blood pressure < 120 mmHg to < 140 mmHg exist. (13) (14) (15) Some of these recommondations are based on an RCT with strict exclusion criteria, e.g. previous stroke or diabetes, and are therefore potentially of limited applicability in clinical practice, since older individuals/patients often suffer from mutiple comorbidities. Observational studies such as the BIS can in this case provide the missing information about benefits and risks of antihypertensive treatment in elderly with and without comorbidities. We assessed whether systolic blood pressure (SBP) values below 140 mmHg and

[1] As this thesis is based on three papers, in the following the personal pronoun 'we' refers to different groups of researchers, but will be used to acknowledge their individual contributions. My own contribution to the three published articles is summarized in the "Anteilserklärung an den erfolgten Publikationen" on page 28.

diastolic blood pressure (DBP) values below 90 mmHg during antihypertensive treatment were beneficial and therefore associated with a lower risk of dying. (10)

Publication 2: Schneider et al. (2020) investigate the effect of social determinants on care dependency onset and progression, just as the effect on various levels of care dependency. (11) As life expectancy of the general population is increasing, the risk of care dependency in daily living increases. The role of functional impairment and morbidities for care dependency is well known but there is a gap in knowledge about the role of social determinants, e.g. about the role of partnership. We assessed whether a partner delays onset or progression of professional care dependency.

Publication 3: Müller-Nordhorn et al. (2020) use yearly aggregated data of infant mortality from 52 countries across the globe from 1969 to 2012 to identify groups of countries with similar time trends in sudden infant death (SID), sudden unexpected infant death (SUID), and all-cause infant mortality. (12) SUID remains one of the main causes of infant mortality worldwide. While Western countries like Western Europe, Canada, Australia, and the United States had a peak in the 1980s and mortality decreased during the 1990s (16), there were countries whose rates were low in the 1980s and later increased. (17) The reduction in SIDS often coincided with sleep position campaigns. (18) Even though the analysis and interpretation of aggregated data have clear limitations, such data are useful in evaluating the association between large campaigns and their effect on the targeted phenomena such as SUID and SID, which remains not very well understood.

This thesis focuses on study design, definition of study cohort, determination of outcome, exposure and confounding variables, data preparation, selection of appropriate analysis methods, and handling of missing data – in the specific setting of three relevant research questions, addressed with data from two observational studies.

2. Methods

2.1 Douros et al. (2019): Blood pressure regulation and mortality

2.1.1 Study Population

The BIS is a longitudinal cohort study, which enrolled of 2,069 participants from 2009 to 2011. Data on socio-demographics, lifestyle, comorbidities, and medication were collected every two years in a standardized face-to-face interview, when also blood and urine samples were taken (data source 1). Inclusion criteria were age ≥ 70 years and membership in a specific statutory health insurance company, the AOK-Nordost; individuals were excluded if they had dialysis prior to

enrolment. An advantage of this study is the combination of survey data and data from the statutory health insurance AOK-Nordost (data source 2), as health insurance data were available even if a participant did not attend a follow-up visit. The main objective of the BIS was the assessment of the progression of chronic kidney disease and the course of kidney function indicated by the glomerular filtration rate (19).

For this research question, the study population was restricted to those BIS participants taking antihypertensive drugs at study entry and the time period was restricted to the time from the first visit until December 2016.

2.1.2 Variables of Interest

The outcome we chose here was the time from study entry until the occurrence of death before December 2016 (n=469), i.e. participants still alive at December 2016 were censored at this time point. The European Society of Cardiology and the European Society of Hypertension presented a guideline for the management of arterial hypertension (15), which recommended a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg. We used these cut-offs to categorise participants into "good" or "poor" regulation of blood pressure at baseline, i.e. participants with normalized blood pressure according to the guideline (< 140 mmHg and < 90 mmHg, good regulation) and participants with non-normalized blood pressure (≥ 140 mmHg or ≥ 90 mmHg, poor regulation), and use this categorised variable as exposure of interest.

The selection of variables possibly introducing confounding was based on expert knowledge and resulted in the adjustment for 13 variables measured at baseline: age, sex, life style (e.g. smoking, alcohol consumption, physical activity), comorbidities (e.g. stroke, myocardial infarction), the number of medications and duration of treated hypertension. As these variables are associated with all-cause mortality but possibly also with quality of blood pressure regulation, an analysis not adjusting for them could give biased results. Moreover, because the starting point of observation is an arbitrary point in a participant's life and not necessarily his/her start of treatment with antihypertensives, the adjustment for age and treatment duration is crucial.

2.1.3 Statistical analysis

To assess the association between exposure and time to death, we used a Cox proportional hazards model and presented the crude, i.e. without adjustment for covariates, just as adjusted hazard ratios (HR) along with 95% confidence intervals (CI). Additionally, we calculated crude incidence rates of all-cause mortality per 1,000 person-years along with 95% CIs, assuming the observed number of cases following a Poisson distribution.

We performed several sensitivity analyses to further investigate and understand the effect of normalized vs. non-normalized blood pressure on all-cause mortality. For example, we examined whether the estimated effect differed between subgroups, such as age groups (>80 years vs. ≤80 years) or participants with and without pre-existing diseases (e.g. cardiovascular event prior to study entry), and how the effect changed given a different cut-off for normalized blood pressure (SBP <150 mmHg and DBP <90 mmHg). We also examined interaction effects between age and blood pressure regulation, just as cardiovascular risk and blood pressure regulation.

Additionally, we performed post-hoc specified sensitivity analyses, where we defined three categories for blood pressure regulation (SBP < 130 mmHg and DBP < 90 mmHg; SBP 130-139 mmHg and DBP < 90 mmHg; SBP ≥ 140 mmHg or DBP ≥ 90 mmHg), and used the latter category as the reference to compare it with the other two. This analysis was additionally performed separately in four subgroups: men < 80, men ≥ 80, women < 80, and woman ≥ 80 years.

To answer the main question of the effect of following guidelines, a dichotomization of the blood pressure values was necessary. However, since important information will be lost using cut-offs, it might be preferable not to dichotomize metric variables from a more statistical point of view. Therefore, we additionally analysed the relationship between SBP and risk of death more flexibly, by modelling SBP using natural splines with 25th, 50th and 75th percentile as three interior knots (131 mmHg, 144 mmHg, and 159 mmHg) and used SBP of 140 mmHg as the reference point.

No imputation procedure for missing values was performed, as all independent variables were recorded at the mandatory baseline visit, where the percentage of missing values was low (<2%). The information on the outcome was available for all participants.

For the analysis SPSS (Version 25.0; IBM Corp, Armonk, NY, USA), Stata (Version 14.0; Stata Corp, College Station, TX, USA), and R (Version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria) was used.

2.1.4 Data handling

The first data source was the BIS survey data, where data of a single participant is available at different time points. This information is stored in long-format, i.e. with multiple rows per participant, where one row represents one study visit. The second data source was the claims data, which was available starting from 3 years prior to study enrolment with information on hospitalization, outpatient visits, care levels and surgery and procedure codes (OPS), stored in six data sets. The information from Health Insurance Company is typically stated with the exact date of the claim. Data of these two data sources had to be partly aggregated and subsequently combined by an anonymized linkage code. The main challenge of the data merge was the correct assignment

of the claims data structured by specific dates, to the survey data structured by visits and their time points.

2.2 Schneider et al. (2020): Social determinants of care dependency

2.2.1 Study Population

Data of the BIS were also used to answer this research question (see Section 2.1.1). It required the exclusion of participants with the highest level of care at baseline, to base the analyses on the set of participants where a progression is still possible. We additionally excluded participants who had improved their care level over the course of the study, since our focus was on progression of care dependency. We followed participants from the first study visit until December 2016.

2.2.2 Variables of Interest

Care dependency was defined based on the daily time during which assistance in activities of daily living was needed, where the German care system defined three levels of care (until December 2016): level one - assistance at least 90 minutes daily, level 2 – assistance at least 3 hours daily, and level 3 - assistance at least 5 hours daily (20). Due to low case numbers of care level 3, we combined level 2 and 3. Therefore, we considered three possible states in the analysis: no care dependency, care dependency level 1, and care dependency level 2 (combined original levels 2 and 3), just as the transition time from one state to another as the study outcomes. Due to a change in the German care system from three levels to five starting from January 1st, 2017, the follow-up period was limited to December 2016.

Exposure variables of interest were social determinants, including partnership status (yea/no), education (CASMIN short (21)), monthly income, sex, and age. Out of these, partnership status changed for some participants over the observation time and was therefore modelled as a time-dependent variable.

Based on knowledge of health care professionals, we included nine variables measured at baseline in the multiple regression model to address confounding, including information about life style (e.g. smoking, alcohol consumption), comorbidities (e.g. stroke, myocardial infarction).

2.2.3 Statistical analysis

Due to the relevance of time in any time-to-event analysis, we reported both the event rate but also unadjusted hazard ratios in the descriptive analysis. We wanted to analyse more than one event of interest in a single model, while estimating the effect of one variable on different transitions as a transition-specific effect and not to have a separate model for each transition. Therefore, a multi-

state model was chosen to assess the effect of social determinants on time to different event types. In this model, three different transitions were possible, (1) transition from no care dependency to care dependency level 1, (2) no care dependency to care level 2, and (3) care level 1 to care level 2. In such a model, several specifications and assumptions have to be made prior to data preparation and analysis (22). We censored participants who died during the observation time, as the focus of the analysis was not mortality, but also because mortality will be reported in subsequent publications. We used participant's age as the time scale in the multi-state model, since the study entry is arbitrary in the participant's life span. Thereby, all effects are automatically age-adjusted. Considering three different transitions, we assumed different baseline hazards for each transition. The models were stratified for the three transition types, which additionally accounted for the dependency of the data. We used the "clock-forward" approach for the definition of time *t* (22), (23). Since we assumed different effects of a variable on each transition, we estimated transition-specific coefficients. However, in favour of a parsimonious model, the necessity of a transition-specific coefficient was evaluated based on the Bayesian Information Criterion (BIC). The Nelson-Aalen cumulative hazard function was used for illustration.

Due to participant dropouts, the amount of missing values in the time-dependent variable partnership increased over the follow-up visits. As we assumed that the missing was due to older age and increased frailty and since the information of care dependency was available from claims data independent of the biannually survey data, we could use it as a proxy and account for missing values by using multiple imputation by chained equations. For the imputation, all variables of the model, age and outcome variables were included to generate 10 imputed datasets. Results of the multiple imputed data sets were pooled by using Rubin´s rules (24).

For data preparation and multiple imputation SPSS (Version 25.0; IBM Corp, Armonk, NY, USA) was used. Multi-state models were calculated with R (Version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria) using the *mstate* package (22, 25, 26) and the *mvna* package for Nelson-Aalen estimator (27).

2.2.4 Data handling

We merged the BIS survey data with health insurance data, as in Douros et al. (2019). In addition, we used follow-up information on partnership status from survey data and the care level from health insurance data. The main challenge in data preparation was again to correctly merge data from different sources, but additionally to arrange it in a way specific to the chosen analysis method, a multi-state model with time-dependent exposure.

For being able to apply a multi-state Cox proportional hazards model, the data have to be in long format, with a separate row for every possible transition of the individual (Table 1). We used the R package *mstate* (22, 25, 26), which requires the dataset to be in a specific format, known as the "counting process" format (28). In this format, there are several rows for one individual, one row for each possible transition for which an individual is at risk. The new dataset includes the *ID* of the participant, the information about the present transition, i.e. *from* which state the transition starts and *to* which it goes, the dummy code of the transition (*trans*), and the *start* and *stop* time. Start and stop is the time period in which the patient is at risk for the specific transition, the *status* variable indicates whether the participant changed his or her state according to the specific transition during the observation time of the study (1: yes, 0: no). For the multi-state model, five scenarios for the participants were possible (see Table 1):

(i) Participant (ID = 1) experienced transition from no care dependency to level 1 only (status=1). For the other two transitions, the participant is at risk (status=0). Therefore in total three rows in the dataset are needed.

(ii) The participant (ID = 2) experienced the transition from no care dependency to level 2 only. In the same time interval, the participant is at risk to experience transition from no care dependency to level 1. The transition from level 1 to level 2 is not possible, as the participant was already in level 2. Therefore in total two rows in the dataset are needed.

(iii) The participant experienced transition from level 1 to level 2 only. The transition starting from no care dependency is not possible, as the participant was in level 1 at the enrolment of the BIS. Here, only one row in the dataset is needed.

(iv) The participant (ID=4) experienced no transition.

(v) The participant (ID=5) experienced transition from no care dependency to level 1 and the transition from level 1 to level 2. Three rows in the dataset are needed.

The dataset also had to be extended by the time-dependent variable partnership status (0: no partner, 1: yes). For each change in this variable, a new row was added to the dataset with the information in which time interval the respective status was valid. For illustration, we assume that participant with ID = 1 changed his/her partnership status at the age of 74 from having no partner to having a partner (Table 2). Therefore, dataset is extended by two additional rows and the time interval from age 73-77 must be split into two intervals 73-74 and 74-77.

Table 1 Exemplary layout of dataset for multi-state modelling, counting process format given five individuals.

ID	from	to	transition	start	stop	status
1	0	1	1	73	77	1
1	0	2	2	73	77	0
1	1	2	3	77	79	0
2	0	1	1	86	88	0
2	0	2	2	86	88	1
3	1	2	3	75	76	1
4	0	1	1	86	89	0
4	0	2	2	86	89	0
5	0	1	1	84	85	1
5	0	2	2	84	85	0
5	1	2	3	85	88	1

Each row contains the specific *transition* (*from* and *to* which state), the time period (*start*- and *stop* time and its difference: *time*), and the *status* (1: if the participant experienced the transition, 0: if not) for each of the 5 individuals

Table 2 Exemplary layout of dataset for multi-state modelling including time-dependent variable, counting process format given one individual.

ID	from	to	transition	start	stop	status	partner
1	0	1	1	73	74	0	0
1	0	1	1	74	77	1	1
1	0	2	2	73	74	0	0
1	0	2	2	74	77	0	1
1	1	2	3	77	79	0	1

Each row contains the specific *transition* (*from* and *to* which state), the time period (*start*- and *stop* time and its difference: *time*), the *status* (1: if the participant experienced the transition, 0: if not), and the *partner* status (0: no, 1: yes) for one individual, whose partnership status changes

2.3 Müller-Nordhorn et al. (2020): International time trends of infant mortality

2.3.1 Study population

For this study, yearly aggregated infant mortality data from 1969 to 2012 from 52 countries worldwide were obtained. Data were collected from the respective national statistical offices of the countries including the information about the two specific causes of death SID, SUID, which were indicated by the ICD code. The aim of the project was the identification clusters of countries with similar time trends regarding SID, SUID and all-cause infant mortality rates.

The focus region of our study was Europe and other regions with selected countries of the world for comparison. We used the derived geographic units of the Global Burden of Disease study (29) for the classification of regions. The following regions and countries were included: “

1) *Western Europe (Austria, Belgium, Cyprus, Denmark, East Germany, England & Wales, Finland, France, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Northern Ireland, Norway, Portugal, Scotland, Spain, Sweden, Switzerland, West Germany) […]*
2) *Central Europe (Albania, Bulgaria, Croatia, Czech Republic, Hungary, Kosovo, Republic of Macedonia, Poland, Romania, Serbia, Slovakia, Slovenia).*
3) *Eastern Europe (Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, the Russian Federation, Ukraine).*
4) *Selected countries from other regions: high-income North America (Canada, USA), Australia (Australia, New Zealand), high-income Asia Pacific (Japan), Southern Latin America (Chile, Uruguay), Central Latin America (Costa Rica, Mexico), and North Africa and Middle East (Turkey).*” (12)

2.3.2 Variables of Interest

The primary diagnosis of interest was SUID, which encompasses the ICD codes R95 - ‘sudden infant death syndrome’, W75 - ‘accidental suffocation and strangulation in bed’, and R99 - ‘other ill-defined or unspecified causes of mortality’ (30). Differences in the use of ICD codes have been shown between countries. Therefore, the broader category R96-R99 "undetermined and unknown causes of death" was used. In addition, SID and all-cause infant mortality were secondary outcomes of interest. Infant mortality, regardless of ICD code, was defined as death in the child's first year of life.

2.3.3 Statistical analysis

We calculated infant mortality rates per 1,000 live births. To remove noise from the data we smoothed all mortality rates over time by using restricted cubic splines with six nodes. To identify similar time trends of SUID and SID between the countries, we performed two hierarchical cluster analyses, first for SUID and all-cause infant mortality and second for SID and all-cause infant mortality. We extracted smoothed values from restricted cubic splines for the cluster analysis from 1980 to 2010, 62 variables in total. Since all-cause mortality had higher values in comparison to SID and SUID, and therefore had a higher weight in each of the two hierarchical cluster analysis, we calculated separate Manhattan distance matrices for SUID, SID, and all-cause mortality. This

allowed us to ensure that the rates for both SUID and all-cause mortality were equally weighted in the cluster analysis, and the same was done for the second cluster analysis on SID and all-cause mortality. We used Ward´s minimum variance method as algorithm in the cluster analysis. Country-specific maxima were calculated from the smoothed curves of mortality rates for SUID and SID.
In case of missing values, the Mortality Database of the World Health Organization (WHO) was checked, to impute the missing values if additional data were available. Due to a high number of missing data at the beginning and the end of the observed time-period, we restricted the time-period for the cluster analysis to the period 1980 to 2010.

For statistical analysis, the software R (R 3.3.2 -R Foundation for Statistical Computing, Vienna, Austria) was used, in particular the function hclust out of the R package rms for the calculation of restricted cubic splines and cluster analysis.

3. Results

3.1 Douros et al. (2019): Blood pressure regulation and mortality

3.1.1 Epidemiologic Findings

The original study population of 2,069 reduced to 1,628 participants, as only they were treated with antihypertensive drugs at study entry. The participants were observed over a median follow-up time of 6 years and 1 month (interquartile range: 5 years 6 months - 6 years 5 months), 469 of them died during the observed time. Of the observed study population, 636 (39%) had normalized blood pressure values, whereas 992 (61%) participants had non-normalized blood pressure values. Both groups were similar in terms of patient characteristics at baseline, except that participants with normalized blood pressure were more likely to suffer from a higher burden of comorbidities at baseline – compared to participants with non-normalized blood pressure.
The crude and adjusted analyses showed that normalized blood pressure was associated with a higher risk of all-cause mortality compared to participants with non-normalized blood pressure (crude HR (95% CI): 1.25 (1.04-1.50); adjusted HR (95% CI): 1.26 (1.40-1.54)). Subgroup analyses showed that this effect was larger in participants with a previous cardiovascular event at baseline (adjusted HR (95% CI): 1.61 (1.14-2.27)) than in participants without such a previous event (adjusted HR (95% CI): 1.16 (0.90-1.48)). Age group analysis showed a higher risk of all-cause mortality with compared to without normalized blood pressure for participants aged 80 years

or above. Interestingly, for participants younger than 80 years, there was an inverse effect (adjusted HR: 0.83 (0.54-1.27)).

3.1.2 Methodologic Findings

Given the complexity of the different data sources it was key to first become familiar with both survey and claims data, to finally be able to merge the information into one dataset. Consideration of confounding was relevant, as well as accounting for age and treatment duration to control for arbitrary starting point of study entry in participants' life. In the light of the unexpected primary result of a higher risk for all-cause mortality in patients with normalized blood pressure compared to patients with non-normalized blood pressure, the sensitivity analyses had to be greatly extended. To better understand this finding, several subgroup analyses were applied, just as an additional analysis on the association of blood pressure and mortality was implemented using natural splines to estimate more accurately the effect of different levels of blood pressure.

3.2 Schneider et al. (2020): Social determinants of care dependency

3.2.1 Epidemiologic Findings

The total of 2,069 BIS participants reduced to 2,021 for this analysis, as they were not in level 2 or 3 of care dependency at baseline (n=44) and did not experience an improvement in level of care at study entry (n=4). The median follow up time for the analysis of research question was 5 years and 2 months (interquartile range: 4 years 8 months - 5 years 6 months). Of those, 431 experienced the transition from no care dependency to level 1 (0→1), 77 from no care dependency to level 2 (0→2), and 146 from level 1 to level 2 (1→2). In total the level of care dependency changed for 556 participants, 98 participants had more than one transition. Older age was associated with a higher risk of progression in care dependency. The advantage of the used multi-state model was to derive effect estimates for the different events parallel in one regression model. Females had a higher risk to enter level 1 care dependency than men, but lower risk for direct entry in level 2 from no care dependency. Participants without a partner had a higher risk for transition from no care dependency to level 1 than participants with a partner, but a lower risk for the transition from care level 1 to care level 2 and the direct entry in level 2. The fact that the partner delays the entry into care level 1 through his support also means that participants with a partner are more likely to enter care level 2 as a result. However, the partner does not delay the worsening of care dependency. Participants with comorbidities experienced worsening in care dependency more frequently than participants without.

In the multiple multi-state model, the variables partnership and sex were included as transition specific, whereas regression coefficients of the other variables were estimated as fixed for the different transitions. The risk of progression from no care level to level 1 was slightly higher for women compared to men (HR (95% CI): 1.07 (0.75–1.53)), and slightly higher for participants with compared to participants without a partner (HR (95% CI): 1.19 (0.79–1.79)). For the other two possible transitions, i.e. from no care dependency to level 2 and from level 1 to level two, there was an inverse association for sex (0→2: HR (95% CI): 0.62 (0.29–1.31); 1→2: HR (95% CI): 0.71 (0.41–1.22)) and partnership (1→2 HR (95% CI): 0.73 (0.38–1.39); 0→2: HR (95% CI): 0.72 (0.28–1.83)), compared to transition from no care dependency to level 1.

3.2.2 Methodologic Findings

To answer this research question, we chose a multi-state model to flexibly analyse different events, where the effect estimates can be defined as fixed or transition-specific. This is not possible when analyzing the different events in separate Cox proportional hazards models which would be an alternative, but not so efficient analysis method. Given this multi-state model with the addition of a time-dependent variable, a specific data format was required, and therefore rendered prior data preparation quite complex. As in Douros et al. (2019), adjusting for confounding played a role. The problem of accounting for the arbitrary start time of the study in the participants' lives was elegantly solved by using the age of the participants as time scale. Through this step, the adjustment for age was also addressed. In addition, the imputation of missing values by chained equations and the associated pooling of results using Rubin's rules (24) was added. The automatically pooling of results of multi-state models with a time-dependent variable from multiple imputed datasets was not implemented in R and had to be additionally programmed.

3.3 Müller-Nordhorn et al. (2020): International time trends of infant mortality

3.3.1 Epidemiologic Findings

In total, infant mortality decreased from 28.5 per 1,000 live births in 1969 to 4.8 in 2012. We could not calculate SUID and SID mortality rates for all countries and years, due to different coding and changes in ICD codes. Therefore, we included data from 29 countries for the cluster analysis of SUID in the years 1980 to 2010 and from 27 countries for the cluster analysis of SIDS.

In both analyses, we deduced four clusters. Clusters 1 and 2 of SUID mortality rates show a similar time trend with an increase in SUID rates until the mid-1980s and a subsequent decline. Rates of all-cause mortality in these two clusters were the lowest compared to the other two. Overall, the rates of countries in cluster 1 are higher with a maximum SUID rate of 3.9 per 1000 live births

(New Zealand) compared to cluster 2 with a maximum of 2.2 per 1000 live births (Norway). Predominantly, countries from Western Europe, Australia, New Zealand, and Canada are in clusters 1 and 2. Clusters 3 and 4 are characterized by low SUID rates < 1 per 1,000 live births throughout the observation period, with the exception of Uruguay in cluster 3. Overall mortality rates are two to three times higher in cluster 3 compared to cluster 1, and are in the middle range in cluster 4. Cluster 3 mainly consists of countries from Central Europe, Chile, and Uruguay, in cluster 4 there are countries of Western Europe (Finland, East Germany, Italy, Portugal, and Spain), Czech Republic, and Japan. The four clusters for SID show a similar time trend of rates as the clusters for SUID.

3.3.2 Methodologic Findings

The main challenge in the statistical analysis was grouping of countries with similar time trends in several outcomes (e.g. overall mortality, SID, SUID). The smoothing step of time trends of the different outcomes was a key pre-process to reduce noise in the fine-grained yearly data. The cluster analysis was then based on derived parameters of the smoothed outcomes at specific time points for each country. At the first step of cluster analysis, we obtained three clusters. However, the first cluster included a range of countries with a variety of time trend, which showed similar all-cause mortality rates, but differences in SUID and SID rates. In order to separate them, we subsequently performed a second cluster analysis with these countries only.

4. Discussion

This thesis encompasses three main research questions, and addresses them with a variety of statistical analyses and data from two different observational studies. It describes the data and analysis methods, the deduced results, and additionally focuses on the challenges associated with the application of statistical methods in observational studies based on these research questions.

4.1 Summary of Epidemiologic Findings

The first data source was the Berlin Initiative Study (BIS), a longitudinal cohort containing data from 2,069 older adults (≥ 70 years). The data were used to investigate the association between following the guideline for blood pressure in antihypertensives treated patients and risk of mortality. This resulted in the quite unexpected finding that patients with normalized blood pressure had a higher risk for all-cause mortality than patients with non-normalized blood pressure (adjusted HR (95% CI): 1.26 (1.04-1.54)). Subsequent stratified analyses according to age group

and previous cardiovascular events showed that the risk for mortality was higher in participants 80 years or above and participants with a previous cardiovascular event.

The BIS data was also used to investigate social determinants of the risk of care dependency or worsening in care levels. The risk to enter care level 1 was slightly higher for women compared to men (HR (95% CI): 1.07 (0.75–1.53)), and slightly higher for participants with compared to participants without a partner (HR (95% CI): 1.19 (0.79–1.79)). For entering directly to level 2 and worsening from level 1 to level 2, there was an inverse association for sex and partnership.

The second data source was a study with aggregated data on infant mortality rates, based on 52 countries worldwide in the period from 1969 to 2012. The aim was to identify countries with similar time trends of mortality rates, with a special focus on the causes of death sudden unexpected infant death (SUID) and sudden infant death (SID). Based on restricted cubic spline smoothing and hierarchical cluster analysis for time trends, we found four clusters for both SUID and SID rates, with a typical peak in the 1980s in cluster 1 and 2 and constantly lower rates in cluster 3 and 4.

4.2 Summary of Methodologic Findings

A first, often underestimated, challenge prior to analysis is the potential complexity of datasets and the need for their adaptation to the chosen type of analysis. This was the case for both projects based on data from the BIS, where it was key to first become familiar with the data its structure to be able to deduce the relevant information in the right format for each research question.

Subsequently, especially in observational studies, the best suitable method might be of higher complexity, as e.g. a multi-state model with an additional time-dependent variable. The latter was the used in Schneider et al. (2020), as we considered more than one event of interest and partnership status as time-dependent. Additionally, in some instances, the appropriate methods might not be implemented in statistical software yet and therefore require additional programming. This was the case for the multi-state model, where pooling of analysis results for multiply imputed datasets was not readily available in R.

As a next step, several sensitivity analyses might be of importance, e.g. to get a better understanding of an estimated effect and to investigate its robustness. In Douros et al. (2019) the primary result of a higher risk for all-cause mortality in patients with normalized blood pressure compared with patients with non-normalized blood pressure was unexpected and therefore the a priori determined sensitivity analyses were extended to a great extent to get a better understanding of the estimated effect and its robustness. In cluster analysis, determining the appropriate number

of clusters usually needs additional evaluation after deriving first results, as was the case in Müller-Nordhorn (2020) where we clustered countries with similar time trends of infant mortality. At the first stage of cluster analysis, we obtained three clusters, with cluster 1 including several countries that showed similar all-cause mortality rates, but differences in SUID and SID. In order to separate them, we performed a second cluster analysis with these countries only.

4.3 Strengths and Limitations

The strength of the BIS lies in providing high quality data in older people over a long period and additionally providing data from a health insurance company. The study on infant mortality trends had the strength of combining this kind of information for many different countries worldwide over a long period of time.

The study by Douros et al. (2019) had the limitation to only use baseline observations of the blood pressure regulation and confounder variables, as the median observation period of 6 years and 1 month in old age is a period in which health status can change rapidly. In order to use all the information, the exposure and confounder variables could be included as time-dependent variables in the model in a further study on this topic. In Schneider et al. (2020) we did not include death as a terminating event in the analysis due to the focus on the risk of onset and progression in care dependency. Although mortality will be analyzed as one of the main outcomes in subsequent work, death as terminating events does play a role in effect estimates of time to event data and multi-state models. One important prerequisite for assuming that a participant is on risk for change in care dependency is that the participant is still alive. Death is thus a competing event and should be additionally considered in the model.

The main limitations of Müller-Nordhorn et al. (2020) lie in the nature of an ecologic study, where data is not available at the individual but only at the aggregated level by diagnosis, year, and country. There is also a lack of information on the distribution of possible risk factors, such as smoking behavior or vaccination rates of the population.

4.4 Conclusion

This research based on three publications focused on the challenges associated with data analysis in observational studies. First, it contributed to the field of research on elderly by investigating the association between guideline-based and the risk for all-cause mortality, just as social determinants of care dependency. Second, it also contributed to the field of global infant mortality trends by showing which countries have similar trends in time for potentially being able to link these to

public health interventions. Research in both of these fields greatly rely on observational data, and therefore sound statistical methods are needed, which can pose challenges from data preparation, implementatation of analyses, to interpretation of results.

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Eidesstattliche Versicherung

„Ich, Alice Schneider, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Application and discussion of advanced statistical methods in observational studies“ (Anwendung und Diskussion anspruchsvoller statistischer Methoden in Beobachtungsstudien) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Alice Schneider hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Douros A, Tölle M, Ebert N, Gaedeke J, Huscher D, Kreutz R, Kuhlmann MK, Martus P, Mielke N, Schneider A, Schuchardt M, van der Giet M, Schaeffner E. Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study. European heart journal. 2019;40(25):2021-8. **Impact factor** (2019): 22.673

Beitrag im Einzelnen:

- Datenaufbereitung, Datensatzzusammenführung aus verschiedenen Datenquellen und Berechnung neuer Variablen
- Statistische Analyse aus der die Tabellen 1, Tabellen 2 und Tabellen 3 und Abbildung 2 hervorgegangen sind
- Korrekturlesen des Manuskripts

Publikation 2: Schneider A*¶, Blüher S*, Grittner U, Anton V, Schaeffner E, Ebert N, Jakob O, Martus P, Kuhlmey A, Wenning V, Schnitzer S. Is there an association between social determinants and care dependency risk? A multi-state model analysis of a longitudinal study. Research in Nursing & Health. 2020;43(3):230-40. **Impact factor** (2019): 2.163

*Dipl. Biomath. (FH) Alice Schneider und Dr. rer. pol. Stefan Blüher teilen sich die Erstautorenschaft

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Beitrag im Einzelnen:

- Datenaufbereitung und Berechnung neuer Variablen
- Statistische Analysen aus der alle Tabellen und Abbildungen des Manuskripts hervorgegangen sind
- Schreiben des Methoden- und Ergebnisteils
- Korrekturlesen des Manuskripts
- Einreichung des Manuskripts
- Bearbeitung der Revisionen
- Korrespondierende Autorin

Publikation 3: Müller-Nordhorn J, **Schneider A**, Grittner U, Neumann K, Keil T, Willich SN, Binting S. International time trends in sudden unexpected infant death, 1969–2012. BMC Pediatrics. 2020;20(1):377. **Impact factor** (2019): 1.909

Beitrag im Einzelnen:

- Datenaufbereitung
- Statistische Analysen aus denen Tabelle 2, Tabelle 3, Tabelle 4, Abbildung 3 und Abbildung 4 hervorgegangen sind
- Schreiben des Methoden-und Ergebnisteils
- Korrekturlesen des Manuskripts

Unterschrift des Doktoranden/der Doktorandin

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Druckexemplare der ausgewählten Publikationen

ESC European Society of Cardiology

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CLINICAL RESEARCH
Hypertension

Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study

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Aims To assess whether blood pressure (BP) values below 140/90 mmHg during antihypertensive treatment are associated with a decreased risk of all-cause mortality in community-dwelling older adults.

Methods and results Within the Berlin Initiative Study, we assembled a cohort of patients ≥70 years treated with antihypertensive drugs at baseline (November 2009–June 2011). End of prospective follow-up was December 2016. Cox proportional hazards models yielded adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality associated with normalized BP [systolic BP (SBP) <140 mmHg and diastolic BP (DBP) <90 mmHg] compared with non-normalized BP (SBP ≥140 mmHg or DBP ≥90 mmHg) overall and after stratification by age or previous cardiovascular events. Among 1628 patients (mean age 81 years) on antihypertensive drugs, 636 exhibited normalized BP. During 8853 person-years of follow-up, 469 patients died. Compared with non-normalized BP, normalized BP was associated with an increased risk of all-cause mortality (incidence rates: 60.3 vs. 48.5 per 1000/year; HR 1.26; 95% CI 1.04–1.54). Increased risks were observed in patients ≥80 years (102.2 vs. 77.5 per 1000/year; HR 1.40; 95% CI 1.12–1.74) and with previous cardiovascular events (98.3 vs. 63.6 per 1000/year; HR 1.61; 95% CI 1.14–2.27) but not in patients aged 70–79 years (22.6 vs. 22.7 per 1000/year; HR 0.83; 95% CI 0.54–1.27) or without previous cardiovascular events (45.2 vs. 44.4 per 1000/year; HR 1.16, 95% CI 0.90–1.48).

Conclusion Blood pressure values below 140/90 mmHg during antihypertensive treatment may be associated with an increased risk of mortality in octogenarians or elderly patients with previous cardiovascular events.

Keywords Arterial hypertension • Antihypertensive drugs • Epidemiology • Cohort study • Elderly

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Introduction

Arterial hypertension has a high prevalence of over 70% in individuals 75 years of age or older.[1] Thus, and in view of an aging population, there has been an intensive debate in the past decade regarding the optimal targets for blood pressure (BP) lowering treatment in elderly hypertensive patients.[2]

In 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) recommended a target systolic BP (SBP) <130 mmHg for community-dwelling hypertensive older adults.[3] This recommendation was largely based on the subgroup analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) that included patients aged 75 years or older, where SBP <120 mmHg resulted in a 33% decrease in the risk of all-cause mortality compared with SBP <140 mmHg.[4] However, the several exclusion criteria of SPRINT (e.g. diabetes or previous stroke) and the method used for BP monitoring have led to some controversy regarding the generalizability of its results in real-world clinical practice.[5,6] In contrast, the recently presented guidelines on management of arterial hypertension of the European Society of Cardiology and European Society of Hypertension (ESC/ESH) recommend target SBP <140 mmHg for elderly patients aged up to 80 years, while suggesting individualized treatment strategies in patients aged over 80 years.[7]

Given the current uncertainty regarding target BP in elderly patients, as well as the scarcity and limitations of randomized controlled trials (RCTs), observational studies could provide much needed complementary information with respect to benefits and harms of antihypertensive treatment in this fast-growing age group. Thus, the objective of our population-based analysis was to assess whether BP values below SBP 140 mmHg and diastolic BP (DBP) 90 mmHg during antihypertensive treatment are associated with a decreased risk of all-cause mortality in community-dwelling older adults.

Methods

Data source

All individuals in our analysis were participants of the Berlin Initiative Study (BIS). The BIS is an ongoing prospective cohort study initiated in 2009 in Berlin, Germany, to evaluate kidney function in older adults,[8] and its population has been shown to be representative of the elderly German general population.[9–13] Inclusion criteria of the BIS were (i) having a specific German statutory health insurance (AOK Nordost – Die Gesundheitskasse; holds ~24% of individuals aged ≥70 years in north-eastern Germany where Berlin is located), (ii) living in Berlin, and (iii) being ≥70 years of age. Exclusion criteria were (i) dialysis treatment or (ii) kidney transplantation. Participants were recruited between November 2009 and June 2011 in one of the 13 study sites across Berlin based on a random sample from the overall pool of insurants. During the visit, a standardized face-to-face interview based on a structured questionnaire was conducted assessing information on demographics, lifestyle variables such as smoking, alcohol consumption, and physical exercise, medications, and comorbidities. Moreover, we measured anthropometric variables such as body mass index (BMI) and sitting BP (defined below). Blood and urine samples were also collected. All subjects gave written informed consent as approved by the local ethics committee.

Study population

For the analysis presented here, cohort entry was defined as the time point of the visit for each participant described above, whereas end of the study period was December 2016. We investigated the subgroup of participants treated with antihypertensive drugs (except for loop diuretic monotherapy). These were followed from cohort entry until the occurrence of the study outcome (defined below) or the end of the study period, whichever occurred earlier.

Utilization of antihypertensive drugs

We assessed the frequency of different antihypertensive drugs at baseline overall and stratified by sex and kidney function [<60 vs. ≥60 mL/min per 1.73 m^2 estimated glomerular filtration rate (eGFR)], as well as the frequency of monotherapy and combination therapy. We also assessed the frequency of drug combinations previously associated with increased risks of serious adverse events: (i) the hyperkalaemia associated dual blockade of the renin angiotensin system (RAS),[14] (ii) the bradycardia associated combination of beta-blockers with the negative chronotropic calcium-channel blockers (CCBs) verapamil, gallopamil, and diltiazem,[15] and (iii) the nephrotoxicity associated combination of non-steroidal anti-inflammatory drugs (NSAIDs) with RAS inhibitors and diuretics.[16] Finally, we assessed the frequency of nephroprotective treatment with RAS inhibitors in patients with diabetes or albuminuria.[17,18]

Study groups

We classified all patients in our study cohort into one of the following groups according to their baseline BP values: (i) 'normalized BP', defined as SBP <140 mmHg and DBP <90 mmHg and (ii) 'non-normalized BP', defined as SBP ≥140 mmHg or DBP ≥90 mmHg. According to the ESC/ESH recommendations on the procedure of routine BP measurement,[7] BP was calculated as the mean of two office measurements within 10 min. Patients were seated before measurement for 5 min, legs uncrossed, and not talking.

Covariates

We considered the following covariates at baseline: age (70–79 years or ≥80 years), sex, BMI category (<30 or ≥30 kg/m^2), smoking status (ever, never), alcohol consumption (less than once monthly, once monthly to twice weekly, and more than twice weekly), physical exercise category (once weekly, one to five times weekly, and more than five times weekly), duration of treated hypertension in years, eGFR (<60 or ≥60 mL/min per 1.73 m^2), albuminuria, previous myocardial infarction (MI), previous stroke, and diabetes. We also assessed the number of classes of antihypertensive drugs received. eGFR was calculated using the BIS2 equation.[19] Albuminuria was defined as an albumin-to-creatinine ratio ≥30 mg/g in spot urine analysis. Diabetes was defined as haemoglobin A1c >6.5% or intake of any antidiabetic drug. Serum creatinine was measured using the isotope dilution mass spectrometry traceable enzymatic method 'creatinine plus cobas' on the Modular P800 System (Roche). Cystatin C was measured using the standardized particle-enhanced nephelometric N Latex assay on the BN II System (Siemens Healthcare Diagnostics).

All-cause mortality

All-cause mortality was assessed in a two-step approach. First, we used information from patients' relatives and hospital discharge notes. Second, we validated the outcome and identified the exact date of death using information from the health insurance company.

Statistical analyses

We used descriptive statistics to summarize patient characteristics in the study cohort and the utilization of antihypertensive drugs. Crude incidence rates of all-cause mortality were calculated based on the Poisson distribution. A Cox proportional hazards model yielded crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of all-cause mortality

associated with normalized BP as compared with non-normalized BP. For this analysis, we adjusted for all covariates mentioned above.

Sensitivity analyses

We conducted five pre-specified sensitivity analyses. First, to assess a possible effect modification by baseline cardiovascular risk, we stratified patients by previous cardiovascular events, i.e. stroke and/or MI. Second, to assess a possible effect modification by age, we stratified patients by age 70–79 years and ≥80 years. Third, we assessed the effect of a more conservative target SBP in patients aged 80 years or older based on previous ESC/ESH guidelines.[20] Thus, we repeated the primary analysis for this age group after redefining normalized BP as SBP <150 mmHg and DBP <90 mmHg. Fourth, we tested for a possible interaction between history of cardiovascular events and BP control as well as between age and BP control by including interaction terms in the primary model. Finally, to assess the potential impact of reverse causality given the previously reported terminal decline in BP at the end-of-life,[21] we repeated the primary analysis using a 1-year lag period.

We also conducted three *post hoc* sensitivity analyses. First, patients with normalized BP were further categorized in two groups: (i) patients with SBP <130 mmHg and DBP <90 mmHg and (ii) patients with SBP 130–139 mmHg and DBP <90 mmHg. Both groups were compared separately with patients with non-normalized BP. Second, we repeated the primary analysis and the two stratified analyses based on previous cardiovascular events and age after additionally adjusting for serum albumin and use of antithrombotic drugs (antiplatelets or oral anticoagulants). Finally, we conducted stratified analyses for the following age-sex combinations: (i) male patients aged 70–79 years, (ii) female patients aged 70–79 years, (iii) male patients aged ≥80 years, and (iv) female patients aged ≥80 years.

Systolic blood pressure and all-cause mortality

We also assessed the association between SBP and the risk of all-cause mortality. We modelled SBP flexibly using natural splines with three interior knots (at the 25th, 50th, and 75th percentile: 131 mmHg, 144 mmHg, and 159 mmHg) to account for potential non-linear associations between SBP and the outcome (reference: SBP 140 mmHg). A two-tailed *P*-value <0.05 was considered significant. All statistical analyses were conducted with Stata (Version 14.0; StataCorp, College Station, TX, USA), SPSS (Version 25.0; IBM Corp, Armonk, NY, USA), and R (Version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Among the 2069 BIS participants, 1628 (79%) were treated with antihypertensive drugs at baseline (Supplementary material online, *Figure S1*). Of those, 636 (39%) exhibited normalized SBP and DBP values below 140 and 90 mmHg, while 992 (61%) showed higher BP values. *Table 1* shows the characteristics of patients classified by BP control. Patients with normalized BP were similar to patients with non-normalized BP regarding demographics, lifestyle factors, diabetes, previous stroke, duration of treated hypertension, and utilization of antihypertensive drugs. However, patients with normalized BP were more likely to have a previous MI or reduced eGFR and less likely to have albuminuria.

Utilization of antihypertensive drugs

The most common antihypertensive drug classes used were diuretics (60%), beta-blockers (59%), angiotensin-converting enzyme (ACE) inhibitors (50%), CCBs (34%), and angiotensin receptor blockers (ARBs) (30%). Overall, 31% of the patients were on monotherapy and 69% on combination therapy. Male patients reported a higher intake of ACE inhibitors (58% vs. 43%) but a lower intake of ARBs (25% vs. 35%) than female patients (Supplementary material online, *Table S1*). Patients with eGFR <60 mL/min per 1.73 m^2 reported a higher intake of beta-blockers (64% vs. 53%) and diuretics (68% vs. 49%) than patients with eGFR ≥60 mL/min per 1.73 m^2 (Supplementary material online, *Table S1*). High-risk combinations were rarely observed [dual RAS blockade, 29 (1.8%); concomitant use of beta-blockers with negative chronotropic CCBs, 5 (0.3%); and concomitant use of NSAIDs with RAS inhibitors and diuretics, 11 (0.7%)]. Finally, 85% of patients with diabetes and 81% of patients with albuminuria received RAS inhibitors.

Blood pressure control and all-cause mortality

The median (interquartile range) follow-up time was 73 months (66–77 months), generating a total follow-up of 8853 person-years. During the study period 469 patients died, resulting in an incidence rate of 53.0 per 1000 person-years (baseline characteristics of patients deceased during the study period and alive at the end of the study period in Supplementary material online, *Table S2*). *Table 2* shows that compared with non-normalized BP, normalized BP was associated with an increased risk of all-cause mortality (crude incidence rates 60.3 vs. 48.5 per 1000 person-years; adjusted HR 1.26; 95% CI 1.04–1.54). The number needed to harm (NNH) was 64 after 3 years and 34 after 6 years (Supplementary material online, *Figure S2A*).

Table 3 presents the results of the stratified analyses (summarized in *Figure 1*). While there was no statistically significant association between normalized BP and all-cause mortality in patients without previous cardiovascular events (adjusted HR 1.16; 95% CI 0.90–1.48), there was an increased risk in patients with respective medical history (adjusted HR 1.61; 95% CI 1.14–2.27; 3-year NNH: 24/6-year NNH: 16; Supplementary material online, *Figure S2B*). Stratifying by age showed a tendency towards a decreased risk of all-cause mortality associated with normalized BP in patients aged between 70 years and 79 years (adjusted HR 0.83; 95% CI 0.54–1.27), but an increased risk in patients aged 80 years or older (adjusted HR 1.40; 95% CI 1.12–1.74; 3-year NNH: 29/6-year NNH: 17; Supplementary material online, *Figure S2C*).

The increased risk in octogenarians was attenuated with the more conservative SBP target of <150 mmHg (adjusted HR 1.21; 95% CI 0.97–1.51) (Supplementary material online, *Table S3*). We did not find any statistically significant interactions between history of cardiovascular events and BP control ($P = 0.141$) or age and BP control ($P = 0.110$). The use of a 1-year lag period did not considerably modify the results of the primary analysis (adjusted HR 1.22; 95% CI 0.99–1.49) (Supplementary material online, *Table S4*). In a *post hoc* analysis where normalized BP was further categorized into SBP 130–139 mmHg and SBP <130 mmHg, we found that compared with non-normalized BP, values below SBP <130 mmHg and DBP <90 mmHg were associated with an increased risk of all-cause mortality (HR

Table 1 Patient characteristics classified by blood pressure control at baseline

	Normalized BP[a] (*n* = 636)	Non-normalized BP[b] (*n* = 992)
Age (years), mean (SD)	81.1 (6.5)	80.6 (6.7)
70–79	295 (46.4)	483 (48.7)
≥80	341 (53.6)	509 (51.3)
Female sex	326 (51.3)	525 (52.9)
Body mass index (kg/m^2), mean (SD)	28.1 (4.4)	28.1 (4.2)
<30	439 (69.0)	711 (71.7)
≥30	197 (31.0)	280 (28.3)[c]
Smoking		
Ever	342 (53.8)	477 (48.1)
Never	294 (46.2)	515 (51.9)
Alcohol consumption		
Less than once monthly	297 (46.7)	448 (45.1)
Once monthly to twice weekly	226 (35.5)	328 (33.1)
More than three times weekly	109 (17.2)	206 (20.8)
Unknown	4 (0.6)	10 (1.0)
Physical activity		
Less than once weekly	170 (26.7)	274 (27.6)
One to five times weekly	304 (47.8)	464 (46.8)
More than five times weekly	159 (25.0)	254 (25.6)
Unknown	3 (0.5)	0 (0)
BP (mmHg), mean (SD)		
SBP	125.2 (11.2)	158.5 (17.0)
DBP	72.2 (8.8)	85.9 (12.9)
$eGFR_{BIS2}$ (mL/min per 1.73 m^2)		
<60	393 (61.8)	560 (56.5)
≥60	240 (37.7)	431 (43.4)
Unknown	3 (0.5)	1 (0.1)
Diabetes	186 (29.2)	292 (29.4)
Albuminuria[d]	143 (22.7)	320 (32.5)
Previous myocardial infarction	143 (22.5)	148 (14.9)
Previous stroke	78 (12.3)	104 (10.5)
Previous angina pectoris	85 (13.4)	117 (11.8)
Duration of treated hypertension (years), mean (SD)	14.6 (11.4)	14.4 (11.0)
Number of antihypertensive drugs, mean (SD)	2.3 (1.1)	2.1 (1.0)
Diuretics	391 (61.5)	582 (58.7)
Beta-blockers	392 (61.6)	575 (58.0)
Angiotensin-converting enzyme inhibitors	321 (50.5)	495 (49.9)
Angiotensin receptor blockers	196 (30.8)	298 (30.0)
Calcium-channel blockers	216 (34.0)	338 (34.1)

Values are expressed as *n* (%) unless stated otherwise.
BIS, Berlin Initiative Study; BP, blood pressure; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; SBP, systolic BP; SD, standard deviation.
[a]SBP <140 mmHg and DBP <90 mmHg.
[b]SBP ≥140 mmHg or DBP ≥90 mmHg.
[c]One patient did not have a body mass index value.
[d]Albumin-to-creatinine ratio ≥30 mg/g.

1.42; 95% CI 1.13–1.79), but no such association was observed for SBP 130–139 mmHg and DBP <90 mmHg (HR 1.08; 95% CI 0.83–1.42; patient characteristics in Supplementary material online, *Table S5*, risk analysis presented in detail in Supplementary material online, *Table S6*). Additional adjustment for serum albumin and use of antithrombotic drugs led to an attenuated effect in the overall cohort (HR 1.17; 95% CI 0.96–1.43; Supplementary material online, *Table S7*). However, the effect estimates in the stratified analyses remained consistent (Supplementary material online, *Table S8*). Finally, the stratified analyses for different age–sex combinations remained inconclusive due to the low number of events (Supplementary material online, *Table S9*).

Systolic blood pressure and all-cause mortality

Figure 2 shows the results of the analysis on SBP and the risk of all-cause mortality. Modelling SBP flexibly and using 140 mmHg as reference produced a U-shaped curve. Indeed, there was an increased risk with lower SBP values that reached statistical significance at ~125 mmHg, while the numerically increased risk with higher SBP values did not reach statistical significance.

Discussion

Our analysis of the BIS population showed that normalized BP, defined as systolic and diastolic values below 140/90 mmHg, was not associated with a decreased risk but instead with a 26% increased risk of all-cause mortality in older adults. This increase in the risk was mainly driven by systolic values <130 mmHg. While there was a tendency towards a decreased risk of all-cause mortality associated with normalized BP in patients aged between 70 years and 79 years, we observed a 40% increased risk in patients aged 80 years or older, and a 61% increased risk in patients with previous cardiovascular events. Finally, assessing the risk of all-cause mortality associated with SBP produced a U-shaped curve.

The increased risk of all-cause mortality associated with lower BP values is in line with previous concerns regarding the intensity of antihypertensive treatment in elderly populations.[2] Indeed, a J-shaped (or even U-shaped) relationship between BP achieved by treatment and cardiovascular morbidity and mortality has long been hypothesized.[22] This hypothesis is based on a presumed BP threshold for organ blood flow autoregulation, and the potential role of BP as a compensatory mechanism for preserving organ function.[22] Interestingly, the risk of all-cause mortality associated with normalized BP in our analysis was highest among patients aged 80 years or older and in patients with previous cardiovascular events, that is in populations where the clinical relevance of haemodynamic alterations and thus the potential harms of BP lowering could be magnified.[2,22]

The observed U-shaped association between SBP and all-cause mortality corroborates recent findings from observational studies with a shorter follow-up than BIS.[23,24] In a cohort of elderly patients (mean age 82 years) treated with antihypertensive drugs in the UK, the risk of all-cause mortality after a mean follow-up of 4.4 years was increased with lower and higher SBP values when compared with SBP 145–155 mmHg.[24] Similarly, in a cohort of elderly individuals

Table 2 Crude and adjusted hazard ratios of all-cause mortality associated with normalized blood pressure in older adults

Groups	Number of patients	Number of events	Person-years	Incidence rate (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Non-normalized BP[b]	992	266	5486	48.5	Reference	Reference
Normalized BP[c]	636	203	3367	60.3	1.25 (1.04–1.50)	1.26 (1.04–1.54)

BP, blood pressure; CI, confidence interval; DBP, diastolic BP; HR, hazard ratio; SBP, systolic BP.
[a]Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical exercise, duration of treated hypertension, glomerular filtration rate, albuminuria, previous myocardial infarction, previous stroke, diabetes, and number of classes of antihypertensive drugs.
[b]SBP ≥140 mmHg or DBP ≥90 mmHg.
[c]SBP <140 mmHg and DBP <90 mmHg.

Table 3 Crude and adjusted hazard ratios of all-cause mortality associated with normalized blood pressure in older adults stratified by previous cardiovascular events or age

Groups	Number of patients	Number of events	Person-years	Incidence rate (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
No previous cardiovascular event						
Non-normalized BP[b]	768	192	4323	44.4	Reference	Reference
Normalized BP[c]	433	109	2411	45.2	1.02 (0.81–1.29)	1.16 (0.90–1.48)
Previous cardiovascular event[d]						
Non-normalized BP[b]	224	74	1164	63.6	Reference	Reference
Normalized BP[c]	203	94	956	98.3	1.56 (1.15–2.11)	1.61 (1.14–2.27)
70–79 years						
Non-normalized BP[b]	483	66	2904	22.7	Reference	Reference
Normalized BP[c]	295	40	1772	22.6	1.00 (0.67–1.47)	0.83 (0.54–1.27)
≥80 years						
Non-normalized BP[b]	509	200	2582	77.5	Reference	Reference
Normalized BP[c]	341	163	1595	102.2	1.34 (1.09–1.65)	1.40 (1.12–1.74)

BP, blood pressure; CI, confidence interval; DBP, diastolic BP; HR, hazard ratio; SBP, systolic BP.
[a]Adjusted for age (not in the analysis stratified by age), sex, body mass index, smoking, alcohol consumption, physical exercise, duration of treated hypertension, glomerular filtration rate, albuminuria, previous myocardial infarction (not in the analysis stratified by previous cardiovascular event), previous stroke (not in the analysis stratified by previous cardiovascular event), diabetes, and number of classes of antihypertensive drugs.
[b]SBP ≥140 mmHg or DBP ≥90 mmHg.
[c]SBP <140 mmHg and DBP <90 mmHg.
[d]Previous cardiovascular event defined as previous stroke or myocardial infarction.

(mean age 92 years) in China, the risk of all-cause mortality at 3 years was also increased with lower and higher SBP values when compared with SBP 143.5 mmHg.[23]

Our results are in relative contrast with the few existing RCTs focusing on antihypertensive treatment in elderly populations.[4,25] In the Hypertension in the Very Elderly Double Blind Trial (HYVET) that included patients aged 80 years or older with SBP ≥160 mmHg, targeting 150/80 mmHg led to a decreased risk of all-cause mortality (HR 0.79; 95% CI 0.65–0.96).[25] Moreover, in a subgroup analysis of the SPRINT trial that included patients aged 75 years or older with SBP ≥130 mmHg, targeting SBP <120 mmHg also led to a decreased risk of all-cause mortality (HR 0.67; 95% CI 0.49–0.91).[4] While both HYVET and SPRINT studied large numbers of older adults treated with antihypertensive drugs, there are some concerns with respect to the generalizability of their results in real-world clinical practice. Indeed, the two RCTs had a relatively short follow-up (HYVET: median follow-up 1.8 years; SPRINT subgroup analysis: median follow-up 3.1 years), and they also excluded patients with common comorbidities (HYVET: previous haemorrhagic stroke, heart failure, dementia, serum creatinine levels >1.7 mg/dL; SPRINT: diabetes, previous stroke, heart failure, dementia).[4,25] Moreover, in SPRINT BP was monitored via unattended, automated measurements instead of the typically performed office measurements, possibly leading to artificially low BP values.[4,5]

Our study has several strengths. First, using the relatively large, well-characterized BIS population as data source and applying a population-based design with few exclusion criteria allowed us to depict real-world clinical practice in community-dwelling older adults, while producing results that are highly generalizable. Second, with a median follow-up of 6 years, we were able to assess the long-term mortality risk associated with BP control in this population. This is of importance given the relatively short follow-up in the SPRINT and

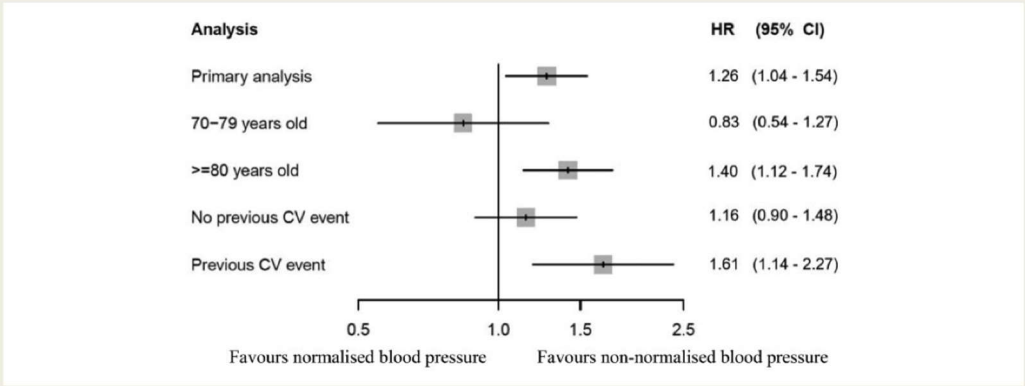


Figure 1 Forest-plot summarizing the primary analysis and the stratified analyses. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

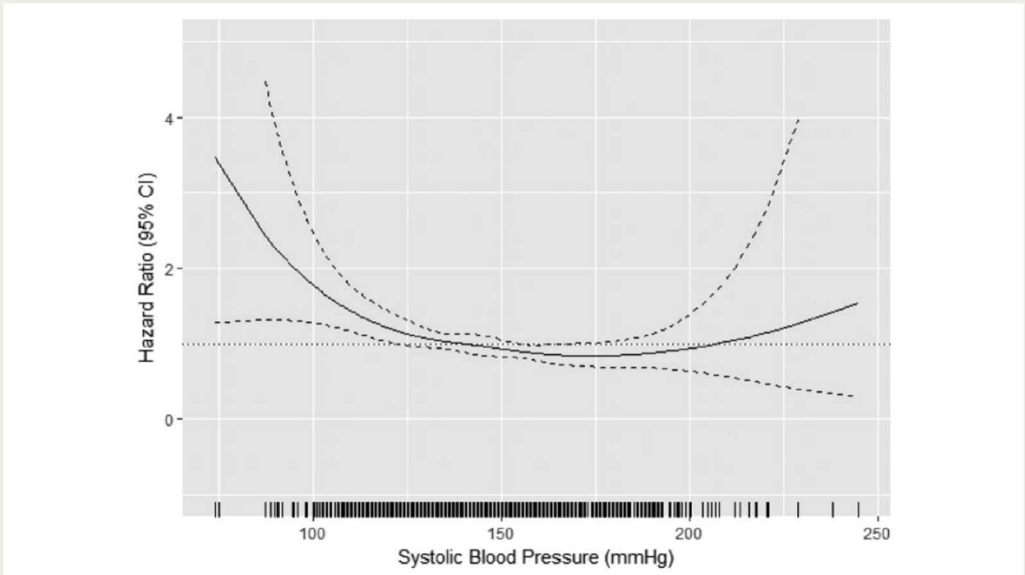
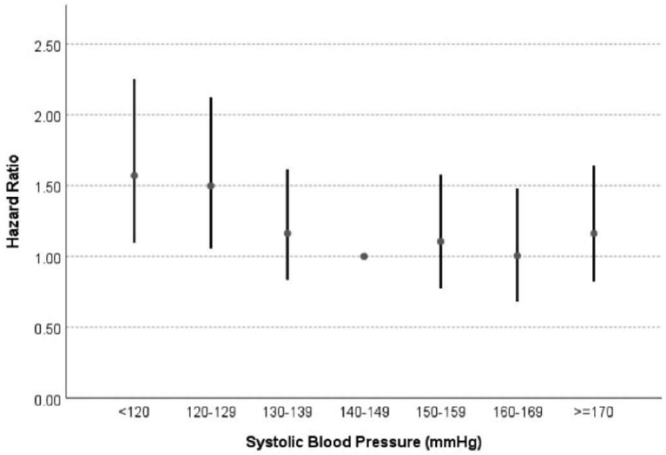


Figure 2 Association of systolic blood pressure as continuous variable with the risk of all-cause mortality. Hazard ratios of the association between systolic blood pressure and risk of all-cause mortality (solid line) with the corresponding 95% confidence intervals (dotted lines) (reference systolic blood pressure: 140 mmHg). Curves were estimated in a Cox proportional hazards model using natural splines, adjusted for age, sex, body mass index, smoking, alcohol consumption, physical exercise, duration of treated hypertension, glomerular filtration rate, albuminuria, previous myocardial infarction, previous stroke, diabetes, and number of classes of antihypertensive drugs. CI, confidence interval; SBP, systolic blood pressure.

HYVET trials.[25,26] Finally, we considered the previously raised concerns over possible reverse causality due to a terminal decline in BP at the end-of-life[21] by using a 1-year lag period in a sensitivity analysis that yielded results highly consistent with those of the primary analysis.

Our study also has some limitations. First, due to its observational nature there is potential for confounding. Moreover, we did not have information on coronary artery disease, an important risk factor of mortality. To alleviate this bias, we adjusted for many variables including demographics, anthropometric and lifestyle



Take home figure Association of systolic blood pressure as categorical variable with the risk of all-cause mortality. Hazard ratios and 95% confidence intervals of the association between different ranges of systolic blood pressure and the risk of all-cause mortality (reference: 140 mmHg), adjusted for age, sex, body mass index, smoking, alcohol consumption, physical exercise, duration of treated hypertension, glomerular filtration rate, albuminuria, previous myocardial infarction, previous stroke, diabetes mellitus, and number of classes of antihypertensive drugs.

variables, as well as important comorbidities (including previous MI) and co-medications. Of note, inclusion of all these variables had a minimal effect on the point estimate (crude HR 1.25 vs. adjusted HR 1.26). Second, a possible diagnosis of heart failure was not captured in our questionnaires. Thus, some patients could have taken antihypertensive drugs such as ACE inhibitors, ARBs, beta-blockers, or diuretics for the treatment of heart failure. However, the aim of our study was to investigate the possible association between specific BP thresholds and mortality regardless of the treatment regime. Third, we assessed BP control at baseline and did not consider changes in BP control during follow-up. However, BP and intake of antihypertensive drugs seem to change only slightly over time in older adults.[27] Moreover, potential misclassification would probably dilute the effects resulting in an underestimation of the true risk. Finally, cause of death was not available in our data. Thus, future studies are needed to assess the specific risk of cardiovascular death.

In summary, our study shows that BP values below 140/90 mmHg could be associated with an increased risk of all-cause mortality in those aged 80 years or older or at increased cardiovascular risk, with the NNH being relatively low. Given the scarcity of RCTs in elderly populations and the challenges regarding the generalization of their results in real-world clinical practice, careful individualized clinical assessment of potential benefits, and harms of antihypertensive treatment should guide physician decision-making.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: D.H. has received travel reimbursement for analysis project meetings from Actelion Pharmaceuticals and Boehringer Ingelheim. R.K. has consultant/advisory arrangements or received honoraria for lectures from Bayer Health Care, Berlin-Chemie, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Recordati Pharma, Servier, and Trommsdorff. E.S. has received honoraria for lectures from Fresenius Kabi and Siemens. And all other authors declare no conflict of interest.

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RESEARCH ARTICLE

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Is there an association between social determinants and care dependency risk? A multi-state model analysis of a longitudinal study

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Abstract

Despite a growing body of knowledge about the morbidities and functional impairment that frequently lead to care dependency, the role of social determinants is not yet well understood. The purpose of this study was to examine the effect of social determinants on care dependency onset and progression. We used data from the Berlin Initiative Study, a prospective, population-based cohort study including 2,069 older participants living in Berlin. Care dependency was defined as requiring substantial assistance in at least two activities of daily living for 90 min daily (level 1) or 3+ hours daily (level 2). Multi-state time to event regression modeling was used to estimate the effects of social determinants (partnership status, education, income, and sex), morbidities, and health behaviors, characteristics, and conditions. During the study period, 556 participants (27.5%) changed their status of care dependency. Participants without a partner at baseline were at a higher risk to become care-dependent than participants with a partner (hazard ratio [HR], 95% confidence interval [CI]: 1.24 (1.02–1.51)). After adjustment for other social determinants, morbidities and health behaviors, characteristics, and conditions the risk decreased to a HR of 1.19 (95% CI: 0.79–1.79). Results indicate that older people without a partner may tend to be at higher risk of care dependency onset but not at higher risk of care dependency progression. Clinicians should inquire about and consider patients' partnership status as they evaluate care needs.

KEYWORDS
activities of daily living, care dependency, cohort studies, marital status, proportional hazards models, social determinants of health

Alice Schneider and Stefan Blüher contributed equally to this study.

1 | INTRODUCTION

One of the consequences of rising life expectancy and aging is that more people are facing the prospect of becoming dependent on assistance and care at some point in their lives. In Germany, three out of four women and approximately one man in every two will become care-dependent as defined in the German Long-Term Care Insurance Act (*Pflegeversicherungsgesetz*) during their lifetime (Rothgang, 2010). Care dependency has thus become a major individual and social risk in long-lived populations.

In this context, care dependency means that a person is receiving benefits covered by long-term care insurance within the German social insurance system. This is contingent on submission of an application by the insured person and an assessment by medical or care professionals that the person concerned has a substantial need for assistance in basic routines and activities of daily living (ADL). In the international context, the Barthel Index (Mahoney, 1965; Shah, Vanclay, & Cooper, 1989)—a weighted scale to measure performance or limitations in ADL—may be regarded as approximating this understanding of care dependency. Under the classification system of relevance to the present study (i.e., to December 31, 2016), the German long-term care insurance system provides benefits based on three levels of care that accounts assistance time required: Care level 1 requires assistance for 90 min daily; care level 2 requires assistance for 3 hr daily; and care level 3 requires 5 hr daily (Maidhof et al., 2002).

1.1 | Care dependency onset

Despite a growing body of knowledge about the morbidities and functional impairment that frequently lead to care dependency, it is to a large extent unclear which other health-related factors, and in which combinations, are associated with the risk of care dependency onset and progression. The relevance of age as a key determinant of need for care has been described repeatedly (Hajek & König, 2016; Schnitzer et al., 2015). The research findings on sex-specific differences are less consistent, varying according to whether they are adjusted for age and morbidities (Hajek, Brettschneider, Lange et al., 2016; Schnitzer et al., 2017). The role of socioeconomic factors (education, income, and occupation) has not been fully explained (Ramsay, Whincup, Morris, Lennon, & Wannamethee, 2008; Sulander et al., 2012). Least researched at present is the impact of basic social determinants for care dependency, such as marital status, social networks, and aspects such as living arrangements.

The research results currently available provide information about social determinants as important characteristics: In a recent publication based on cross-sectional cohort data we could show that—next to older age, urinary incontinence, stroke, falls, cancer, diabetes, education, limited mobility, and limited physical activity—care dependency was associated with "having no partner" (Schnitzer et al., 2019). Hajek, Brettschneider, Ernst et al. (2016) identified a higher risk of functional impairment for persons who lost a partner compared to those with a partner. A Danish study by Nilsson, Avlund, and Lund (2010) analyzed participation and networks and found evidence that social resources protect against risk for mobility limitations. And as early as 2008, Borchert and Rothgang (2008) emphasized the protective effect of partnerships on care dependency risk for older men.

As regards prevention strategies for care dependency, knowledge of the factors causing care dependency onset is key. Another question of interest in this context is whether the determinants of care dependency onset differ (in scope and direction of the association) from those causing a worsening of care dependency. In their longitudinal study, Borchert and Rothgang (2008) differentiate between individual levels of care but analyze them as dependent variables in different models, meaning that possible transitions to a different level of care were not examined within one model (Beyersmann, Allignol, & Schumacher, 2011). Analyzing time to competing events and transitions from one state to another in one single statistical model (multi-state model) allows us to determine whether the scope and direction of the associations between covariates and various transitions differ. The use of multi-state models for similar research questions with time-to-event data is still novel.

1.2 | Aim of the study

Researchers have not fully answered the question about the association between social determinants and the risk of onset or worsening of care dependency. The present study addresses this study gap, analyzing several events in one model and focusing on social determinants such as partnership status, education, income, and sex. The aims of this study are (a) to examine the effect of social determinants on care dependency onset and progression, and (b) to analyze the effect of social determinants on various levels of care dependency.

2 | MATERIALS AND METHODS

2.1 | Data and design

We used data from the ongoing Berlin Initiative Study (BIS). The BIS is a prospective, longitudinal, population-based cohort study designed to evaluate the epidemiology of chronic kidney disease in older adults (≥70 years of age). Data included information on sociodemographics, lifestyle variables, morbidities, medication, and measurements of blood and urine samples, which were collected every 2 years in a face to face interview since 2009. Inclusion criteria were having a specific German statutory health insurance (AOK-Nordost Die Gesundheitskasse), living in Berlin, and not being on dialysis or kidney transplanted. Participant's survey data were also linked with their health insurance data. The study was approved by the local ethics committee (Ethics Committee of Charité—Universitätsmedizin Berlin, Ref. EA2/009/08) and the participants gave written informed

consent. For further details of study design and methodology see Schaeffner et al. (2010).

2.2 | Outcome measures of care dependency

Care dependency is determined by the amount of time needed daily for substantial assistance in at least two ADLs in the personal hygiene, nutrition, and mobility categories, and, additionally, assistance with domestic tasks (at least 90 min per day over a period of at least 6 months; Schnitzer et al., 2017). We considered two levels of care dependency as outcomes: Level 1 (90 min of assistance per day), and levels 2 and 3, which were combined because of the small sample size ($n = 47$) for level 3 (at least 3 hr assistance per day). The information regarding the need for care was obtained from claims data provided by the participant's health insurance provider. Data on time points of change in registered care dependency were linked to patient survey data (last updated information from health insurer AOK-Nordost January 12, 2016). The dataset thus includes all information about the care dependency level and dates of change in care dependency for all participants (including those with loss to follow up) from the start of the study in 2009 until January 2016. Insured persons who needed at least 5 hr assistance per day (level 3 care dependency) at baseline were not included in this study, as they were at the highest level of dependency and no further worsening was possible.

2.3 | Measures of social determinants

Our term "social determinants" subsumes partnership ("do you have a partner"), monthly individual income, and education. In addition, age and sex were considered as social determinants in the analysis, because they are associated to a high degree with the allocation of social roles (Hradil, 2006). Educational attainment was assessed using the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN) index (Kunst, 2009), with participants classified into three categories: (a) no school-leaving qualifications or low educational level (primary education), (b) intermediate educational level (lower and upper secondary education), and (c) high educational level (Bachelor's, Master's, and PhD).

2.4 | Additional variables of interest

With focus on our research question, we included the following variables: Smoking (never smoked or stopped smoking >10 years ago, current smoker or stopped ≤10 years ago), alcohol consumption (no regular consumption; moderate consumption: women ≤12 g alcohol/day, men ≤24 g alcohol/day; risky drinking: women >12 g alcohol/day, men >24 g alcohol/day), body mass index (BMI; <25, 25–30, >30), arterial hypertension (intake of antihypertensive medication); history of stroke, myocardial infarction, or cancer (all self-reported yes/no and validated by physician letters); kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73 m^2); and diabetes mellitus (intake of antidiabetic medication and/or HbA1c level > 6.5%, yes/no); see Schaeffner et al. (2010) and Ebert et al. (2016) for further details.

2.5 | Statistical analyses

We evaluated the effect of social determinants and morbidities on the transition time to different events. As we were considering more than one event and different transitions, we used a multi-state model with three possible states: no care dependency, care dependency level 1 and care dependency level 2 (composite level 2 and level 3). We analyzed the three transitions from no care dependency to level 1 (transition 1: $0 \rightarrow 1$), from no care dependency to level 2 (transition 2: $0 \rightarrow 2$), and from level 1 to level 2 (transition 3: $1 \rightarrow 2$). For this analysis, participants who died during the study period were censored, since mortality was not the focus of this analysis and is one of the primary outcomes of the BIS that will be analyzed and reported in future publications. With a multi-state model, it is possible to include all given information in one statistical model. The model allows different effects of a single covariate corresponding to the different transitions by estimating transition-specific covariate effects.

2.5.1 | Specifications and assumptions

With one exception, we used participant age as the time scale in our time-to-event models. Due to this specification these models are by definition age-adjusted; therefore, age was not additionally included in the models as a covariate. For the definition of time t the "clock forward" approach was used (Beyersmann et al., 2011; Putter, Fiocco, & Geskus, 2007). We assumed different baseline hazards for the three types of transition. We therefore calculated a stratified Cox proportional hazards model by transition (Andersen & Keiding, 2002). By doing so, we also accounted for the dependency of the data that results from repeatedly using information from the same participants. To examine the bivariate association between age and time to care dependency levels, we fitted a separate multi-state model with time-on-study as the time scale variable and with age as covariate (Table 1).

2.5.2 | Transition-specific hazards

Based on our research question, we assumed different effects of participant characteristics on each transition; for example, the association between sex and care dependency is different for the transition from no care dependency to level 1 than for the transitions from levels 1 to 2 and from no care dependency to level 2. We therefore estimated transition-specific coefficients in the complex model. To decide whether regression coefficients should be fixed or transition-specific, we used the Bayesian Information

TABLE 1 Age-adjusted hazard ratio (HR) estimates (95% CI) for separate single-variable multi-state models

	Overall	*n* (%), HR (95% CI)			
		0 → 1	1 → 2	0 → 2	Transition-specific coefficients improve model fit[a]
	n = 2,021	*n* = 431	*n* = 146	*n* = 77	
Social determinants					
Age[b]					–
≤75	572	48 (8.4)	6 (1.0)	7 (1.2)	
75–85	892	173 (19.4)	50 (5.6)	31 (3.5)	
		2.62 (1.90–3.61)	2.60 (1.11–6.06)	3.24 (1.43–7.35)	
>85	557	210 (37.7)	90 (16.2)	39 (7.0)	
		8.83 (6.44–12.11)	3.20 (1.40–7.32)	11.48 (5.12–25.78)	
Sex					Yes
Male	958	197 (20.6)	79 (8.2)	50 (5.2)	
Female	1,063	234 (22.0)	67 (6.3)	27 (2.5)	
		1.31 (1.08–1.59)	0.48 (0.35–0.67)	0.60 (0.37–0.96)	
Income, EUR					No
<1,000	562	107 (19.0)	21 (3.7)	12 (2.1)	
≥1,000	1,167	264 (22.6)	95 (8.1)	52 (4.5)	
(292 Missing)		0.85 (0.67–1.07)	1.97 (1.21–3.19)	1.55 (0.82–2.95)	
Education					No
Low	1,212	248 (20.5)	87 (7.2)	51 (4.2)	
Middle	398	104 (26.1)	27 (6.8)	9 (2.3)	
(CASMIN-short) (10 missing)					
		1.15 (0.91–1.45)	0.92 (0.60–1.42)	0.47 (0.23–0.96)	
High	401	79 (19.7)	32 (8.0)	17 (4.2)	
		0.79 (0.61–1.02)	1.39 (0.92–2.11)	0.78 (0.45–1.35)	
Partner (2 missing)					Yes
Yes	1,193	208 (17.4)	69 (5.8)	49 (4.1)	
No	827	223 (27.0)	77 (9.3)	28 (3.4)	
		1.24 (1.02–1.51)	0.66 (0.47–0.93)	0.63 (0.39–1.02)	
Health conditions					
Smoking (5 missing)					No
Never, stop > 10 years	1,824	384 (21.1)	136 (7.5)	66 (3.6)	
Current, stop ≤ 10 years	192	47 (24.5)	10 (5.2)	10 (5.2)	
		1.79 (1.31–2.43)	0.85 (0.44–1.64)	2.37 (1.21–4.65)	
Alcohol (25 missing)[c]					No
Not regularly	494	108 (21.9)	38 (7.7)	21 (4.3)	
Moderate	1,283	272 (21.2)	96 (7.5)	50 (3.9)	
		0.88 (0.70–1.11)	1.26 (0.86–1.84)	0.82 (0.49–1.37)	
Risky	220	50 (22.7)	11 (5.0)	5 (2.3)	
		0.99 (0.70–1.38)	0.85 (0.43–1.67)	0.53 (0.20–1.42)	
Diabetes mellitus					No
Yes	527	123 (23.3)	51 (9.7)	20 (3.8)	
		1.27 (1.03–1.57)	1.14 (0.80–1.62)	1.11 (0.66–1.84)	
No	1,494	308 (20.6)	95 (6.4)	57 (3.8)	
Stroke (25 missing)					No
Yes	163	38 (23.3)	18 (11.0)	9 (5.5)	
		1.24 (0.89–1.74)	0.99 (0.60–1.63)	1.69 (0.84–3.40)	
No	1,833	388 (21.2)	128 (7.0)	68 (3.7)	
Myocardial infarction (24 missing)					
Yes	274	76 (27.7)	34 (12.4)	12 (4.4)	
		1.27 (0.99–1.63)	1.59 (1.07–2.35)	1.05 (0.56–1.94)	
No	1,723	348 (20.2)	110 (6.4)	65 (3.8)	

(Continues)

TABLE 1 (Continued)

	Overall	*n* (%), HR (95% CI)			
		0 → 1	1 → 2	0 → 2	Transition-specific coefficients improve model fit[a]
	n = 2,021	*n* = 431	*n* = 146	*n* = 77	
Cancer (9 missing)					No
Yes	452	109 (24.1)	48 (10.6)	23 (5.1)	
		1.24 (1.00–1.54)	1.35 (0.95–1.91)	1.51 (0.92–2.46)	
No	1,560	322 (20.6)	98 (6.3)	54 (3.5)	
Kidney disease[d]					No
Yes	752	209 (27.8)	84 (11.2)	38 (5.1)	
		1.14 (0.93–1.40)	1.16 (0.83–1.62)	1.06 (0.66–1.71)	
No	1,268	222 (17.5)	62 (4.9)	39 (3.1)	
BMI (1 missing)					No
≤25	552	126 (22.8)	48 (8.7)	28 (5.1)	
25–30	935	178 (19.0)	64 (6.8)	30 (3.2)	
		0.97 (0.77–1.22)	1.01 (0.69–1.49)	0.71 (0.42–1.20)	
>30	533	127 (23.8)	34 (6.4)	19 (3.6)	
		1.39 (1.08–1.79)	0.87 (0.54–1.40)	0.94 (0.52–1.71)	
Hypertension					No
Yes	1,586	369 (23.3)	129 (8.1)	61 (3.8)	
		1.69 (1.29–2.22)	1.20 (0.72–2.00)	1.02 (0.59–1.77)	
No	435	62 (14.3)	17 (3.9)	16 (3.7)	

Note: The provided row percentages do not take the censoring into account, but refer only to baseline number of participants.
Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CASMIN, Comparative Analysis of Social Mobility in Industrial Nation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.
[a]Comparison of the Bayesian Information Criterion (BIC) for a model with versus without transition-specific coefficients.
[b]Estimated hazard ratios from multi-state model with time-on-study as the time scale.
[c]Alcohol consumption; moderate: women ≤12 g alcohol/day, men ≤24 g alcohol/day; risky: women >12 g alcohol/day, men >24 g alcohol/day.
[d]Kidney disease: eGFR <60 ml/min/1.73 m^2 (GFR estimated by the CKD-EPI(crea) equation).

Criterion (BIC). For each explanatory variable, we calculated the BIC for a simple single-variable model (only one of the independent variables included) with the regression coefficient fixed and the BIC for the more complex single-variable model with transition-specific coefficients. We estimated transition-specific coefficients for a given explanatory variable in the final model if the BIC was smaller (indicating better fit) in its more complex model (Table 1). For visualization we estimated the Nelson–Aalen cumulative hazard function for each transition.

The covariate "partnership" was included as a time-dependent variable (Kleinbaum & Klein, 2010), since we noticed that for 218 participants (11%), partnership status changed over study time. We were especially interested in how partnership was related to changes in care dependency levels. The exact date of change of partner status was unknown, hence date of change was estimated as the midpoint between two visits or 1 year after the last visit, if one visit was missed by the participant.

We accounted for missing data by using multivariate imputation by chained equation. We included all covariates from Table 1, age, the time-dependent variable partner status, and the information of transition times to generate 10 imputed datasets. For continuous variables, we used predictive mean matching. The estimated hazard ratios (HRs) in Table 2 are based on multiple imputed datasets.

For data handling and multiple imputation IBM SPSS 25 statistics software was used. Multi-state models were calculated in R version 3.4.2 using the package "mstate" (Putter et al., 2007; de Wreede, Fiocco, & Putter, 2010, 2011), and the package "mvna" for the Nelson–Aalen estimator (Allignol, Beyersmann, & Schumacher, 2008). No adjustment for multiple testing was applied.

3 | RESULTS

Figure 1 shows the BIS data flowchart. Four participants who showed an improvement (downgrading) in their level of care during the study period and participants in level 2 care at baseline (V1) ($n = 44$) were excluded from the analysis because the present study investigated the progression of care levels. In total we included $n = 2{,}021$ participants in Visit 1 (V1). Of these, 1,669 (83%) took part in Visit 2 (V2), and 1,423 (70%) in Visit 3 (V3). The median observation period was 5 years and 2 months (interquartile range: 4 years 8 months–5 years 6 months).

During the study period, the care dependency status of 556 participants changed, including 98 participants with more than one transition (total number of transitions = 431 + 77 + 146 = 654). In total 431 participants changed from "no care dependency" to care level 1, 77 participants from no care dependency directly to levels

TABLE 2 Hazard ratio (HR) estimates for multiple multi-state model adjusted for smoking, arterial hypertension, alcohol consumption, and BMI (estimates are based on 10 multiple imputed datasets; transition-specific estimates for sex and partner status)

	0 → 1		1 → 2		0 → 2	
n = 2,021	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Sex						
Male						
Female	1.07 (0.75–1.53)	.723	0.71 (0.41–1.22)	.220	0.62 (0.29–1.31)	.216
Education (CASMIN-short)						
Low						
Middle	1.04 (0.80–1.35)	.781	1.04 (0.80–1.35)	.781	1.04 (0.80–1.35)	.781
High	0.88 (0.65–1.19)	.415	0.88 (0.65–1.19)	.415	0.88 (0.65–1.19)	.415
Partner						
Yes						
No	1.19 (0.79–1.79)	.412	0.73 (0.38–1.39)	.347	0.72 (0.28–1.83)	.503
Income, EUR						
Unknown						
<1,000						
≥1,000	1.05 (0.64–1.72)	.857	1.05 (0.64–1.72)	.857	1.05 (0.64–1.72)	.857
Diabetes mellitus						
Yes	1.15 (0.93–1.42)	.197	1.15 (0.93–1.42)	.197	1.15 (0.93–1.42)	.197
No						
Stroke						
Yes	1.14 (0.76–1.69)	.531	1.14 (0.76–1.69)	.531	1.14 (0.76–1.69)	.531
No						
Myocardial infarction						
Yes	1.16 (0.86–1.56)	.334	1.16 (0.86–1.56)	.334	1.16 (0.86–1.56)	.334
No						
Cancer						
Yes	1.26 (0.99–1.60)	.059	1.26 (0.99–1.60)	.059	1.26 (0.99–1.60)	.059
No						
Kidney disease[a]						.438
Yes	1.09 (0.88–1.35)	.438	1.09 (0.88–1.35)	.438	1.09 (0.88–1.35)	

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CASMIN, Comparative Analysis of Social Mobility in Industrial Nation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.
[a]Kidney disease: eGFR <60 ml/min/1.73 m^2 (GFR estimated by the CKD-EPI(crea) equation).

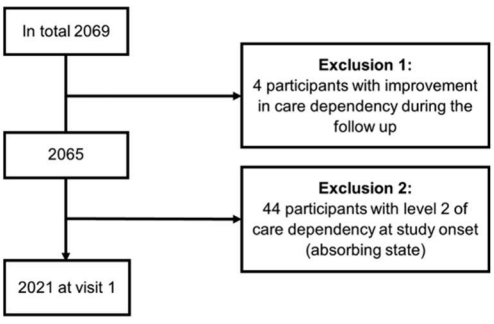

FIGURE 1 Flowchart

2 (*n* = 68) or 3 (*n* = 9), and 146 from care levels 1–2 (*n* = 131) or 3 (*n* = 15; Figure 2).

Descriptive and exploratory analysis of demographics, social determinants, health behaviors, characteristics conditions, and morbidities for persons with changes in care dependency (0 → 1, 1 → 2, 0 → 2) are provided in Table 1. Descriptive statistics are based on the raw (not imputed) data. Table 1 also includes age-adjusted HRs, 95% confidence intervals (95% CIs) and whether the model for each explanatory variable improved by including transition-specific regression coefficients (based on comparison of BIC).

The older the participant, the more likely they were to be affected by onset or worsening of care level (all HRs were >2.60 [Table 1]). Women had a higher risk to enter care level 1 than men (HR [95% CI]: 1.31 [1.08–1.59]) but lower risk for a direct entry into care level 2 (HR [95% CI]: 0.60 [0.37–0.96]). The risk to switch from

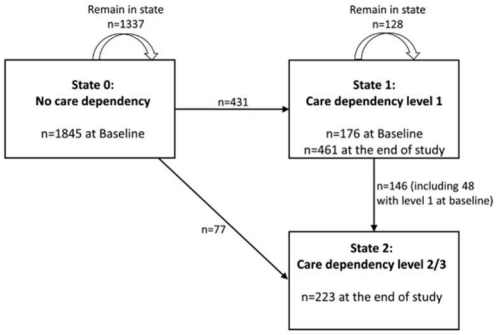

FIGURE 2 Multi-state model to study care dependency related to social determinants. Of 2,021 participants, 1,845 had not been assigned to any level of care at the beginning of the study (the remaining 176 participants had already level 1 care). A total of 1,337 of these participants remained in this state during follow up and had not been assigned to any care level. For 431 of the 1,845 participants the care dependency status changed from no care dependency to level 1, 77 participants changed to level 2. At the conclusion of the three study phases (median observation period was 5 years and 2 months), 461 participants received care at level 1 and 223 participants received care at level 2

care level 1 to care level 2 was lower for women (HR [95% CI]: 0.48 [0.35–0.67]). Approximately a third of women and men were care-dependent at the end of the study (33.1% men/34.5% women). Compared to participants in the low or high education category, those in the intermediate education category had a higher risk to enter care level 1 but lower risk for a direct entry into care level 2 or a worsening of their existing care level. Looking at the income groups, those in the highest income group were affected by transitions more often than those of the lowest income group (transition 1 → 2: HR [95% CI]: 1.97 [1.21–3.19]; transition 0 → 2: HR [95% CI]: 1.55 [0.82–2.95]). Overall, persons who reported having no partner at baseline experienced higher risk of onset in care level 1 (HR [95% CI]: 1.24 [1.02–1.51]) but lower risk of worsening of their care level (HR [95% CI]: 0.66 [0.47–0.93]) than participants with a partner (Figure 3). With regard to direct entry into care level 2, risk of participants with a partner was somewhat lower than for participants without a partner. However, the HR estimate was too imprecise to draw firm conclusions (HR [95% CI]: 0.72 [0.28–1.83]).

Smokers entered care level 1 more often than nonsmokers or ex-smokers. Participants with stroke, myocardial infarction or hypertension at baseline entered a care level or experienced a worsening of care dependency more often than participants without these morbidities (at baseline).

For the multiple model, we included the variables sex and partnership as transition specific, as the BIC was smaller in the more complex models for these covariates. All regression coefficients of the other covariates were estimated as fixed for the different transitions.

Table 2 shows the results of the multiple multi-state model. There was some evidence that having no partner compared to having a partner is associated with a somewhat higher risk of transition from no care dependency to level 1 (HR: 1.19, 95% CI: 0.79–1.79). With regard to transition from level 1 to level 2 and from no care dependency to level 2, there was some evidence of an inverse association between having no partner and the onset and worsening of care dependency (1 → 2 HR: 0.73, 95% CI: 0.38–1.39/0 → 2: HR: 0.72, 95% CI: 0.28–1.83).

Overall, there was little evidence of differences between women and men for the transition from no care dependency to level 1 (Table 2, HR: 1.07, 95% CI: 0.75–1.53). For the transition from no care dependency to level 2 and for the transition from levels 1–2 there was some evidence of lower risk for women compared to men (0 → 2: HR: 0.62, 95% CI: 0.29–1.31; 1 → 2: HR: 0.71, 95% CI: 0.41–1.22). The results on educational status and income showed no substantial differences. Regarding morbidities (stroke, myocardial infarction, cancer, kidney disease, and diabetes mellitus), participants with a morbidity had a higher risk for changes in care dependency levels than participants without morbidities. Here, the estimated effects were similar between the various transitions (Table 1) for each of the morbidity variables without model improvement compared to a more simple model (fixed estimates over transitions), evaluated with the BIC. Therefore the coefficients were set as fixed for the multiple model (Table 2).

As we were also interested in the question of different effects of partnership on care dependency for men and women, we additionally performed analyses stratified by sex for a more thorough understanding of differences, even small ones, between men and women. In separate models, men without a partner had somewhat higher risk for onset of care dependency compared to women without a partner (HR from no care dependency to level 1, men: HR: 1.29, 95% CI: 0.74–2.26, women: HR: 1.06, 95% CI: 0.55–2.06).

4 | DISCUSSION

4.1 | Main results

This study investigated the association between social determinants and care dependency onset and progression in a cohort of older adults. The results suggest, first of all, that care dependency risk may be associated with sex, partnership, and morbidities. The direction of the association with sex was the same for the transition from no care dependency to level 2 and from levels 1–2 (men had a higher care dependency risk), but the strength of the associations varied with level of care. Partnership status appears to be associated with care dependency: Persons with no partner entered level 1 care more often. However, the direction of the association is reversed on onset in care level 2 and on worsening of care dependency; here, persons with no partner tend to be affected less often. The effects were similar in the adjusted model. There was no substantial association between care dependency and income or between care dependency and education after adjustment for morbidity.

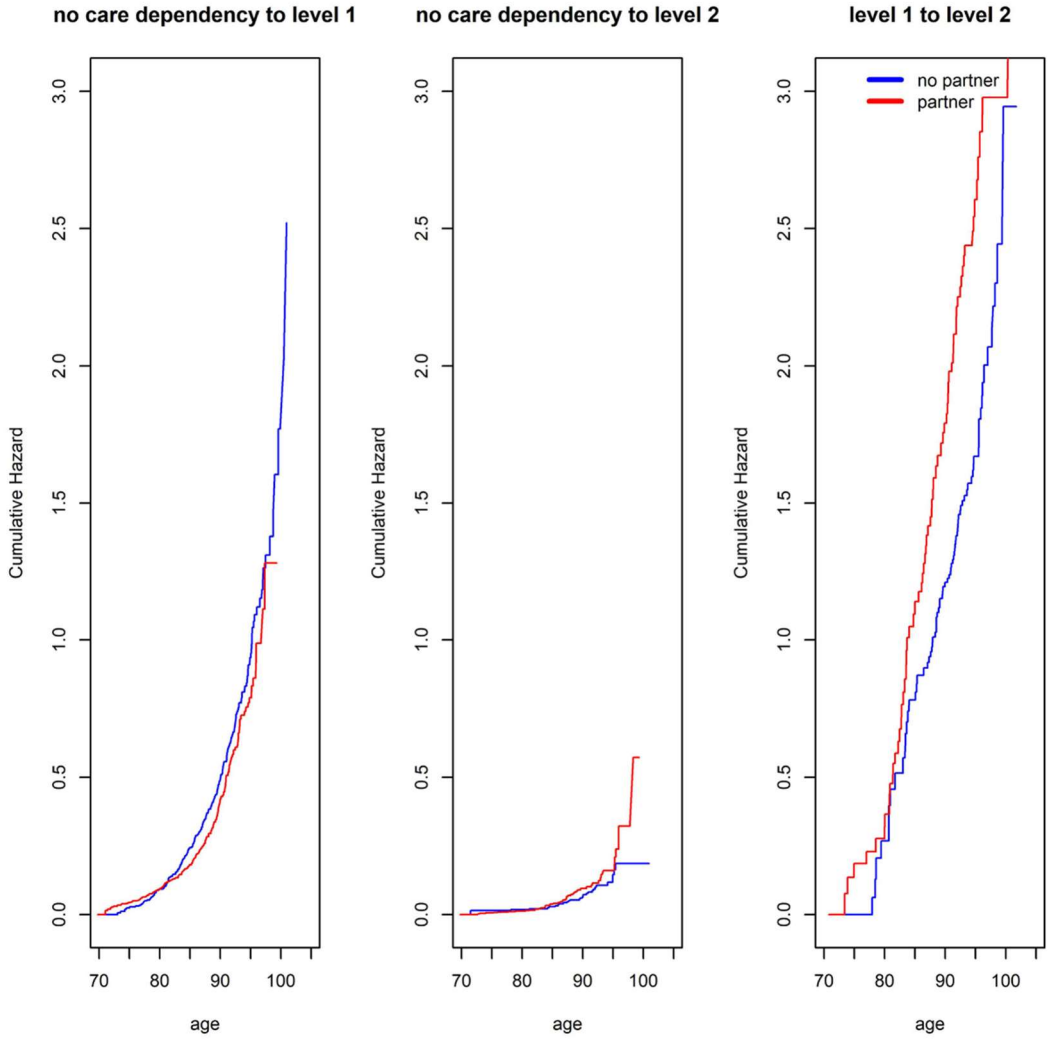

FIGURE 3 Nelson–Aalen cumulative hazard function for each transition

4.2 | Partnership, sex, and care dependency risk

The few studies that investigated the effect of partnership on care dependency risk or physical functional impairment differ in terms of the relationship indicators used: Some used marital status (married, divorced, widowed, and single), while others used cohabitation or partnership status (existing partnership irrespective of marital status). Schneider, Rapp, Klein, and Eckhard (2014) examined if the use of these different indicators leads to different health outcomes and concluded that future health research could benefit from the use of indicators other than marital status. A direct comparison between our study, which used partnership without regard to marital status, and studies that used other relationship indicators is only possible to a limited extent.

In AgeCoDe, a population-based prospective cohort study, participants aged 75 and above were surveyed in a total of four phases (baseline, n = 3,217), and marital status data were collected. Based on this dataset, Hajek et al. (2017) investigated determinants of functional impairment (Barthel Index and instrumental ADL) among elderly Germans in one study, and determinants of care levels in the German health system in another (Hajek, Brettschneider, Lange et al., 2016). In both studies, they found that living without a

spouse/partner was related to higher levels of functional impairment/care dependency. Sex-specific analyses of the determinants of functional impairment point to a higher risk only for women who have lost their spouse compared to women with spouse (Hajek & König, 2016). This contrasts with other studies where results show that having a partner is more beneficial for men than for women: Men have a lower risk of onset in care level 1 if they are married (Borchert & Rothgang, 2008; Unger, Giersiepen, & Windzio, 2015). One possible explanation discussed is that support arrangements are mainly made by women, who are more likely than men to mitigate and compensate for limitations in ADL. This hypothesis—that a sex difference exists in the effect of partnership—was not confirmed by our sex-specific analyses as the direction of the association was the same for women and men. An explanation for different findings in other studies could be that sex-specific morbidity structures underlie the finding that men experience onset in care level 1 less often. This is also confirmed by a study of Schnitzer et al. (2017) which indicates that women have a higher risk of becoming care-dependent after stroke than men because they are older on average and suffer more often from geriatric conditions, especially from urinary incontinence.

4.3 | Education, income, and care dependency risk

Studies on the effect of education and income on care dependency risk are scarce, and their findings are inconsistent. In the study by Nilsson et al. (2010) and in their subsequent work on the risk factors for mobility limitations (Nilsson et al., 2014), the authors identified an increased risk for low income groups. Unger et al. (2015) examined lifetime prevalence for care dependency and found a higher incidence of care in lower income groups. In these three studies it was not possible to adjust for morbidities and diagnosis which contribute to care dependency and may be assumed to be the background to the higher disease burden in persons with low socioeconomic status (Avendano, Aro, & Mackenbach, 2005; Ramsay et al., 2008). This assumption is reasonable, as in our study, after adjusting for morbidities, there was no evidence of a substantial association between income and level of care dependency.

Few studies provide information about educational level and care dependency risk. Huisman et al. (2005) investigated educational inequalities in relation to disability in Italy and the Netherlands. They found higher prevalence and incidence of disabilities in persons with a low level of formal education. However, as in the age group that formed the cohort for the present study, inequality was much less marked in the older age group (70–85 years) than in the younger group (55–69 years). Furthermore, the results were not adjusted for morbidities. The same applies to the study by Sulander et al. (2012), which analyzed longitudinal changes in functional capacity in three cohorts of participants born in or after 1926. In the German study by Hajek and König (2016) about factors influencing care dependency, the CASMIN classification is used to operationalize educational level (analogous to BIS). Consistent with our own study, no substantial relation between education and care dependency was observed.

In summary, our findings are consistent with the hypothesis that inequalities in care dependency between education and income groups can be explained in terms of morbidities. This is confirmed by Ramsay et al., who studied a sample of men in the 63–82 age range in the United Kingdom and found that most socioeconomic inequalities in care dependencies are explained by health behavior and morbidities (Ramsay et al., 2008).

4.4 | Strengths and weaknesses

In the BIS cohort, morbidities, laboratory, and study parameters such as BMI and a broad range of survey data including sociodemographic variables were collected. These data were merged with health insurance data to determine entry into and progression through different levels of care. This combination of survey, study, and health insurance data and the longitudinal nature of the research, along with the high average age of participants, are our study's particular strengths. Few previous studies have combined these various data sources; however, this approach is increasingly recommended (Unger et al., 2015).

Some limitations should be mentioned. First, there was a low response rate of 8.1% of the contacted individuals eligible for inclusion in the baseline survey. However, it should be noted that this low response rate can be expected in similar studies with older adults (Murphy, Schwerin, Eyerman, & Kennet, 2008). The BIS population has been shown to be representative of the German general population of older adults with regard to the morbidity structure of the participants of the same age and sex (Busch, Schienkiewitz, Nowossadeck, & Gosswald, 2013; Ebert et al., 2016; Gosswald, Schienkiewitz, Nowossadeck, & Busch, 2013; Jacob, Breuer, & Kostev, 2016; Tamayo, Brinks, Hoyer, Kuß, & Rathmann, 2016). A second limitation is that we were not able to use mortality data, so estimated effects may be partially distorted by the censoring of participants who died. Third, the partnership variable used does not distinguish between couples who live together and those who live apart, and no information about living arrangements was available. This fact restricts our findings especially since it is assumed that a partner will provide assistance with ADL. On the other hand, we also assume that partnership is a protective factor irrespective of cohabitation status, as an existing partnership presumably correlates positively with health-promoting behavior (more physical activity, more social participation; Nilsson et al., 2010).

5 | CONCLUSION

Our findings add to the limited research on social determinants of health and care dependency. Results indicate that older people without a partner may be at higher risk of care dependency onset but

not on a higher risk of care dependency progression. After adjustment for morbidities, however, the association was not statistically significant at the traditional 0.05 level. The hypothesis that a sex difference exists in the effect of partnership could not be confirmed by our sex-specific analyses as the direction of the association was the same for women and men. Regarding the effect of socioeconomic position on care dependency risk, we found that where differences existed, they could be partly explained in terms of morbidities. Clinicians should inquire about and consider patients' partnership status as they evaluate care needs.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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BMC Pediatrics

RESEARCH ARTICLE Open Access

International time trends in sudden unexpected infant death, 1969–2012

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Abstract

Background: Sudden unexpected infant death (SUID) - including sudden infant death syndrome (SIDS) - continues to be a major contributor to infant mortality worldwide. Our objective was to analyse time trends and to identify country-clusters.

Methods: The National Statistical Offices of 52 countries provided the number of deaths and live births (1969–2012). We calculated infant mortality rates per 1000 live births for SUID, SIDS, and all-cause mortality. Overall, 29 countries provided sufficient data for time course analyses of SUID. To sensitively model change over time, we smoothed the curves of mortality rates (1980–2010). We performed a hierarchical cluster analysis to identify clusters of time trends for SUID and SIDS, including all-cause infant mortality.

Results: All-cause infant mortality declined from 28.5 to 4.8 per 1000 live births (mean 12.4; 95% confidence interval 12.0–12.9) between 1969 and 2012. The cluster analysis revealed four country-clusters. Clusters 1 and 2 mostly contained countries showing the typical peak of SUID mortality during the 1980s. Cluster 1 had higher SUID mortality compared to cluster 2. All-cause infant mortality was low in both clusters but higher in cluster 1 compared to cluster 2. Clusters 3 and 4 had low rates of SUID without a peak during the 1980s. Cluster 3 had the highest all-cause infant mortality of all clusters. Cluster 4 had an intermediate all-cause infant mortality. The time trends of SUID and SIDS mortality were similar.

Conclusions: The country-specific time trends in SUID varied considerably. The identification of country-clusters may promote research into how changes in sleep position, smoking, immunisation, or other factors are related to our findings.

Keywords: Sudden unexpected infant death, Sudden infant death syndrome, Time trends, Country-clusters

Background

Mortality from sudden infant death syndrome (SIDS) is still a major contributor to mortality in the first year of life worldwide [1]. In many Western countries, including Western Europe, Australia, Canada, New Zealand, and the United States, mortality from SIDS peaked in the 1980s and decreased during the 1990s [2–6]. In other countries, such as Japan, SIDS mortality was low during the 1980s and subsequently increased [7, 8]. The decrease in SIDS mortality in Western countries has been attributed mainly to the 'Back to Sleep' campaigns promoting the supine sleep position [2, 3, 9]. In the United States, for example, the National Infant Sleep Position Study showed an increase in the supine sleep position from 17% in 1993 to 72% in 2007 [10].

Gilbert et al. assessed the time frame for 'Back-to-Sleep' campaigns in various countries in a systematic review [9]. The campaigns often coincided with reductions in SIDS. The International Child Care Practice Study, however, found large variations in infant sleep position

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between countries [11]. For example, the prevalence of the supine sleep position was 33% in Denmark compared to 89% in Japan in the late 1990s. While infant sleep position and other risk factors act as triggering factors, the underlying cause(s) for SIDS are still unknown [12]. The success of the 'Back-to-Sleep' campaigns might have covered concurrent changes in other factors at the population level. Known risk factors for SIDS other than the prone or side sleep position include bed sharing, soft bedding, mothers' smoking and alcohol use, overheating, and lack of immunisation [4, 12, 13].

Determining regional time trends for SIDS mortality and identifying clusters of time courses might instigate new research into the aetiology of SIDS. As the coding of SIDS varies between countries, the broader category of sudden unexpected infant death may be more appropriate for international comparisons [14]. The term sudden unexpected death in infancy (SUDI) is often used interchangeably with SUID as an umbrella term for unexplained infant deaths [15]. During recent years, diagnostic shifts have been reported from SIDS to other diagnoses [16, 17]. Sudden unexpected infant death (SUID) typically includes SIDS, accidental suffocation and strangulation in bed, or other ill-defined or unspecified causes of death [13]. When comparing SUID mortality, all-cause infant mortality needs to be taken into account as well. In countries with high all-cause infant mortality, vulnerable infants might die earlier from other causes. Therefore, the objective of the present study was to identify country-clusters with similar time trends in SUID and SIDS as well as in all-cause infant mortality in an international comparison.

Methods

Study design

The present study is a comparison of historical time trends in SUID, SIDS, and all-cause infant mortality between countries across the globe (1969–2012). Infant deaths were defined as deaths in children during the first year of life. We obtained data from the National Statistical Offices of the respective countries. In the case of missing data, we checked the World Health Organization (WHO) Mortality Database and included additional data if available [18]. Diagnoses were used according to the International Classification of Diseases (ICD) systems [19]. Our primary diagnosis of interest was SUID. The diagnosis of SUID commonly includes SIDS (ICD-10, R95), accidental suffocation and strangulation in bed (ICD10, W75), or other ill-defined or unspecified causes of mortality (ICD-10, R99) [14, 16]. We used the broader category ill-defined and unknown causes of mortality (ICD-10, R96–99), as international comparisons have shown differences in the use of individual codes of diagnoses between countries [14]. For example, a high percentage of SUID was coded as other sudden death, cause unknown (ICD-10, R96) in Japan [14]. Codes of diagnoses used for SUID and related diagnoses might differ both between and within countries over time. During the period of interest, the ICD systems changed [19]. We used the following ICD systems: the 8th revision (ICD-8), the 9th revision (ICD-9), and the 10th revision (ICD-10) (Table 1). The years in which ICD systems changed differed between countries.

A number of countries used other classification systems, such as the 09 N – ICD 9th revision, Special List of causes (tabulation list) (countries of the former Union of Soviet Socialist Republics, USSR), the 09A/09B – List ICD 9th revision, Standard Basic Tabulation (Croatia, Greece, Iceland, Japan, New Zealand), or the Finnish Classification of Diseases 1987. The German Democratic Republic (GDR), which existed until 1990, used a special version of the ICD for the coding of deaths. For the latest years of our study, all countries - apart from Greece - had adopted the ICD-10 codes. The causes of death in Greece were coded with ICD-9 until 2013.

Regions and countries

For the classification of regions, we used geographic units that were adapted from the Global Burden of Disease Study [1]. We included the following regions and countries of interest in our study, focusing on Europe, with selected countries from other regions of the world for comparisons:

1) Western Europe (Austria, Belgium, Cyprus, Denmark, East Germany, England & Wales, Finland, France, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Northern Ireland, Norway, Portugal, Scotland, Spain, Sweden, Switzerland, West Germany) excluding Andorra, Liechtenstein, Monaco, and San Marino due to the small population sizes (≤90,000 inhabitants). We did not provide a total estimate for the United Kingdom due to the differential use of ICD systems. Similarly, we included East and West Germany separately due to differences in coding and classification systems used over time.
2) Central Europe (Albania, Bulgaria, Croatia, Czech Republic, Hungary, Kosovo, Republic of Macedonia, Poland, Romania, Serbia, Slovakia, Slovenia).
3) Eastern Europe (Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, the Russian Federation, Ukraine).
4) Selected countries from other regions: high-income North America (Canada, USA), Australia (Australia, New Zealand), high-income Asia Pacific (Japan), Southern Latin America (Chile, Uruguay), Central Latin America (Costa Rica, Mexico), and North Africa and Middle East (Turkey).

Table 1 International Classification of Diseases (ICD) codes for sudden infant death syndrome, related diagnoses and all causes of death

Codes of diseases	ICD-8	ICD-9	ICD-10
Sudden infant death syndrome	795	798.0	R95
Accidental suffocation and strangulation in bed	E913.0	E913.0	W75
Ill-defined and unknown causes of mortality	796	798.1–798.9, 799	R96-R99
All causes of death	000-E999	001-E999	A00-Y89

Time period and data collection

We used all data on infant mortality with the respective codes of diagnoses for the time period from 1969 to 2012 for the descriptive analyses [20]. For the cluster analyses of time trends, we restricted the time period to the years from 1980 to 2010 due to the large amount of missing data for the earlier and later years. We included 29 countries for the cluster analyses of time trends in SUID mortality and 27 countries for SIDS mortality, respectively.

The format (paper-based, digital) and degree of segregation of the data varied considerably between countries. Some countries only provided aggregated data for the ICD category symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (ICD-10, R00-R99) but not separately for the diagnoses SIDS (ICD-10, R95), accidental suffocation and strangulation in bed (ICD-10, W75), or ill-defined and unknown causes of mortality (ICD-10, R96–99).

Statistical analyses

We calculated infant mortality rates per 1000 by dividing the number of infant deaths with the respective diagnoses

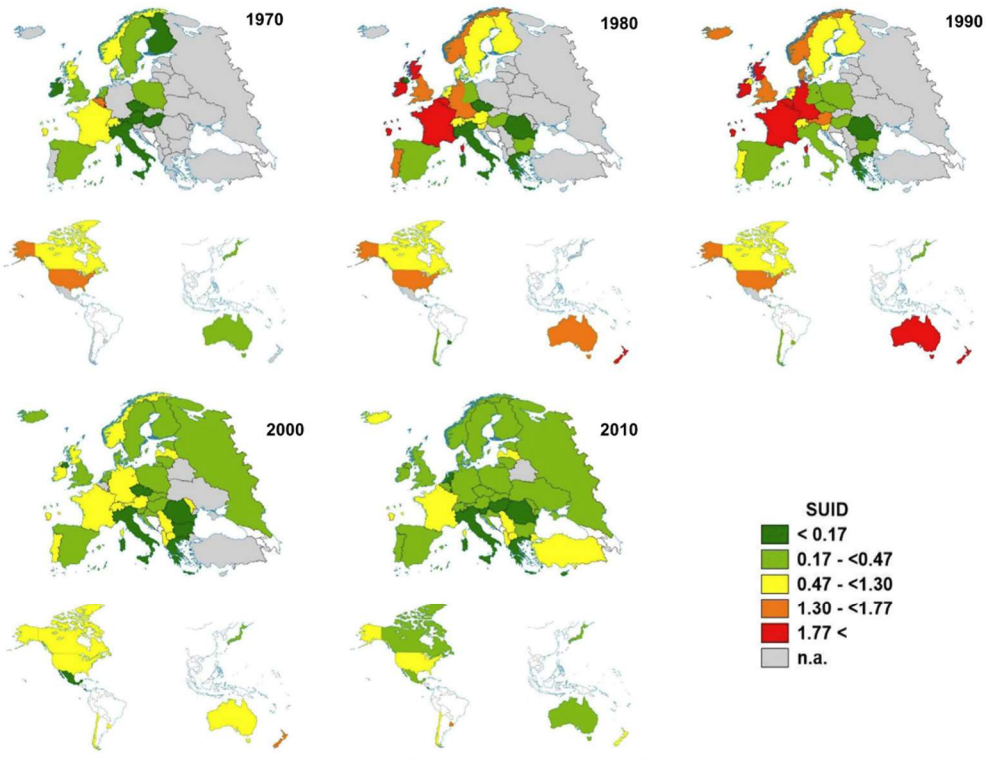

Fig. 1 Regional distribution of infant mortality rates from sudden unexpected infant death (SUID) per 1000 live births in 10-year intervals; top: Europe, bottom left: Americas, bottom right: Australia, Japan, New Zealand

by the number of live births multiplied by 1000. For the descriptive analyses, we divided mortality rates from SUID mortality into quintiles over 3-year periods. We calculated the distribution over these quintiles with 1980–1982 as the reference years for both previous and subsequent years. We used maps to display the distribution of SUID mortality rates graphically for the years 1970, 1980, 1990, 2000, and 2010. To create the maps, we used the software EASYMAP 11.0 SP 6 (@2018 Luttum+ Tappert DV-Beratung GmbH, Bonn, www.lutumtappert.de).

Mortality rates from SUID can be affected by all-cause mortality rates. Therefore, we examined the time trends of mortality rates from SUID, SIDS, and death from all-causes. The time series of mortality rates were smoothed before further analysis using restricted cubic splines with six nodes. Smoothing data removed noise from the data and allowed us to sensitively model changes over time. We performed hierarchical cluster analyses to identify similar time courses of SUID and SIDS across countries. Countries were clustered for SUID and all-cause mortality as well as for SIDS and all-cause infant mortality. We used the values of the smoothed SUID, SIDS, and all-cause infant mortality curves from 1980 to 2010 for the cluster analyses. In total, 62 variables were the basis for each of the two cluster analyses. Because the higher levels of all-cause infant mortality would give all-cause infant mortality a greater weight in the cluster analyses, we calculated Manhattan distance matrices for SUID and all-cause mortality separately and averaged both distance matrices. Thus, we were able to ensure equal weight of SUID and all-cause mortality in the cluster analysis. The distance matrix for clustering SIDS mortality was calculated accordingly. Finally, the hierarchical cluster algorithm used Ward's minimum variance method. We calculated country-specific maxima over time based on the smoothed curves for the mortality rates from SUID and SIDS. For the calculation of the restricted cubic splines, we used the R package "rms". The cluster analyses were carried out using the hclust function from the statistical software R 3.3.2 (R Foundation for Statistical Computing, Vienna).

Results

In total, 52 countries provided data on infant mortality. All-cause infant mortality decreased from an average of 28.5 per 1000 live births in 1969 to 4.8 in 2012 (mean mortality rate over all years: 12.4; 95% confidence interval 12.0–12.9). While all-cause infant mortality rates were available for all countries from 1969 to 2012, the completeness of available mortality data to calculate SUID mortality was initially low; however, it improved during the time period of interest. Data on SUID were available for 22 countries in 1970, 32 in 1980, 35 in 1990, 45 in 2000, and 49 in 2010. Mortality from SUID

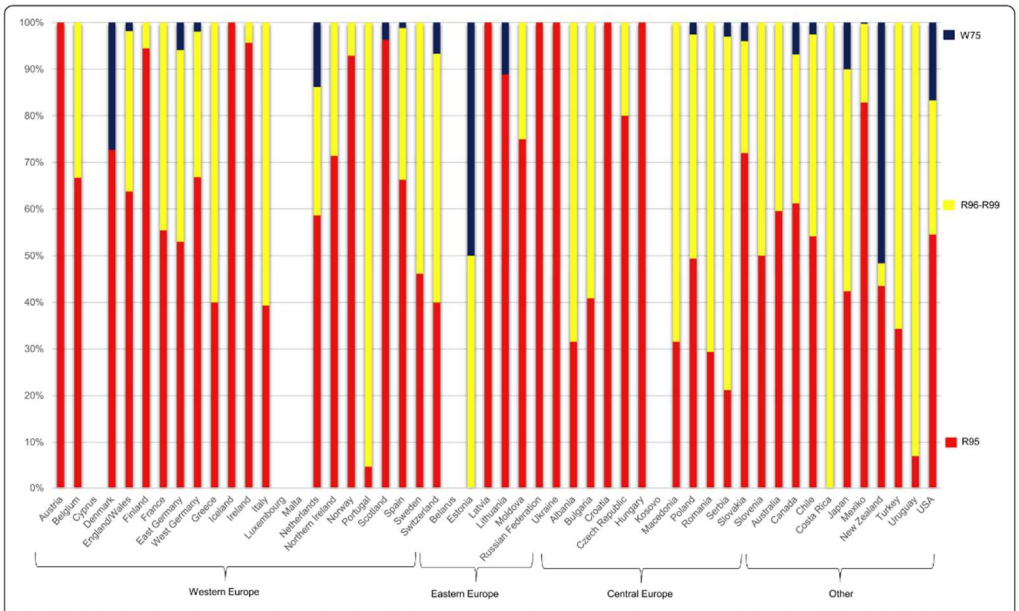

Fig. 2 Distribution of sudden unexpected infant death by its component diagnoses, according to country (2010); SIDS (ICD-10, R95), ill-defined and unknown causes of mortality (ICD-10, R96–99), accidental suffocation and strangulation in bed (ICD10, W75)

declined in most regions. Figure 1 shows the geographical distribution of SUID mortality rates for the years 1970, 1980, 1990, 2000, and 2010.

Differences existed in the use of codes of diagnoses between countries. The percentage of SIDS mortality among SUID mortality ranged between 30 and 40% from 1969 to 1976, rose steadily to 83% in 1994, and declined again, ranging between 60 and 70% from 1995 onwards. In 1970, for example, Austria, Finland and France did not code any cases of SUID as SIDS, whereas the Czech Republic, Luxembourg, and Poland coded all SUID cases as SIDS. Differences persisted over time. In 2010, only a low percentage of SUID cases was coded as SIDS in Costa Rica and Estonia (both 0%) and Portugal (5%), whereas Austria, Croatia, Hungary, Iceland, Latvia, the Russian Federation, and Ukraine coded all SUID as SIDS. Figure 2 shows the distribution of the respective diagnoses among SUID mortality rates according to country (year 2010). The distribution of diagnoses over time for the preceding decades (1980, 1990, 2000) is shown in the Additional file 1.

Time trends for SUID mortality rates from 29 countries were grouped into four clusters (Fig. 3, Table 2). Table 2 shows the maxima of SUID mortality per country-cluster, based on smoothed curves. The main difference between cluster 1 and cluster 2 countries with regard to SUID were the lower SUID and all-cause mortality rates in cluster 2. The maximum of SUID rates was 3.9 per 1000 live births (New Zealand) with the lowest value of 1.9 for West Germany in cluster 1, the maximum of SUID rates in cluster 2 was 2.2 (Norway) with the lowest value of 1.1 for Switzerland. With regard to the dynamic, SUID rates decreased from around 2.1 in 1990 to 1.1 in 1995 in cluster 1, while they decreased from around 1.3 to 0.6 during the same time period in cluster 2. Cluster 1 included mainly countries from Western Europe (Belgium, France, Ireland, Luxembourg, Scotland, West Germany) as well as Australia, New Zealand and the USA. Cluster 2 included Austria, Canada, Denmark, England & Wales, Netherlands, Norway, Sweden, Switzerland. In cluster 3 (Bulgaria, Chile, Hungary, Poland, Uruguay), mortality rates from SUID were low, while all-cause infant mortality was approximately 2-fold higher compared to clusters 1 and 2. Mortality rates from SUID remained below 1 (except for Uruguay in 2001). Cluster 4 (Czech Republic, East Germany, Finland, Italy, Japan, Portugal, Spain), similarly, had low mortality rates from SUID. All-cause infant mortality rates were lower in cluster 4 compared to cluster 3.

Time trends for SIDS mortality rates from 27 countries were grouped into four clusters (Fig. 4, Table 3).

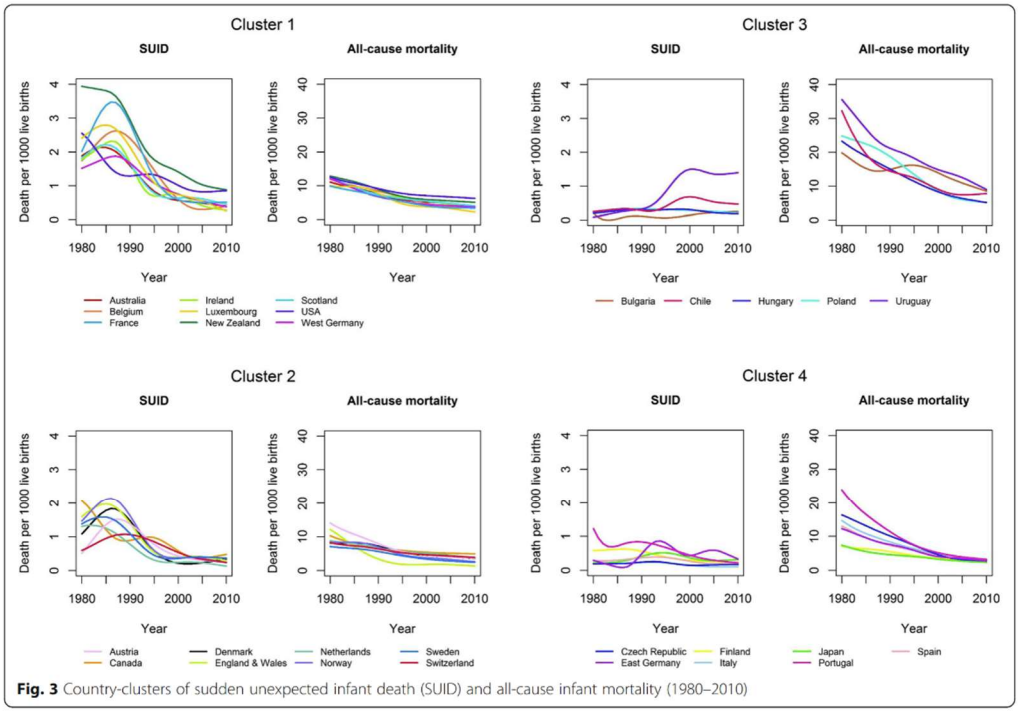

Fig. 3 Country-clusters of sudden unexpected infant death (SUID) and all-cause infant mortality (1980–2010)

Table 2 Maximum of sudden unexpected infant death (SUID) per 1000 live births per country-cluster (based on smoothed curves)

	Maximum of SUID	Year of maximum
Cluster 1		
Australia	2.14	1984
Belgium	2.63	1987
France	3.48	1986
Ireland	2.32	1986
Luxembourg	2.80	1985
New Zealand	3.94	1980
Scotland	2.22	1985
USA	2.56	1980
West Germany	1.88	1987
Cluster 2		
Austria	1.52	1987
Canada	2.07	1980
Denmark	1.83	1986
England & Wales	1.98	1985
Netherlands	1.34	1982
Norway	2.15	1986
Sweden	1.59	1984
Switzerland	1.07	1989
Cluster 3		
Bulgaria	0.25	2010
Chile	0.69	2000
Hungary	0.32	1998
Poland	0.33	1990
Uruguay	1.50	2001
Cluster 4		
Czech Republic	0.26	1992
East Germany	0.86	1994
Finland	0.63	1986
Italy	0.24	1992
Japan	0.52	1994
Portugal	1.23	1980
Spain	0.39	1993

Table 3 shows the maxima of SIDS mortality per country-cluster, based on smoothed curves. The differences between clusters 1 and 2 in the cluster analysis of SIDS were similar to those of SUID (Table 2, Table 3). Most of the countries were in the same clusters (Cluster 1: Australia, Belgium, France, Ireland, New Zealand, Scotland, USA, West Germany; Cluster 2: Canada, Sweden, Switzerland, the Netherlands) in both analyses. Some of the countries could only be analysed with regard to one of the outcomes SIDS or SUID (Luxemburg, Finland, Japan). In four countries, the cluster allocation was different for SIDS compared to SUID: Austria, Denmark, England & Wales and Norway. All four were in cluster 1 for SIDS but in cluster 2 for SUID. For these countries, rates of SIDS and SUID were almost identical and rates of SIDS were higher than in countries of cluster 2 (SIDS). When analysing SUID rates in these countries, they were lower than in other countries of cluster 1. Cluster 1 included 12 countries predominantly from Western Europe as well as Australia, New Zealand and the USA. A peak of SIDS mortality was reported between 1980 and 1988 (range: 1.6–3.9). Following the peak in mortality, SIDS mortality rates decreased until 2010. New Zealand had the highest SIDS mortality of all countries. All-cause infant mortality in cluster 1 was between 7 and 15 and decreased continuously from 1980 onwards. Countries of cluster 2 (Canada, Finland, Japan, Netherlands, Sweden, Switzerland) showed similar trends in SIDS mortality compared to cluster 1 but at a lower level. A maximum of SIDS mortality was reported between 1980 and 1995 (range: 0.4–1.3). Clusters 3 (Chile, Hungary, Poland, Uruguay) and 4 (Czech Republic, East Germany, Italy, Portugal, Spain) had low SIDS mortality rates (below 1) but differed with regard to all-cause infant mortality. Cluster 3 had the highest all-cause infant mortality of all clusters, while cluster 4 had intermediate infant all-mortality.

Discussion

All-cause infant mortality as well as SUID and SIDS mortality declined in most countries. The cluster analyses yielded four country-clusters for both SUID and SIDS. Two of the clusters showed the typical peak in SUID and SIDS mortality observed during the 1980s, mainly in countries from Western Europe as well as Australia, Canada, New Zealand, and the United States. These clusters had a low all-cause infant mortality but differed with regard to their levels of SUID and SIDS mortality. The remaining two clusters had high and intermediate all-cause infant mortality, with low mortality from SUID and SIDS. These clusters predominantly included countries from Central Europe as well as some countries from the Mediterranean region.

Most studies comparing international time trends have focused on SIDS but not SUID mortality [1, 2]. Coding practices for SIDS and SIDS-related diagnoses, however, vary considerably between countries [14]. In Japan, for example, only approximately 40% of SUID cases are coded as SIDS [14]. Whereas the R96 diagnosis (other sudden death, cause unknown) is predominantly used as an alternative to SIDS in Japan, other countries, such as Canada, England & Wales, Germany, or the United States, are more likely to use the code R99 (other ill-defined and unspecified causes of mortality) or W75 (accidental

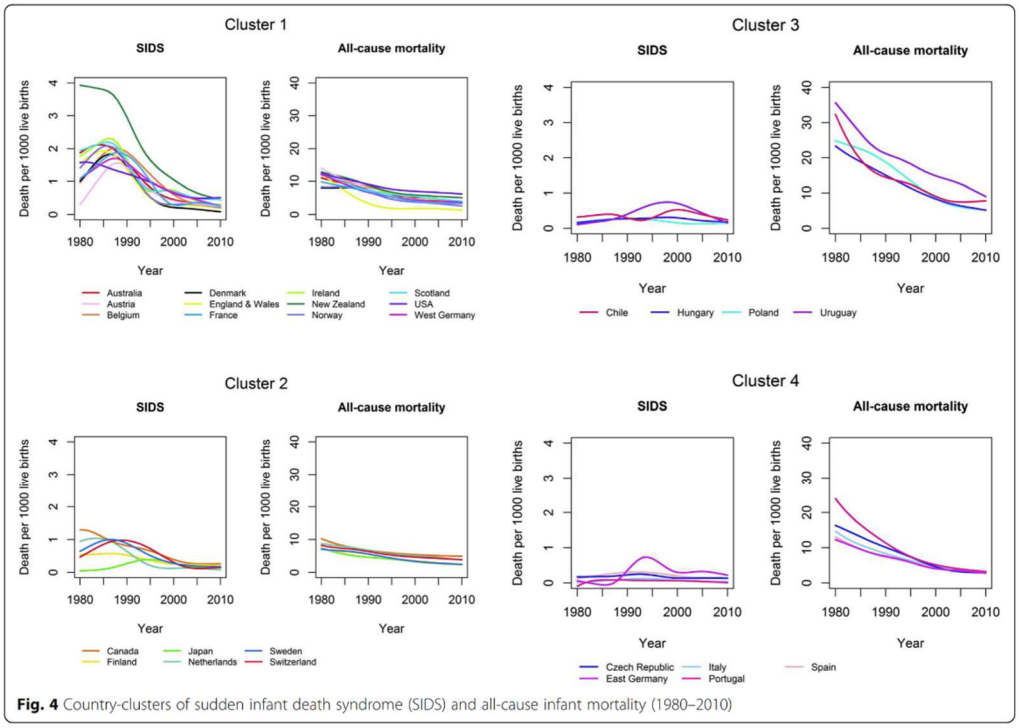

Fig. 4 Country-clusters of sudden infant death syndrome (SIDS) and all-cause infant mortality (1980–2010)

suffocation and strangulation in bed). Comparing time trends in SUID thus allows for a more robust comparison between countries and over time. We also included all-cause infant mortality in our cluster analyses. The low SUID mortality found in the clusters with high and intermediate all-cause infant mortality may at least partially be due to vulnerable children dying earlier from other causes. In particular, mortality from perinatal conditions was increased in the countries with high and intermediate all-cause mortality, as well as mortality from infections in countries with high all-cause mortality [18].

The initial increase and subsequent decrease in SIDS mortality in many countries has been attributed to changes in infant sleep position [3, 5, 9]. Campaigns promoting the supine sleep position started in most countries during the early 1990s [9]. While the change in infant sleep position is a major factor associated with reducing SIDS mortality, other changes in potential risk factors at the population level have received less attention. For example, immunisation against pertussis decreased in a number of countries during the 1980s due to reports of neurological complications [21]. In countries such as the United Kingdom, West Germany, or the United States, the uptake of pertussis immunisation only recovered in the late 1980s and early 1990s [4, 21]. Immunisation was found to be associated with a reduced risk of SIDS in case-control and cohort studies [22, 23]. Reductions in other risk factors for SIDS, such as smoking, could also be observed at the population level [24]. Many risk factors for SIDS are associated with socioeconomic status and tend to cluster in high-risk populations [12, 25, 26].

Limitations

One limitation of our study was the missing data on SUID and SIDS for certain periods of time in a number of countries. Another limitation is that some of the observed differences may have been caused by artefacts as definitions of SIDS as well as diagnostic procedures varied between countries and over time [2, 27]. The definition of SIDS has changed since its original implementation in 1969, with a stronger focus on death scene investigation including a complete autopsy as requirement for the diagnosis [28]. An increasing reluctance by death certifiers to diagnose SIDS without a thorough investigation might have led to the increase in other diagnoses, as observed in the United States [17]. To our knowledge, there is no systematic assessment of international autopsy rates in infants dying

Table 3 Maximum of sudden infant death syndrome (SIDS) per 1000 live births per country-cluster (based on smoothed curves)

	Maximum of SIDS	Year of maximum
Cluster 1		
Australia	2.12	1984
Austria	1.57	1988
Belgium	2.01	1988
Denmark	1.83	1986
England & Wales	1.93	1985
France	1.88	1988
Ireland	2.31	1986
New Zealand	3.93	1980
Norway	2.09	1986
Scotland	2.20	1986
USA	1.59	1981
West Germany	1.70	1987
Cluster 2		
Canada	1.30	1980
Finland	0.57	1986
Japan	0.39	1995
Netherlands	1.04	1983
Sweden	1.00	1987
Switzerland	0.98	1989
Cluster 3		
Chile	0.53	2000
Hungary	0.31	1998
Poland	0.28	1990
Uruguay	0.75	1998
Cluster 4		
Czech Republic	0.25	1993
East Germany	0.74	1994
Italy	0.13	1993
Portugal	0.09	1986
Spain	0.31	1992

from SIDS in countries over time. In a study comparing eight countries, the estimated percentage of SIDS cases being autopsied differed largely between countries with, for example, particularly low autopsy rates reported for Japan and the Netherlands [14, 16]. The low autopsy rate in Japan might be associated with the observed higher rate of the diagnoses ill-defined and unknown causes of mortality. The comprehensiveness of the autopsy protocol may vary between countries [29]. Often, no systematic information is available on whether an autopsy and/or death-scene investigation was performed according to standard protocols [16]. In general, death certifiers and pathologists may individually or regionally be more likely to over- or underdiagnose SIDS [16]. The age of inclusion as SIDS differed between countries [2]. Some countries defined SIDS as death from 1 week to 12 months, while others used birth to 12 months or beyond. As the majority of SIDS occurs between two and four months, the effect is likely to be minor [12, 30]. The definition of live births similarly varied between countries [8]. However, most countries adopted the standard definition of the WHO in the late 1980s or early 1990s [31]. During the time period of interest, the ICD coding systems changed, which might have impaired comparability over time. The changes in ICD systems, definitions, and coding are less likely to affect the comparability of the aggregate diagnosis of SUID than of SIDS and other individual diagnoses.

Conclusions

The identification of country clusters in our study may promote research into how changes of risk factors such as smoking, immunisation, or other factors on the population level are related to SUID mortality. Of particular interest are comparisons of time trends between countries with a low - or intermediate - all-cause infant mortality, showing differential levels of SUID and SIDS mortality. While some data on the prevalence of risk factors may already be available, more international collaboration is needed to assess sleep environment and other risk factors in a standardized way for comparison between countries. Compliance with definitions for SIDS and SUID/SUDI will further increase the validity of international comparisons. Innovative methods of statistical analysis and data linkage may be of added value to generate new hypotheses for the prevention of sudden infant death.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12887-020-02271-x.

Additional file 1. Distribution of sudden unexpected infant death by its component diagnoses, according to country (1980, 1990, 2000); SIDS (ICD-10, R95), ill-defined and unknown causes of mortality (ICD-10, R96–99), accidental suffocation and strangulation in bed (ICD10, W75)

Abbreviations

CDC: Centers for Disease Control and Prevention; CI: Confidence interval; GDR : German Democratic Republic; ICD: International Classification of Deaths; SIDS: Sudden infant death syndrome; SUID : Sudden unexpected infant death; USSR: Union of Soviet Socialist Republics; WHO: World Health Organization

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Authors' contributions

JMN and SB conceptualized and designed the study, performed the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. AS, UG, and KN performed the analyses, reviewed and revised the

manuscript. TK and SNW contributed to the design of the study and reviewed and revised the manuscript. All authors read and approved the final manuscript. All authors agreed to be accountable for the work.

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Availability of data and materials
The National Statistical Offices of the respective countries provided the data. In the case of missing data, we included additional data from the WHO Mortality Database if available [18].

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Competing interests
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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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