From the Institute for Medical Information Processing, Biometry and Epidemiology
(IBE)
of the Ludwig-Maximilians-Universität München
Director: Univ. Prof. Dr. Ulrich Mansmann

TRAJECTORIES OF DEFICIT ACCUMULATION AND THEIR PREDICTORS IN OLDER AGE.

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

submitted by
Anna-Janina Stephan, MPH
from
Waiblingen, Germany
on
April 30th 2019

LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

From the Institute for Medical Information Processing, Biometry and Epidemiology
(IBE)
of the Ludwig-Maximilians-Universität München
Director: Univ. Prof. Dr. Ulrich Mansmann

TRAJECTORIES OF DEFICIT ACCUMULATION AND THEIR PREDICTORS IN OLDER AGE.

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

submitted by
Anna-Janina Stephan, MPH
from
Waiblingen, Germany
on
April 30th 2019

Supervisor: Prof. Dr. Eva Grill, MPH

Second evaluator: Prof. Dr. Rolf Holle

Dean: Prof. Dr. Reinhard Hickel

Date of oral defense: August 7th 2019

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Affidavit

Stephan, Anna-Janina

Surname, first name

Address

I hereby declare, that the submitted thesis entitled

Trajectories of deficit accumulation and their predictors in older age.

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

München, 30. April 2019	Anna-Janina Stephan
Place, Date	Signature doctoral candidate

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Confimation of congruency between printed and electronic version of the doctoral thesis

Doctoral Candidate: Anna-Janina Stephan

Address:

I hereby declare that the electronic version of the submitted thesis, entitled

Trajectories of deficit accumulation and their predictors in older age.

is congruent with the printed version both in content and format.

München, 30.04.2019

Place, Date

Anna-Janina Stephan

Signature doctoral candidate

Table of contents

List of figures

List of abbreviations

APC	Age-Period-Cohort
BMI	Body Mass Index
DA	Deficit Accumulation
DNA	Deoxyribonucleic acid
DAG	Directed Acyclic Graph
ERFC	Early reconstruction and food crisis
FI	Frailty Index
KORA	Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Region of Augsburg)
MONICA	Monitoring of Trends and Determinants in Cardiovascular Diseases
PCR	Post-currency reform
PWW	Pre-war and war
Q	Quarter
SHARE	Survey of Health, Ageing and Retirement in Europe

Doctoral Thesis: Trajectories of deficit accumulation and their predictors in older age

1. Introductory Summary

1.1 Relevance

Understanding trends and predictors of successful ageing is of utmost relevance due to three major developments in industrialized countries: Demographic change, the epidemiologic transition and growing live expectancy. Demographic change will lead to a growing percentage of the population being of older age. In Germany, the share of adults who are at least 60 years old is expected to rise from 27.2% in 2013 to up to 40.8% by 2060 [1]. The epidemiologic transition [2] is marked by non-communicable disease (as opposed to communicable disease and injuries) being the main driver of the disease burden in many present-day societies, with non-communicable diseases including cancer, diabetes and cardiovascular diseases contributing to 88% of the burden of disease in Germany [3]. In addition, in Germany each newborn generation can currently expect to live longer than their predecessors: Life expectancy for a newborn child increased from 39 years in men and 42 years in women in 1871 to 84 years in men and 88 years in women in 2017 [4]. It has been prognosticated that children born in 2060 will be crossing the 100-year life expectancy threshold for the first time [5]. While until the 1920s, this trend was mainly due to decreases in infant mortality [6], in recent decades it is largely driven by survival increases in older age [5, 7]. In sum, these three trends will lead to a higher share of older people (with respect to chronological age) in industrialized societies, who potentially have to live with multiple chronic health deficits (representing their biological age).

The resulting individual burden as well as the future resource strain on health systems depends on the determinants and trends in the biological ageing process. Clearly, on an individual level, a late onset of this process and a slow progression thereafter are desirable. However, health trajectories exhibit considerable heterogeneity throughout adult life [8, 9]. Individual life course experiences, socio-economic and socio-demographic differences as well as lifestyle choices may be driving factors for this heterogeneity. Identifying their individual contributions to biological ageing will provide potential target points for behavior-based or structural and situational preventative interventions. Differences in health trajectories across space and time, i.e. between older populations of different countries as well as between different birth cohorts within a country can provide additional insights in the driving political and economic determinants of biological aging as well as potential underlying mechanisms and the associated prevention potential.

1.2 Theoretical background

1.2.1 Individual level: Defining and measuring biological age

Aging can be defined as progressing failure to maintain body structures and functions [10]. The question why organisms age has long been regarded as an unsolved problem in biology [11]. Two solutions to this problem have been suggested, with the concept of aging as a deterministic process on the one hand, and the concept of biological ageing as a result of (accumulated) insults to the body system throughout the life course on the other hand.

Aging as a deterministic process

Aging has sometimes been explained by a mechanism inherent to every species which is essentially deterministic, i.e. genetically programmed and hardly modifiable. This idea goes along with a pre-defined maximum life span for each species (which was recently estimated to be around 115 years for humans and has sparked controversial debate [12]) and a programmed life cycle throughout childhood and adulthood, which is followed by programmed cell-death after a period of reproduction [11]. In this paradigm, there is no need for the idea of biological age because it is determined by chronological age.

Aging as a result of life course exposures

On the other hand, voices have grown stronger that “there is no such thing as aging” [13], suggesting that aging is instead a “fundamentally [...] event-dependent, and not a time-dependent process” [10]. Aging can thus also be seen as a consequence of “allostatic load”, i.e. latent subclinical damage which stems from individual exposures to external stressors over the life course [14] and is not genetically programmed or initiated. These stressors may negatively affect physiological resilience and regenerative capacity, which in turn increases vulnerability towards future stressors [9]. As a consequence, and possibly after surmounting a threshold value [15], an accumulation of clinically measureable health deficits results, which ultimately culminates in death as a biological system crash [16].

If aging is seen as a result of life course exposures, the concept of biological age can be a helpful complement in defining deteriorating health in older age, as it accommodates the considerable heterogeneity in health status between people of the same age group [17].

Measuring biological age requires putting into perspective not a specific single health condition, but following a more comprehensive approach to health status assessment [18]. While various attempts to identify a single valid (bio)marker of biological age are under way with some promising but not unequivocal candidates, such as the apolipoprotein E-polymorphism [19, 20], telomere length [21, 22] or DNA methylation [23], to date, no satisfactory single proxy measure for biological age has been established. In this situation,

one of the most convincing approaches to measuring biological age is the concept of deficit accumulation (DA): Even though biological age may not be directly measurable (yet), it is still possible to measure the impact external stressors have exerted on health by counting the present accumulated health deficits. The concept of health deficit accumulation can be operationalized using a Frailty Index (FI). The Frailty Index is interesting for population-based research because it tries to capture the whole picture of morbidity and because it is applicable across a wide range of situations [24]. In addition, this operationalization fulfills the requirement to condense the synergies and complex interactions of the biological aging process into a single statistical measure without negating its inherent “multiplicity and stochasticity” [25]: Although different individuals will accumulate different health deficits in different chronological sequence, they may have the same Frailty Index value, mirroring the fact that a certain biological age can be reached by very diverse routes of damage to the biological system [25].

To construct a Frailty Index from a list of potential health deficits, these deficits need to fulfill certain inclusion criteria: They need to be associated with health status, increase in prevalence with age and should not saturate too early (i.e. no prevalence over 80% even in the oldest age groups). In conjunction, these deficits should cover of a wide spectrum of body systems and structures [26]. In addition, sufficient population coverage (prevalence in at least 1% of the population under investigation [26] and not more than 5% missing values for each deficit [27] have been described as auxiliary criteria. It has been postulated that information on at least 30 health deficits is needed to construct a valid Frailty Index [26]. All deficits are coded as values between 0 (indicating that a deficit is not present in a person) and 1 (indicating that the deficit is fully present in a person). All present deficits in an individual are added up and divided by the sum of all listed potential deficits, resulting in a Frailty Index value between 0 (no health deficits) and 1 (all health deficits). If an individual study participant is missing information on more than 20% of deficits in the list, his or her FI value is considered to be missing [28, 29].

It has been found that a Frailty Index of 0.7 constitutes an upper limit to deficit accumulation, after which vital functions can usually not be maintained [16]. The Frailty Index has proven predictive validity for adverse outcomes such as institutionalization, dependency and death [9, 30, 31].

The Frailty Index can be used as a continuous measure of biological age, but it can also be used to for the definition of risk groups: Using the Frailty Index, older adults can be categorized into three different stages of the deficit accumulation process: As “non-frail” (equivalent to $FI \leq 0.08$), “pre-frail” (equivalent to $0.08 < FI < 0.25$), or “frail” (equivalent to $FI \geq 0.25$). This categorization has, despite its simplicity, been reported to predict risk of death better than chronological age [27].

1.2.2 Population level: Hypotheses on morbidity trends

Aggregated on a population level, changes in individual health deficit accumulation trajectories over time may result in different potential morbidity trends for a given society. The resulting scenarios are summarized by the compression of morbidity and expansion of morbidity hypotheses. The compression of morbidity hypothesis postulates that with increasing life expectancy we are gaining healthy life years, while morbidity is simultaneously compressed into a smaller time period towards the end of life. As a result, healthy life expectancy increases [32]. In contrast, the expansion of morbidity hypothesis postulates that the life years gained with growing life expectancy are additional life years spent with health deficits [33]. Depending on the health conditions under study, previous analyses have presented evidence for both compression and expansion of morbidity [34]. Various increments in between those two extreme scenarios have subsequently been suggested. One of these is relative compression, indicating that the absolute amount of time lived in ill health may remain stable, but decrease in relation to the absolute number of years lived as life expectancy increases. This scenario is also sometimes referred to as stable morbidity or receding horizon [35]. Also, a dynamic equilibrium has been suggested, meaning that the number of years spent in ill health increases with increasing life expectancy, but at the same time the severity of health deficits decreases. This scenario might result, for example, if health deficits can be better controlled due to modern treatment options [36]. The different hypotheses on morbidity trends are graphically represented in Fig.1.

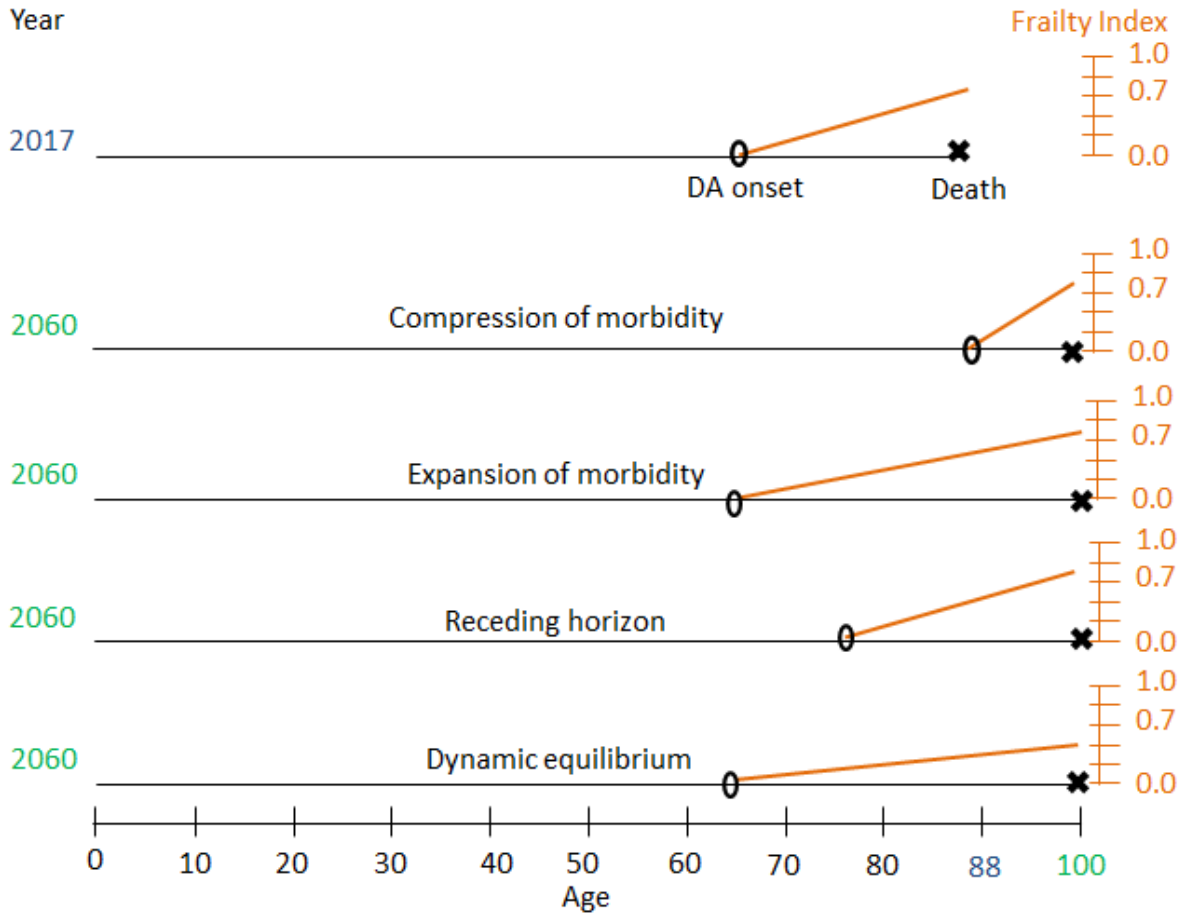


Fig.1: Hypotheses on morbidity trends.

Schematic representation of the relative timing of deficit accumulation onset (O), DA trajectories (orange lines) and death (X) for four different hypotheses on future morbidity trends (compression of morbidity, expansion of morbidity, receding horizon and dynamic equilibrium) as compared to the status quo (as of 2017).

1.2.3 Towards considering DA predictors from a life course point of view

Recent epidemiological research has increasingly stressed the importance of taking "a life course perspective" on predictors of health [37]. The idea of life course epidemiology is that multiple biographical experiences throughout the life course may shape health outcomes such as biological age. Two different, but not mutually exclusive models reflect this concept: The "critical period" or "sensitive period" model and the "accumulation of risk" model [37].

The former model, on the one hand, assumes that detrimental changes in the human ageing process occur as a response to non-recurring exposures in critical or sensitive developmental age. In critical developmental age, the organism reacts especially adaptive to external circumstances, sometimes paying the resulting short-term health advantages off with long-term adverse health effects. Potential pathways may be biological such as higher

propensity for inflammation [38] as well as social-behavioral such as the development of adverse consumption or physical activity patterns [39]. Exposure to adverse conditions during critical or sensitive developmental age may vary between individuals, but may also be shared by entire populations or generations, for example in the case of economic crises, hunger, war, or political instability. In this case, historical circumstances may have influenced the morbidity trends we observe today. Thus, analyses of morbidity trends have to take into account potential cohort effects as well as age and period effects [40].

The accumulation of risk model, on the other hand, assumes that health deficit accumulation results from sustained or repeated exposure to social, physical or psychological environmental stressors. These stressors lead in turn to decreased physiological resilience and reduced regenerative capacity [9]. Most available research to date has focused on DA from an accumulation of risk perspective, investigating socio-demographic, socio-economic, and lifestyle characteristics as individual risk factors, such as sex [41], marital status [42], education [43-46], wealth [35, 44], income [44, 47], occupation [44, 46], alcohol consumption [42, 43], smoking [42, 48], and physical activity [48-50]. The assumed pathways behind these potential predictors vary: For some predictors such as alcohol consumption or smoking, potential direct health effects (cell damage [51], epigenetic changes [52], alteration of the immune system [53]) have been suggested. For socio-economic factors, next to direct health effects such as increased stress levels induced by social comparisons, also indirect pathways through detrimental housing or working environments are plausible [54, 15]. One major limitation of many epidemiological studies investigating the association of individual risk factors and DA is their cross-sectional design, which precludes causal inference. Furthermore, even studies which used longitudinal data have mainly focused on DA levels as outcome at a certain cross-section in time instead of trying to capture DA as a process with different stages (onset, trajectories thereafter and final health decline towards death). For example, there is evidence on varying age-specific DA levels between individuals with different health-risk profiles and from different countries, respectively [55]. Nevertheless, before the start of this thesis it remained unclear if these differences stemmed from differences in age at DA onset or, for example, from differences in the speed of deficit accumulation thereafter. Knowledge about the specific stage in the DA process at which differences arise might indicate appropriate target points for prevention, though. Fig.2 illustrates the hypothesis that different DA levels in people of the same age might be a consequence of differential timing of the onset of the DA process depending on the individual risk profile.

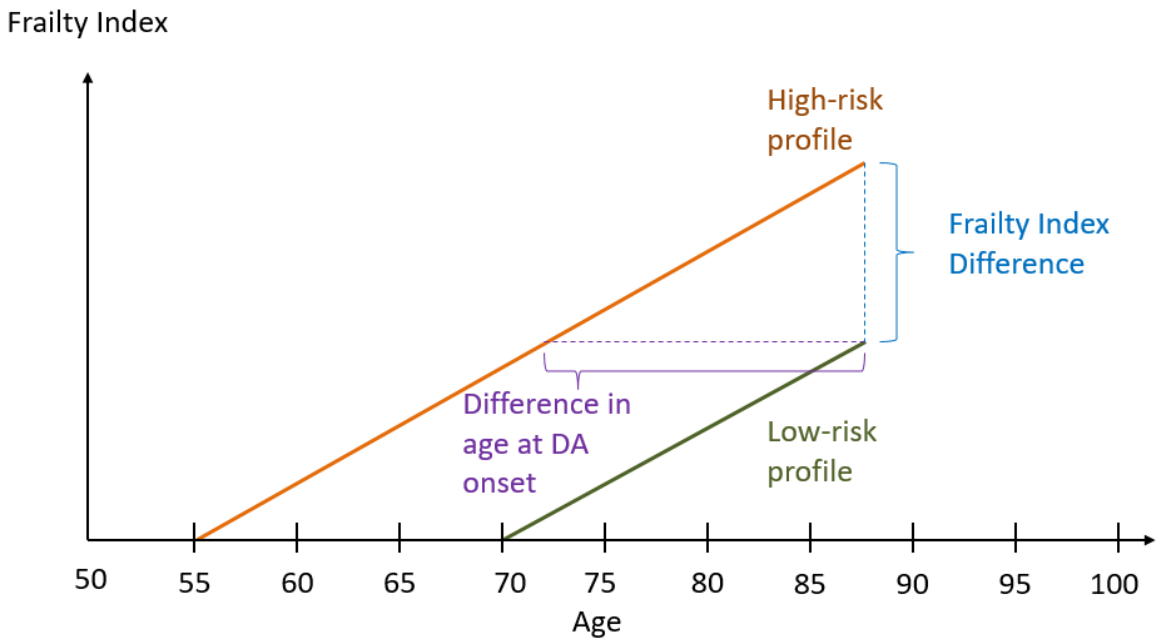


Fig.2: Hypothesized association of DA levels with age at DA onset.

The peak influence of some individual risk factors might also vary according to the current stage of the DA process. While, for example, education may help postpone DA onset through health literacy, income may help slow down the DA process once it has started, e.g. by providing access to the highest standards of care [56, 57]. Also, it is unclear if income as ongoing stream of resources is still equally relevant in older age or if its effects are buffered by wealth as the stock of accumulated resources [58]. Especially for occupation, wealth, and income, the focal points of influence throughout the DA process were still unclear prior to work on this thesis.

Apart from knowledge gaps regarding the effect of individual risk factors on the DA process, even descriptions of DA transitions (improvement, stability, or decline) between health states (non-frail, pre-frail and frail) are still sparse. For example, to our knowledge, prior to the work for this thesis, there was no information available for a German population regarding the distribution of DA states and the frequency of DA transitions over time [59].

In summary, knowledge gaps existed with regard to the distribution of DA states and transition patterns over the population. In addition, the question remained if the same individual risk factors are relevant throughout the whole DA process (onset, trajectories thereafter and final health decline towards death). Evidence on these questions could help inform targeted interventions, which could then specifically be tailored to the stage of the DA process and the observed transition patterns.

Also, research on morbidity trends across birth cohorts in Germany was sparse, with one analysis suggesting an expansion of morbidity based on data from 1911 to 1932 birth cohorts [60]. As a consequence, cohort effects on DA trends are yet incompletely understood. These effects are currently especially interesting with regard to the European (including German) populations, as cohorts born shortly before, during and shortly after World War II are now reaching retirement age. Their future morbidity trajectories will determine the future functional capacity of the respective health care systems.

1.3 Research question and objectives

This PhD project aimed to answer the following research questions:

A) Individual level:

What is the distribution and what are the determinants of health deficit accumulation trajectories in older adults in Germany?

Specifically, we wanted to explore:

1. **How frequently** do different DA states (non-frail, pre-frail, frail) occur in the German population and which **individual factors** determine if an individual deteriorates, improves or remains stable with regard to DA over time?
2. What are the determinants of deficit accumulation and its subsequent **speed** of progression?
3. What are the factors which determine the chronological age **when** individual health deficit accumulation **starts** in European populations?

B) Population level:

How does the German population compare to its European neighbors and against historical cohorts with regard to health deficit accumulation?

Specifically, we wanted to explore:

4. How large are the differences in age at DA onset between European **countries**?
5. Do different **cohorts** born between 1937 and 1950 differ with regard to their DA levels at age 65 to 71 years?

1.4 Overview of the analyses comprised in this doctoral thesis

This doctoral thesis comprises three scientific articles that were published in international peer-reviewed journals:

- Stephan A-J, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig K-H, et al. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. *Preventive Medicine*. 2017;102:31-8. doi: 10.1016/j.ypmed.2017.06.032
  (hereafter termed “Publication 1” or “the first publication”)
- Stephan A-J, Strobl R, Holle R, Grill E. Wealth and occupation determine health deficit accumulation onset in Europe – Results from the SHARE study. *Experimental Gerontology*. 2018;113:74-9. doi: 10.1016/j.exger.2018.09.021
  (hereafter termed “Publication 2” or “the second publication”)
- Stephan A-J, Strobl R, Schwettmann L,· Meisinger C, Ladwig K-H, Linkohr B, Thorand B, Peters A, Grill E. Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age: results from the KORA-Age study. *European Journal of Epidemiology*. 2019. doi: 10.1007/s10654-019-00515-4
  (hereafter termed “Publication 3” or “the third publication”).

These articles document a four-year research process which aimed at answering the abovementioned research questions.

1.4.1 Methods

1.4.1.1 Data

The research questions were answered using longitudinal data from two large population-based cohort studies, KORA (Cooperative Health Research in the Region of Augsburg)-Age (waves 1, 2 and 3) and SHARE (Survey of Health, Ageing and Retirement in Europe, waves 1, 2, 4, 5, and 6), applying generalized linear models, generalized linear mixed models, multi-level time-to-event analysis and age-period-cohort (APC) analysis.

KORA-Age

The KORA (Cooperative Health Research in the Region of Augsburg)-Age study is a cohort study which comprises all study participants of the population-based MONICA (Monitoring of Trends and Determinants in Cardiovascular Diseases)/KORA Surveys S1–S4 (1984–2001) in the city of Augsburg and two surrounding counties (Augsburg and Aichach-Friedberg) in Southern Germany, who were aged 65 years or older on December 31st 2008 (i.e. born

≤1943). Out of a total of 17,602 former MONICA/KORA participants, 9,197 fulfilled this inclusion criterion. At the time of data collection for the first KORA-Age wave in 2008/09, 2,734 of these eligible participants had died, 45 had moved away and 427 had withdrawn their consent to participate. A self-administered health questionnaire was mailed to the remaining 5,990 eligible persons and completed by 4,565 persons (response 76.2%). Additionally, 5,986 eligible persons were contacted by trained interviewers with medical background to complete an extended telephone interview in which 4,127 persons (response 68.9%) participated. An age- and sex-stratified randomly drawn sub-sample (n=1,079) additionally underwent medical examinations and personal interviews. These sub-sample participants were re-invited for the first follow-up medical examination and mailed questionnaires in 2012 (KORA-Age 2), which resulted in longitudinal data for 822 participants. In 2015, all participants originally eligible for KORA-Age 1 and still eligible in 2016 (n=3,982) were re-invited to participate in structured telephone interviews and complete a paper-based questionnaire (response rate: 65.9%). In addition, a younger enrichment sample (aged 65-71 years in 2015, i.e. born 1944 to 1950), which also derived from the MONICA/KORA surveys, was added to the study population. For this enrichment sample, out of 1,929 eligible former MONICA/KORA participants, 1,457 returned the paper-based questionnaire and participated in the 2016 structured telephone interview.
Details about KORA-Age can be found elsewhere [61, 62]. All participants provided written informed consent before data collection. Approval for the KORA-Age study was obtained from the Ethics Committee of the Bavarian Medical Association.

SHARE

The Survey of Health, Ageing and Retirement in Europe (SHARE) includes representative samples of the populations aged 50 years and older from 20 European countries and Israel with biannual follow-ups since 2004. In addition to the original cohort, occasional refreshment samples have been added in later waves. All SHARE participants are asked to complete a multi-module computer-assisted personal interview on socio-economic, family network, individual history and health topics. Details about study design, sampling methods and data collection for SHARE can be found elsewhere [63-67]. Approval for SHARE was obtained from the Ethics Committee of the University of Mannheim until 2011 and from the Ethics Council of the Max-Planck-Society for the Advancement of Science from 2011 onwards. Written informed consent was obtained from all participants.

1.4.1.2 Statistical methods

To quantify the prevalence of different DA transitions in KORA-Age, four transition patterns were defined in the first publication: “improving”, “stable”, “gradually declining” and “abruptly declining”. These were derived from 3-year transitions between the three abovementioned different DA states (“non-frail”, equivalent to FI≤0.08, “pre-frail”, equivalent to 0.08<FI<0.25, and “frail”, equivalent to F≥0.25 [27] and “death” as an absorbing state). Participants were classified into the “improving” pattern if they were in a better health state at follow-up as compared to baseline and as “stable” if they had remained in the same health state. In addition, two categories of decline were defined: “gradually declining” if a participant had moved to the next worse health state and “abruptly declining” if they had accumulated so many health deficits that they had skipped at least one health state.

Multiple multinomial regression models were used to identify predictors of different deficit accumulation patterns in the first publication. For the identification of predictors of DA trajectories, generalized linear mixed models were applied.

For the second publication, which was based on SHARE data, I used the same cut-off of FI≤0.08 for the transition between a “non-frail” and a “pre-frail” health state to define health deficit accumulation onset. After an initial FI value ≤0.08, a participant had to have at least two consecutive FI measurements >0.08 to be considered as having experienced a DA onset. The reason for this definition was that a repeated FI value over the threshold should prevent mistaking transitory disease or temporary disability after injury with an actual onset of the DA process. To estimate the effect of different socio-economic indicators on DA onset in Europe, a mixed-effects model was applied. This model accounted for clustering of individuals within countries through random effects. Furthermore, it accounted for the different ages of participants at study entry by basing the risk set calculation for each event time only on the observed participants of the respective age interval. The minimal sufficient adjustment set of covariates in this analysis was systematically selected through directed acyclic graphs. Geographical differences in age at DA onset between countries within Europe were compared using non-parametrically estimated survival curves and median age at onset with corresponding 95% confidence intervals. Also this analysis took age at study entry into account.

In the third publication, three different birth cohorts were defined depending on the co-occurrence of the KORA-Age participants’ critical developmental age (defined as the nine-month gestation period and the first two years of life) and the early reconstruction and food crisis (ERFC) period from June 1945 to June 1948 after World War II in Germany. The pre-war and war (PWW) cohort (born between Q1 1937 and Q2 1943) was already past critical developmental age during the ERFC period. In contrast, the ERFC cohort was in critical developmental age during the ERFC period and the post-currency reform (PCR) cohort was

conceived and born after the end of the ERFC period (i.e. born after Q2 1949). These three cohorts were compared with regard to their age-specific DA levels at ages 65-71 years using generalized linear models and controlling for individual life course characteristics.

1.4.2 Main results and scientific contribution

1.4.2.1 Prevalence of different DA states and patterns (Publication 1)

A majority of KORA-Age participants (59%) was classified as pre-frail in 2008/09. Stable (59%) and gradually declining (30%) DA patterns prevailed over the following three-year observation period. The least frequently observed DA pattern was improvement in 5% of all cases [68].

1.4.2.2 Predictors of DA patterns in Germany (Publication 1)

Several socio-demographic characteristics such as age, sex and marital status, socio-economic factors (namely income and education) and lifestyle-related characteristics (including smoking status, physical activity, Body Mass Index [BMI] and alcohol consumption) were considered as predictors for DA patterns in Germany. Out of these, male sex and income below the poverty threshold in addition to higher age resulted from the multinomial model as significant predictors of abrupt decline, which frequently, but not always, culminated in death [68].

1.4.2.3 Predictors of DA trajectories in Germany (Publication 1)

This mixed-model analysis used data from the first two waves of KORA-Age and confirmed female sex, obesity, low household and low leisure time physical activity as significant predictors of cross-sectional DA baseline levels. None of the investigated factors significantly influenced the speed of deficit accumulation [68].

The scientific contribution of Publication 1 is summarized in Box 1.

Box 1: Scientific contribution of Publication 1 [68].

1. While stability is a frequent DA pattern, spontaneous improvements without intervention are less frequently observed than it might be assumed when stability and improvement are combined in one category.
2. Deficit accumulation levels are higher for lower household and leisure time physical activity, women and obese people. This underlines the importance of weight-reduction and physical activity as potential target points for intervention.
3. Male sex and poverty predict abrupt health decline toward the end of life. Underlying mechanisms need to be identified and targeted interventions for these population sub-groups should be developed.

1.4.2.4 Predictors of DA onset in Europe (Publication 2)

This analysis suggested low wealth, elementary (last) occupation and low education as significant socio-economic risk factors for earlier DA onset. In contrast, low income did not contribute to explaining differences in age at DA onset [69].

1.4.2.5 Geographical differences in DA onset in Europe (Publication 2)

Cross-country comparisons suggested that the median age at DA onset differed considerably between the nine European countries under investigation, from 66 years in Germany to 76 years in Switzerland [69] (Fig.3).

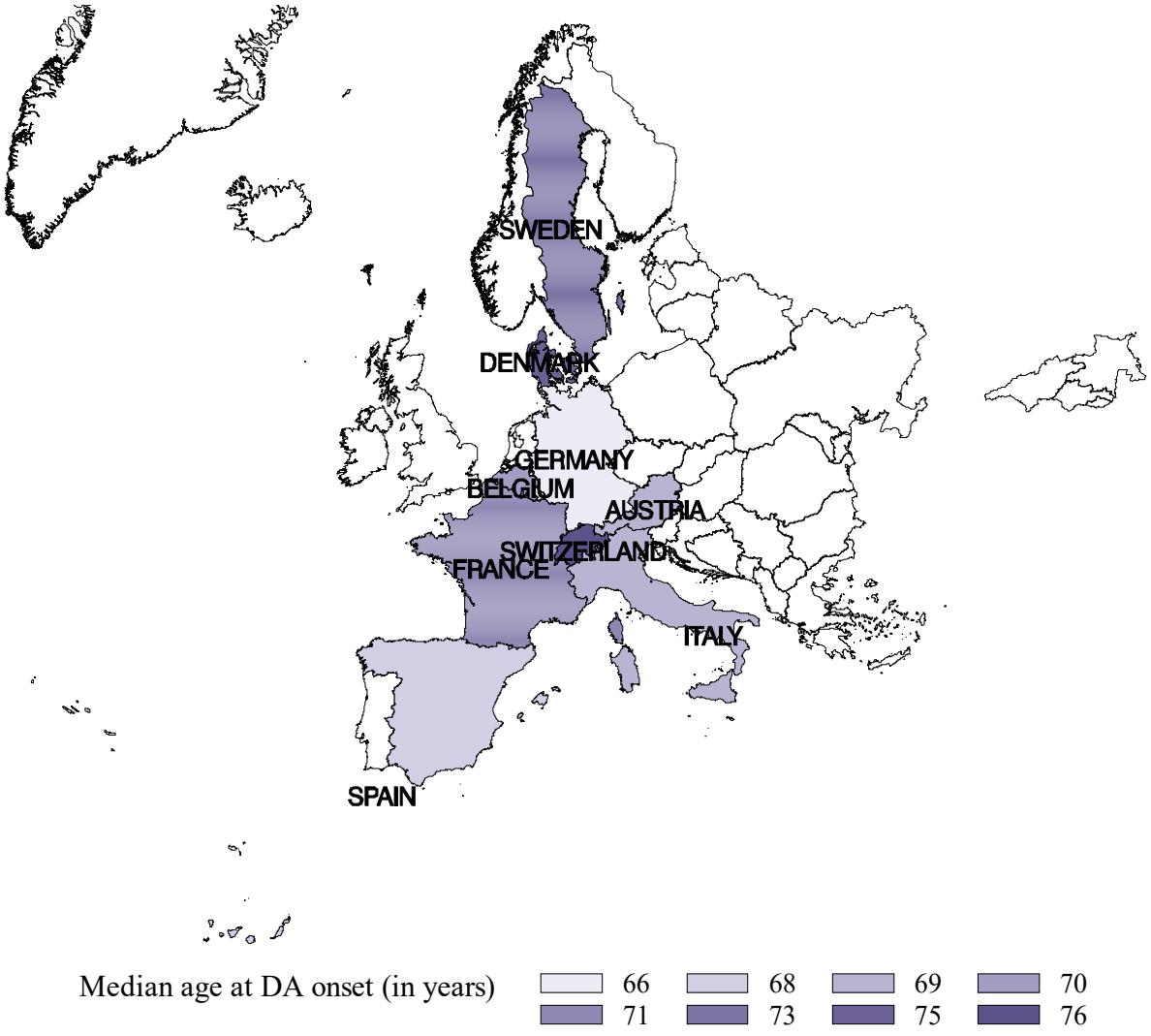


Fig.3: Median age at DA onset by country.

The scientific contribution of Publication 2 is summarized in Box 2.

Box 2: Scientific contribution of Publication 2 [69].

- We found that there were large differences in European countries with regard to health deficit accumulation onset, suggesting an immense unused prevention potential, especially in Germany with its premature median age at DA onset of 66 years.
- The age at deficit accumulation onset depends on education, occupation and wealth, but not on income. It is possible that the effects of different indicators of socio-economic position peak in different stages of the DA process.
- Women experience earlier DA onset than men. This could explain their constantly higher average DA levels throughout the subsequent DA process.

1.4.2.6 Cohort differences in DA levels in Germany (Publication 3)

KORA-Age participants whose critical developmental age coincided with the early reconstruction and food crisis period after World War II in Germany had significantly higher DA levels at ages 65-71 years as compared to participants from the earlier PWW cohort whose critical developmental age had ended before the ERFC period and also compared to the PCR cohort participants who were conceived and born after the ERFC period. Although sex, age, education, marital status, smoking status and BMI (but not physical activity and alcohol consumption) distributions differed between the three cohorts, these factors did not explain the cohort differences in DA levels in older age [70].

The scientific contribution of Publication 3 is summarized in Box 3.

Box 3: Scientific contribution of publication 3 [70]

- Co-occurrence of the early reconstruction and food crisis period with critical developmental age increased the risk for higher deficit accumulation levels at ages 65-71 years.
- Differences in DA levels between PWW, ERFC and PCR cohorts were not mediated by socio-economic, socio-demographic or life style related factors, indicating a direct effect of co-occurrence of critical developmental age and the ERFC period on health at age 65-71 years.
- While the expansion of morbidity, which has been reported for birth cohorts between 1911 to and 1932 in Germany, seems to have continued between 1937 and 1949, a quantitative or even qualitative change of morbidity trends may have occurred in cohorts born after 1949.
- When investigating morbidity trends over time, historical conditions in critical developmental age should be taken into account.

1.4.3 Strengths and limitations

This doctoral thesis has both conceptional and methodological strengths and limitations. Conceptionally, finding an appropriate definition of DA transition patterns and of DA onset was not trivial. The same applied to defining critical developmental age and meaningful historical birth cohorts. From a methodological perspective, we had to consider the consequences of assessing exposure effects in critical developmental age when only aggregated information on exposures was available. Furthermore, decisions had to be made regarding covariate selection and the treatment of correlated values both in repeated measurements and in country clusters. An additional challenge was the separation of age, period and cohort effects with regard to morbidity trends. We also had to carefully assess the feasibility of time-to-event analyses in the context of population-based cohort study data, when study inclusion does not represent a time of risk modification. In addition, each population-based data set has its specific advantages and drawbacks.

For both definition of DA onset and DA transition patterns, we relied on published thresholds from the literature [27] for frail, pre-frail and non-frail participants to allow for potential future comparisons across papers. Although other analyses have relied on comparable thresholds [71-74], there is currently no generally agreed-upon standard and these cut-offs can reasonably be challenged. Especially for the definition of age at DA onset, I thus ran sensitivity analyses with multiple alternative cut-offs to assess the effect of specific cut-offs on the results.

Also in defining critical developmental age as a nine-months-gestation-plus-first-two-years-of-life time frame and in defining the ERFC period as a critical time in German history, we followed definitions and results from previous scientific publications. In combination, these specifications resulted in the definition of three historic cohorts born between 1937 and 1950, for which we hypothesized different health risks. Still, there exists no final agreed-upon definition of critical developmental age and a multitude of other historical periods may be enumerated which may have additionally affected morbidity trends in Germany. In addition, we did not have individual-level data on exposure to traumatic experiences or exposure to hunger during the ERFC period for the KORA-Age participants. Thus, we may have underestimated the true effects of these exposures. To attenuate these shortcomings, we ran extensive sensitivity analyses with regard to the necessary length of exposure to adverse condition early in life and also with different risk-cohort and exposure definitions.

One of the strengths of this thesis is its foundation in large high-quality population-based data sets. KORA-Age is one of the largest epidemiological aging cohorts in Germany [75], and its value steadily increases further with the growing longitudinal dimension and with the 2016 enrichment sample consisting of a younger birth cohort. KOR-Age provided thus ideal preconditions for investigating prevalence of DA states and transition patterns in Germany and a solid base for a first longitudinal analysis on DA trajectories over time. It also allowed for the comparison of DA levels in different birth cohorts. For the analysis of predictors for DA onset I used European data from the SHARE study for the following three reasons: First, SHARE starts collecting data already in 50 year-olds as opposed to the 65 years and older participants in KORA-Age. Whereas in KORA-Age, only 23% of the participants had not yet experienced a DA onset at their time of study entry [68], in SHARE, due to the lower average participant age, the respective percentage was 41%. Second, measurement on indicators of socio-economic position is specifically elaborated and detailed in SHARE. Third, the SHARE dataset also allowed for cross-country comparisons with regard to the age at DA onset.

In the first two publications of this thesis, the clustering of individual measurements had specifically to be considered: In the first publication, the longitudinal follow-up of participants implied repeated measurements clustered within individuals, whereas in the second publication individuals were clustered within countries. Both types of correlated measurements could be dealt with effectively by implementing mixed-effect models [76], with random effects for individual participants or countries, respectively.

For the longitudinal analysis of deficit accumulation trajectories from KORA-Age wave 1 to wave 2, limitations include the short follow-up period, the relatively low number of invited participants in the second KORA-Age wave and the limited number of longitudinal measurements per person (a maximum of two). To attenuate these shortcomings, the

analysis has recently been repeated including data from the third KORA-Age wave, which essentially confirmed the results from the analysis presented here (manuscript submitted).

One major challenge in every multivariable regression analysis is covariate selection. For my first publication I did not focus on a predefined single most important exposure. Therefore, I relied on existing literature to identify potentially relevant predictors of DA trajectories and assess their relative contributions. For the second publication, in contrast, the objective was to investigate the effect of three specific pre-defined exposures (wealth, income and occupation). Here, it was important to identify a minimal adjustment set which allowed estimating an unbiased effect of these exposures on age at DA onset. I thus chose directed acyclic graphs (DAGs) [77] as a cutting-edge, methodologically thorough approach to covariate selection.

A further challenge when investigating morbidity trends in populations across time are the potential underlying effects of up to three time-related factors: Age, cohort and period effects. A first sight, health may seem cross-sectionally related to chronological age, but actually stem from differences in the underlying birth cohorts. These differences may result from collective experiences which affect whole generations such as war or economic crisis and political instability. When age is held constant to compare the effects of birth cohort membership on health, differences may be artefacts which stem from the different periods in which the health of the respective birth cohorts was measured. A valid prognosis for the future thus depends crucially on the correct attribution of observed trends to age, birth cohort or measurement period, which can be achieved using APC analysis.

Finally, applying time-to-event analyses on population-based cohort study data where study inclusion does not represent a time of risk modification can introduce bias due to left truncation [78]. This potential bias was controlled for by taking age at entry into account in both the non-parametric and the semi-parametric models [79].

1.5 Contribution of the doctoral thesis and outlook

This doctoral thesis adds evidence to predictors of deficit accumulation trajectories and biological aging as a complex and multifaceted process. It does so by putting into perspective different stages of the DA process (onset, accumulation trajectories, abrupt decline shortly before death) and by providing comparisons across countries and generations. Methodologically, this thesis stands out for its use of high-quality data from large national and international population-based cohorts, which allow for more generalizable results than smaller or highly selected samples of participants from a specific context.

For the general population in Germany, a new and alarming finding is the low frequency (5%) of spontaneous improvement with regard to health deficit accumulation which was observed in the absence of targeted interventions. This fact may have been masked hitherto by the frequent reporting of improvements in a combined category with stability [80, 72], possibly making spontaneous improvement seem more common than it actually is.

Furthermore, this thesis supports the hypothesis that different measures of socio-economic position are of varying relevance for the DA process, depending on the timing: For the onset of health deficit accumulation, education, wealth and occupation seem to matter more than income. In contrast, income becomes of major relevance towards the end of life, when abrupt decline frequently results in an accelerated system crash. In between these two points in time, during the DA trajectory after onset, but before abrupt deterioration, both (cohort) experiences in critical developmental age and accumulation of risk through modifiable health risk behaviors over the life course such as low physical activity and obesity may add to the observed heterogeneity in DA levels between individuals of the same age (Fig.4).

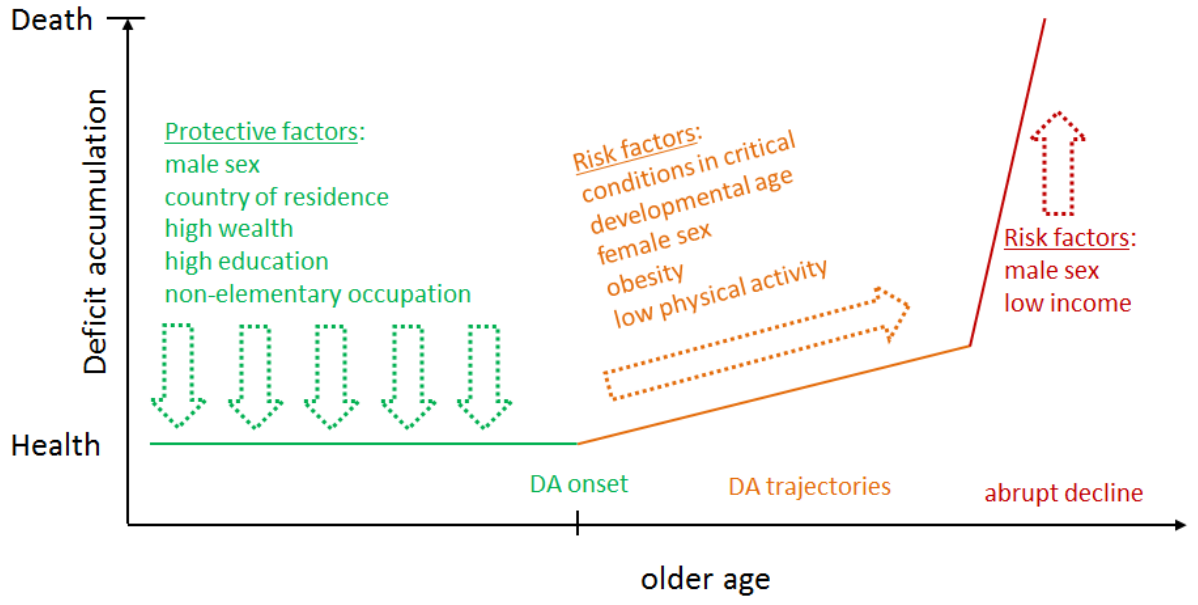


Fig.4: Protective factors and risk factors throughout the DA process.

In addition, this thesis points to the varying preventative potential between and within countries. The large between-country differences in median age at DA onset prove the existence of a large unused prevention potential in some countries, especially in Germany. How this prevention potential is used in the next decade may turn out to be decisive for the question if European societies will witness an expansion of morbidity in the future or succeed in compressing morbidity into the last years of life. Future studies should focus on the mechanisms contributing to some countries lagging behind more than others. Furthermore, the results of this thesis can serve as benchmark for future studies aiming to compare morbidity trends between countries and within countries across generations based on the age at DA onset. Within countries, occupational safety and workplace health promotion measures might be worth pursuing from a political perspective. The same may apply to policies which encourage financial precautions, such as the accumulation of wealth for older age. Furthermore, this thesis points to the observable impact of broader historical and societal conditions such as war and its consequences on health trajectories even decades later. At the same time, it reminds us that historical developments are all but linear. Similar to life expectancy, which decreased considerably all over Europe around World War II [81], the results of this thesis suggest that today's observed trends in healthy life expectancy may be a distant result of historical events and conditions in Europe. Prognoses for future trends which are based on sole extrapolation of existing measurements may be misleading. Ideally, such prognoses would take into account the complex interplay of historic and current conditions as well as individual life course characteristics which have contributed to the observed health status of today's older population.

This thesis has also contributed to disentangling cohort, age and period effects in deficit accumulation, and further stresses the importance of longitudinal studies and cohort comparisons as opposed to observations from simple cross-sections.

Lastly, the analyses presented here shed further light on gender differences in deficit accumulation trajectories: While women experience earlier onset of deficit accumulation, which persists in higher levels at any point in the DA trajectories thereafter, men are at higher risk for abrupt and fatal deficit accumulation patterns towards the end of life. In conjunction with the lower life expectancy for men, these results further support the male-female health survival paradox (women live longer than men but with higher health burden at all ages) [82], which can be summarized as "women bend, men break" [83]. Several underlying pathways have been proposed, amongst them biological pathways such as the protective function of estrogen, but also underlying behavioral patterns such as delayed help-seeking behavior [82] in men (possibly resulting from different role perceptions and societal expectations), which potentially preclude timely medical support at early disease stages [84]. Further research is

also needed with regard to the underlying mechanisms which lead from low income to abrupt health decline towards the end of life. Last but not least, monitoring vulnerable subgroups and developing tailored interventions to prevent or decelerate deficit accumulation in all stages of the DA process may be worth pursuing.

1.6 References

1. Pötzsch O, Rößger F. Bevölkerung Deutschlands bis 2060. 13. Koordinierte Bevölkerungsvorausberechnung Statistisches Bundesamt, Wiesbaden. 2015.
2. Omran AR. The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. The Milbank Quarterly. 2005;83(4):731-57. doi:doi:10.1111/j.1468-0009.2005.00398.x.
3. Plass D, Vos T, Hornberg C, Scheidt-Nave C, Zeeb H, Krämer A. Trends in disease burden in Germany: results, implications and limitations of the Global Burden of Disease study. Deutsches Arzteblatt international. 2014;111(38):629-38. doi:10.3238/arztebl.2014.0629.
4. Statistisches Bundesamt (Destatis). Kohortensterbetafeln für Deutschland - Ergebnisse aus den Modellrechnungen für Sterbetafeln nach Geburtsjahrgang 1871 – 2017. 2017.
5. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science (New York, NY). 2002;296(5570):1029-31. doi:10.1126/science.1069675.
6. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. The lancet. 2009;374(9696):1196-208.
7. Crimmins EM, Beltrán-Sánchez H. Mortality and morbidity trends: is there compression of morbidity? J Gerontol B Psychol Sci Soc Sci. 2011;66(1):75-86.
8. Mitnitski A, Rockwood K. Decrease in the relative heterogeneity of health with age: a cross-national comparison. Mechanisms of ageing and development. 2006;127(1):70-2.
9. Mitnitski A, Song X, Rockwood K. Assessing biological aging: the origin of deficit accumulation. Biogerontology. 2013;14(6):709-17.
10. Arking R. Biology of aging: observations and principles. Oxford University Press; 2006.
11. Holliday R. Aging is no longer an unsolved problem in biology. Annals of the New York Academy of Sciences. 2006;1067(1):1-9.
12. Geddes L. Human age limit claim sparks debate. Nat News. 2016.
13. Peto R, Doll R. There is no such thing as aging. BMJ: British Medical Journal. 1997;315(7115):1030.
14. McEwen BS. Protective and Damaging Effects of Stress Mediators. New England Journal of Medicine. 1998;338(3):171-9. doi:10.1056/nejm199801153380307.
15. Kondo N. Socioeconomic disparities and health: impacts and pathways. Journal of epidemiology. 2012;22(1):2-6.
16. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mechanisms of ageing and development. 2006;127(5):494-6.
17. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC geriatrics. 2002;2(1):1.

18. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The lancet. 2013;381(9868):752-62.
19. Rockwood K, Nassar B, Mitnitski A. Apolipoprotein E-polymorphism, frailty and mortality in older adults. Journal of cellular and molecular medicine. 2008;12(6b):2754-61.
20. Jazwinski SM, Kim S, Dai J, Li L, Bi X, Jiang JC et al. HRAS1 and LASS1 with APOE are associated with human longevity and healthy aging. Aging Cell. 2010;9(5):698-708. doi:doi:10.1111/j.1474-9726.2010.00600.x.
21. Mather KA, Jorm AF, Parslow RA, Christensen H. Is Telomere Length a Biomarker of Aging? A Review. The Journals of Gerontology: Series A. 2011;66A(2):202-13. doi:10.1093/gerona/glq180.
22. Oeseburg H, de Boer RA, van Gilst WH, van der Harst P. Telomere biology in healthy aging and disease. Pflügers Archiv - European Journal of Physiology. 2010;459(2):259-68. doi:10.1007/s00424-009-0728-1.
23. Bollati V, Schwartz J, Wright R, Litonjua A, Tarantini L, Suh H et al. Decline in Genomic DNA Methylation through Aging in a Cohort of Elderly Subjects. Mechanisms of ageing and development. 2009;130(4):234-9. doi:10.1016/j.mad.2008.12.003.
24. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. The Scientific World Journal. 2001;1:323-36.
25. Kirkwood TB. A systematic look at an old problem. Nature. 2008;451(7179):644.
26. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatrics. 2008;8(1):24.
27. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. Journal of the American Geriatrics Society. 2010;58(4):681-7. doi:10.1111/j.1532-5415.2010.02764.x.
28. Yang Y, Lee LC. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the US older adult population. Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2009;65(2):246-55.
29. Kulminski A, Yashin A, Ukraintseva S, Akushevich I, Arbeev K, Land K et al. Accumulation of health disorders as a systemic measure of aging: Findings from the NLTCS data. Mechanisms of ageing and development. 2006;127(11):840-8. doi:10.1016/j.mad.2006.08.005.
30. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. Journal of the American Geriatrics Society. 2006;54(6):975-9.
31. Kulminski AM, Ukraintseva SV, Kulminskaya IV, Arbeev KG, Land K, Yashin AI. Cumulative deficits better characterize susceptibility to death in elderly people than

phenotypic frailty: lessons from the Cardiovascular Health Study. Journal of the American Geriatrics Society. 2008;56(5):898-903.

32. Fries JF. The compression of morbidity. The Milbank Memorial Fund quarterly Health and society. 1983:397-419.
33. Gruenberg EM. The failures of success. The Milbank Memorial Fund Quarterly Health and Society. 1977:3-24.
34. Geyer S. Die Morbiditätskompressionsthese und ihre Alternativen. Das Gesundheitswesen. 2015;77(06):442-6.
35. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. J Epidemiol Community Health. 2015;69(4):316-21.
36. Manton KG. Changing concepts of morbidity and mortality in the elderly population. The Milbank Memorial Fund Quarterly Health and Society. 1982:183-244.
37. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Oxford University Press; 2002.
38. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proceedings of the National Academy of Sciences. 2009;106(34):14716-21. doi:10.1073/pnas.0902971106.
39. Kesternich I, Siflinger B, Smith JP, Winter JK. Individual behaviour as a pathway between early-life shocks and adult health: evidence from hunger episodes in post-war Germany. The Economic Journal. 2015;125(588):F372-F93.
40. Yang Y, Land KC. Age-period-cohort analysis: New models, methods, and empirical applications. Chapman and Hall/CRC; 2016.
41. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. Journal of the American Geriatrics Society. 2005;53(12):2184-9.
42. Yu R, Wong M, Chong K, Chang B, Lum C, Auyeung T et al. Trajectories of frailty among Chinese older people in Hong Kong between 2001 and 2012: an age-period-cohort analysis. Age and ageing. 2017;47(2):254-61.
43. Chamberlain AM, St Sauver JL, Jacobson DJ, Manemann SM, Fan C, Roger VL et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. BMJ open. 2016;6(5):e011410. doi:10.1136/bmjopen-2016-011410.
44. Stolz E, Mayerl H, Waxenegger A, Rásky É, Freidl W. Impact of socioeconomic position on frailty trajectories in 10 European countries: evidence from the Survey of Health,

Ageing and Retirement in Europe (2004–2013). Journal of Epidemiology and Community Health. 2017;71(1):73.

45. Hoogendijk EO, Rockwood K, Theou O, Armstrong JJ, Onwuteaka-Philipsen BD, Deeg DJH et al. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. Age Ageing. 2018;47(5):727-33. doi:10.1093/ageing/afy081.
46. Herr M, Robine J-M, Aegerter P, Arvieu J-J, Ankri J. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. Annals of Epidemiology. 2015;25(9):674-80.e1. doi:https://doi.org/10.1016/j.annepidem.2015.05.006.
47. Romero-Ortuno R. F railty Index in Europeans: Association with determinants of health. Geriatr Gerontol Int. 2014;14(2):420-9.
48. Brinkman S, Voortman T, Kiefte-de Jong JC, van Rooij FJA, Ikram MA, Rivadeneira F et al. The association between lifestyle and overall health, using the frailty index. Archives of Gerontology and Geriatrics. 2018;76:85-91. doi:https://doi.org/10.1016/j.archger.2018.02.006.
49. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. The association between sedentary behaviour, moderate–vigorous physical activity and frailty in NHANES cohorts. Maturitas. 2015;80(2):187-91.
50. Rogers NT, Marshall A, Roberts CH, Demakakos P, Steptoe A, Scholes S. Physical activity and trajectories of frailty among older adults: Evidence from the English Longitudinal Study of Ageing. PLoS ONE. 2017;12(2):e0170878. doi:10.1371/journal.pone.0170878.
51. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco Smoke: Involvement of Reactive Oxygen Species and Stable Free Radicals in Mechanisms of Oxidative Damage, Carcinogenesis and Synergistic Effects with Other Respirable Particles. International Journal of Environmental Research and Public Health. 2009;6(2):445.
52. Alegría-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. Epigenomics. 2011;3(3):267-77. doi:10.2217/epi.11.22.
53. Diaz L, Montero A, Gonzalez-Gross M, Vallejo A, Romeo J, Marcos A. Influence of alcohol consumption on immunological status: a review. European journal of clinical nutrition. 2002;56(S3):S50.
54. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health affairs. 2002;21(2):60-76.
55. Harttgen K, Kowal P, Strulik H, Chatterji S, Vollmer S. Patterns of frailty in older adults: comparing results from higher and lower income countries using the Survey of Health,

Ageing and Retirement in Europe (SHARE) and the Study on Global AGEing and Adult Health (SAGE). PLoS One. 2013;8(10):e75847.

56. Herd P, Goesling B, House JS. Socioeconomic Position and Health: The Differential Effects of Education versus Income on the Onset versus Progression of Health Problems. Journal of Health and Social Behavior. 2007;48(3):223-38. doi:10.1177/002214650704800302.
57. House JS, Lantz PM, Herd P. Continuity and change in the social stratification of aging and health over the life course: evidence from a nationally representative longitudinal study from 1986 to 2001/2002 (Americans' Changing Lives Study). The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2005;60(Special_Issue_2):S15-S26.
58. Pollack CE, Chideya S, Cubbin C, Williams B, Dekker M, Braveman P. Should health studies measure wealth?: A systematic review. American journal of preventive medicine. 2007;33(3):250-64.
59. O'Caoimh R. Transitions and trajectories in frailty states over time: a systematic review of the European Joint Action ADVANTAGE. Annali dell'Istituto superiore di sanita. 2018;54(3):246-52.
60. Mergenthaler A. Die Entwicklung der gesunden Lebenserwartung im Alter. Ein Kohortenvergleich auf der Grundlage des deutschen Alterssurveys. Bevölkerungsforschung Aktuell. 2011;32:2-7.
61. Holle R, Happich M, Löwel H, Wichmann H-E, Group nftMKS. KORA-a research platform for population based health research. Gesundheitswesen. 2005;67(S 01):19-25.
62. Peters A, Döring A, Ladwig K, Meisinger C, Linkohr B, Autenrieth C et al. Multimorbidity and successful aging: the population-based KORA-Age study. Z Gerontol Geriatr. 2011;44:41-54.
63. Alcser KH, Benson G, Börsch-Supan A, Brugiavini A, Christelis D, Croda E et al. The Survey of Health, Aging, and Retirement in Europe - Methodology. Mannheim Research Institute for the Economics of Aging (MEA). 2005.
64. Börsch-Supan A, Brugiavini A, Jürges H, Kapteyn A, Mackenbach J, Siegrist J et al. First results from the Survey of Health, Ageing and Retirement in Europe (2004-2007). Starting the longitudinal dimension Mannheim: MEA. 2008.
65. Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F et al. Data resource profile: the Survey of Health, Ageing and Retirement in Europe (SHARE). International journal of epidemiology. 2013:dyt088.
66. Malter F, Börsch-Supan A. SHARE Wave 4: Innovations & Methodology. Munich: MEA, Max Planck Institute for Social Law and Social Policy. 2013.

67. Malter F, Börsch-Supan A, (Eds.). SHARE Wave 5: Innovations & Methodology. Munich: MEA, Max Planck Institute for Social Law and Social Policy. 2015.
68. Stephan A-J, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig K-H et al. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. Preventive Medicine. 2017;102:31-8.
69. Stephan A-J, Strobl R, Holle R, Grill E. Wealth and occupation determine health deficit accumulation onset in Europe–Results from the SHARE study. Experimental gerontology. 2018;113:74-9.
70. Stephan A-J, Strobl R, Schwettmann L, Meisinger C, Ladwig K-H, Linkohr B et al. Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age: results from the KORA-Age study. European journal of epidemiology. 2019:1-13.
71. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. Journal of the American Geriatrics Society. 2013;61(9):1537-51.
72. Hubbard RE, Fallah N, Searle SD, Mitnitski A, Rockwood K. Impact of exercise in community-dwelling older adults. PLoS One. 2009;4(7):e6174.
73. Hoover M, Rotermann M, Sanmartin C, Bernier J. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Health Rep. 2013;24(9):10-7.
74. Romero-Ortuno R. An alternative method for Frailty Index cut-off points to define frailty categories. European geriatric medicine. 2013;4(5):299-303.
75. Fuchs J, Scheidt-Nave C, Gaertner B, Dapp U, von Renteln-Kruse W, Saum K-U et al. Frailty in Deutschland: Stand und Perspektiven. Zeitschrift für Gerontologie und Geriatrie. 2016;49(8):734-42.
76. Singer JD, Willett JB, Willett JB. Applied longitudinal data analysis: Modeling change and event occurrence. Oxford university press; 2003.
77. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology. 2008;8(1):70.
78. Cain KC, Harlow SD, Little RJ, Nan B, Yosef M, Taffe JR et al. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. American journal of epidemiology. 2011:kwq481.
79. Foreman AJ, Lai GP, Miller DP, editors. Surviving left truncation using PROC PHREG. Western Users of SAS Software Meeting, University City, CA; 2008: Citeseer.
80. Mitnitski A, Song X, Rockwood K. Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. Experimental gerontology. 2007;42(11):1109-15.

81. Mackenbach JP. Political conditions and life expectancy in Europe, 1900–2008. Social Science & Medicine. 2013;82:134-46.
82. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. Aging Clin Exp Res. 2008;20(2):91-102.
83. Balard F, Beluche I, Romieu I, Willcox DC, Robine J-M. Are men aging as oaks and women as reeds? A behavioral hypothesis to explain the gender paradox of French centenarians. Journal of aging research. 2011;2011.
84. Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Social science & medicine. 2000;50(10):1385-401.

2. Articles

2.1 Article 1: Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study

Stephan A-J, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig K-H, et al. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. *Preventive Medicine*. 2017;102:31-8. doi: 10.1016/j.ypmed.2017.06.032

Preventive Medicine 102 (2017) 31–38

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study

Anna-Janina Stephan [a,b,*], Ralf Strobl [a,b], Rolf Holle [c], Christa Meisinger [d], Holger Schulz [e,f], Karl-Heinz Ladwig [d,g], Barbara Thorand [d], Annette Peters [d], Eva Grill [a,b,h]

[a] Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany
[b] German Center for Vertigo and Balance Disorders, Klinikum der Universität München, Munich, Germany
[c] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[d] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[e] Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg, Germany
[f] Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany
[g] Department for Psychosomatic Medicine and Psychotherapy, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany
[h] Munich Center of Health Sciences, Ludwig-Maximilians-Universität München, Munich, Germany

ARTICLE INFO

Article history:
Received 27 February 2017
Received in revised form 21 June 2017
Accepted 22 June 2017
Available online 27 June 2017

Keywords:
Aged
Ageing
Health status
Social determinants of health
Epidemiologic factors
Longitudinal studies
Models
Statistical

ABSTRACT

Ageing individuals differ both in their deficit accumulation (DA) trajectories and resulting DA patterns (improvement, stability, gradual or abrupt decline). This heterogeneity is still incompletely understood.
The objectives of this study were thus to identify determinants of DA trajectories and DA patterns in people aged 65 and older. Data originates from the 2009 baseline assessment and 2012 follow-up of the KORA (Cooperative Health Research in the Region of Augsburg)-Age study from Southern Germany. DA was measured with a Frailty Index (FI). The effects of socio-demographic, socio-economic and lifestyle factors were analyzed using generalized linear mixed models and multinomial regressions. FI scores were available for 1076 participants at baseline (mean age 76 years, 50% female) and 808 participants at follow-up. Higher baseline FI levels were significantly associated with higher age, female sex, lower physical activity, moderate alcohol consumption and obesity. Longitudinal increase in FI levels over 3 years was 31% (CL: [−3%; 77%]) independent of all examined predictors. The most frequent DA patterns were stability (59%) and gradual decline (30%). Compared to stability, higher age, male sex and low income predicted (mostly fatal) abrupt decline. In conclusion, several factors are associated with FI levels at baseline whereas the change in FI levels over time seems hardly modifiable. Thus, future research should investigate if the same factors predicting older-age FI levels constitute predictors of DA onset earlier in life. Towards the end of life, being male with low income may increase the risk for abrupt decline, indicating need for early detection.

1. Introduction

Deficit accumulation (*DA*) describes the successive accumulation of health deficits in ageing individuals leading to increased risk for institutionalization and, ultimately, death (Mitnitski and Rockwood, 2016). DA can be conceptualized as the result of a complex interplay between decreasing physiological resilience towards external stressors and increasing recovery time from injury or disease. Stressors may result from an individual's social environment (Mitnitski et al., 2013), complex life course experiences (Brothers et al., 2014), changes in the physical environment including weather conditions, environmental pollution, changes in routine medication or minor surgical procedures (Clegg et al., 2013) as well as exposure to infectious diseases (Mitnitski et al., 2013).

While most people gradually accumulate deficits over time, also patterns of stability, abrupt decline, and even improvements have been reported (Mitnitski et al., 2012). To date, it is not only unclear how frequent these four different *DA patterns* occur in the general population, but also which factors predict the occurrence of a specific DA pattern.

Deficit accumulation is strongly related to increasing age, even if considerable differences in the number of accumulated health deficits can be found in cross-sections of people of the same age (Mitnitski et al., 2012). Additionally, socio-demographic, socio-economic, and lifestyle factors such as sex, age, income, education, BMI, physical activity,

* Corresponding author at: Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistraße 17, 81377 Munich, Germany.
E-mail address: anna_janina.stephan@med.uni-muenchen.de (A.-J. Stephan).

http://dx.doi.org/10.1016/j.ypmed.2017.06.032
0091-7435/

smoking and alcohol consumption have been shown to be cross-sectionally associated with deficit accumulation (Blodgett et al., 2015; Hubbard et al., 2010; Romero-Ortuno, 2014; Stephan et al., 2016; Woo et al., 2005). Still, determinants of *DA trajectories* are incompletely understood as to date only few studies allow valid conclusions about causal associations and longitudinal development of DA over time (Hubbard et al., 2009; Marshall et al., 2015; Wang et al., 2013; Yang and Lee, 2009).

Part of the heterogeneity in DA trajectories may be explained by genetic differences (Jazwinski et al., 2010; Kim and Jazwinski, 2015; Romero-Ortuno, 2014), but it is also assumed that modifiable individual characteristics may decelerate DA, postpone its onset or both

Table 1
Mean Frailty Index levels by covariate categories at baseline 2009 (n = 1076) and follow-up 2012 (n = 808).

Baseline covariates	Frailty Index (FI)[a]									
	All baseline participants				Follow-up participants only					
			Baseline				Baseline		Follow-up	
	N	(%)	Mean	(SD)[b]	N	(%)[c]	Mean	(SD)[b]	Mean	(SD)[b]
All	1076	(100.0)	0.17	(0.13)	808	(100.0)	0.15	(0.11)	0.20	(0.14)
Age categories										
<70	228	(21.2)	0.11	(0.08)	195	(24.1)	0.10	(0.07)	0.12	(0.09)
70–74	229	(21.3)	0.13	(0.10)	201	(24.9)	0.13	(0.10)	0.17	(0.11)
75–79	243	(22.6)	0.17	(0.12)	178	(22.0)	0.16	(0.10)	0.21	(0.14)
80–84	241	(22.4)	0.19	(0.13)	164	(20.3)	0.17	(0.10)	0.24	(0.14)
>84	135	(12.6)	0.30	(0.17)	70	(8.7)	0.26	(0.14)	0.35	(0.15)
Sex										
Male	537	(49.9)	0.15	(0.11)	408	(50.5)	0.13	(0.09)	0.18	(0.13)
Female	539	(50.1)	0.19	(0.15)	400	(49.5)	0.17	(0.12)	0.22	(0.14)
PASE subscore leisure time[d]										
Missing values	51	(4.7)	0.47	(0.19)	13	(1.6)	0.39	(0.19)	0.55	(0.11)
1st quartile	252	(23.4)	0.21	(0.14)	177	(21.9)	0.19	(0.12)	0.25	(0.16)
2nd quartile	253	(23.5)	0.17	(0.10)	188	(23.3)	0.16	(0.11)	0.22	(0.14)
3rd quartile	263	(24.4)	0.13	(0.08)	214	(26.5)	0.12	(0.07)	0.17	(0.10)
4th quartile	257	(23.9)	0.11	(0.08)	216	(26.7)	0.11	(0.08)	0.15	(0.10)
PASE subscore household[e]										
Missing values	51	(4.7)	0.47	(0.19)	13	(1.6)	0.40	(0.17)	0.55	(0.11)
1st quartile	227	(21.1)	0.21	(0.14)	164	(20.3)	0.20	(0.13)	0.26	(0.17)
2nd quartile	316	(29.4)	0.16	(0.10)	244	(30.2)	0.15	(0.10)	0.20	(0.13)
3rd quartile	206	(19.1)	0.13	(0.07)	159	(19.7)	0.11	(0.07)	0.16	(0.10)
4th quartile	276	(25.7)	0.13	(0.08)	228	(28.2)	0.12	(0.08)	0.16	(0.10)
Smoking status										
Smoker	49	(4.6)	0.15	(0.11)	39	(4.8)	0.14	(0.08)	0.24	(0.16)
Ex-smoker	412	(38.3)	0.17	(0.13)	289	(35.8)	0.14	(0.10)	0.19	(0.13)
Never-smoker	615	(57.2)	0.17	(0.14)	480	(59.4)	0.15	(0.11)	0.20	(0.14)
Daily alcohol intake										
Missing values	5	(0.5)	0.64	(0.04)	1	(0.1)	0.62	(−)	0.63	(−)
0 g/day	391	(36.3)	0.19	(0.15)	273	(33.8)	0.17	(0.12)	0.23	(0.15)
>0 to <20 g/day	373	(34.7)	0.17	(0.12)	301	(37.3)	0.15	(0.11)	0.20	(0.13)
20 to <40 g/day	217	(20.2)	0.14	(0.11)	163	(20.2)	0.12	(0.09)	0.17	(0.13)
≥40/day	90	(8.4)	0.12	(0.08)	70	(8.7)	0.11	(0.07)	0.15	(0.09)
Marital status										
Missing values	11	(1.0)	0.32	(0.21)	9	(1.1)	0.26	(0.19)	0.39	(0.21)
Unmarried	45	(4.2)	0.17	(0.11)	28	(3.5)	0.18	(0.13)	0.21	(0.14)
Married	675	(62.7)	0.14	(0.11)	527	(65.2)	0.13	(0.09)	0.18	(0.13)
Divorced	50	(4.7)	0.18	(0.14)	39	(4.8)	0.16	(0.12)	0.21	(0.14)
Widowed	295	(27.4)	0.22	(0.16)	205	(25.4)	0.18	(0.12)	0.24	(0.15)
Per capita household income group										
Missing values	61	(5.7)	0.17	(0.14)	43	(5.3)	0.15	(0.11)	0.21	(0.15)
Highest income decile	114	(10.6)	0.13	(0.09)	92	(11.4)	0.12	(0.08)	0.14	(0.09)
Middle income group	685	(63.7)	0.17	(0.14)	512	(63.4)	0.15	(0.11)	0.20	(0.14)
Below poverty level[f]	243	(20.1)	0.17	(0.13)	161	(19.9)	0.15	(0.10)	0.22	(0.14)
Level of school education										
Primary	738	(68.6)	0.18	(0.14)	546	(67.6)	0.15	(0.11)	0.21	(0.14)
Secondary	193	(17.9)	0.16	(0.13)	153	(18.9)	0.15	(0.12)	0.19	(0.14)
Tertiary	145	(13.5)	0.13	(0.10)	109	(13.5)	0.11	(0.08)	0.16	(0.12)
BMI category										
Underweight or normal weight	227	(21.1)	0.18	(0.15)	161	(19.9)	0.14	(0.11)	0.19	(0.15)
Overweight	524	(48.7)	0.16	(0.12)	407	(50.4)	0.13	(0.10)	0.18	(0.13)
Obesity grade I	241	(22.4)	0.17	(0.12)	179	(22.2)	0.15	(0.10)	0.21	(0.13)
Obesity grade II or obesity grade III	84	(7.8)	0.23	(0.14)	61	(7.6)	0.21	(0.13)	0.29	(0.17)

[a] Frailty Index (FI): Range from 0 to 1 with higher values indicating more present deficits, i.e. a worse health status.
[b] Standard deviation.
[c] This number refers to all baseline participants who also participated in the follow-up survey and for whom information on FI levels at baseline and follow-up is available. Participant who died before follow-up (n = 97) and participants who were lost to follow-up (n = 171) are not included in this table.
[d] Physical Activity Score for the Elderly (PASE): leisure time subscore. Lower quartiles indicate less frequent/vigorous activity.
[e] Physical Activity Score for the Elderly (PASE): household subscore. Lower quartiles indicate less frequent/vigorous activity.
[f] Poverty threshold: 859 Euro per person per month for Bavaria in 2009.

(Kulminski et al., 2007; Marshall et al., 2015; Mitnitski et al., 2012; Yang and Lee, 2009).

Thus, identifying predictors of DA trajectories using longitudinal designs is crucial to fully understand the process of DA. In addition, quantifying DA patterns and investigating their predictors in the general population can inform public health decision-makers to project future costs for health systems and identify vulnerable population groups for preventive measures.

The objectives of this study were to quantify the occurrence of different DA patterns and to identify potentially modifiable predictors of DA patterns and DA trajectories in a population of older adults in Germany.

2. Methods

2.1. Study design, participants and data collection procedures

Data for this study originates from the 2009 baseline assessment and the 2012 follow-up of the KORA (Cooperative Health Research in the Region of Augsburg)-Age study from Southern Germany which includes all participants of the MONICA (Monitoring of Trends and Determinants in Cardiovascular Diseases)/KORA Surveys S1–S4 (1984–2001) aged 65 years or older on December 31st 2008.

The KORA-Age baseline assessment included a self-administered health questionnaire, an extended telephone interview and, for an age- and sex-stratified randomly drawn sub-sample (n = 1079), additional medical examinations. This sub-sample was included in the present study.

In 2012, 98 of these 1079 baseline participants had died. Of the remaining 981 participants, 822 participated in the follow-up examination. Of these, 703 participants were examined at the study center, 111 during home visits, and eight persons were approached via a proxy telephone interview.

Details about study design, sampling method, data collection and response rates for MONICA/KORA and KORA-Age can be found elsewhere (Holle et al., 2005; Löwel et al., 2005; Peters et al., 2011). A participant recruitment flow chart from MONICA/KORA up to the KORA-Age follow-up can be found in Appendix A.

Approval for KORA-Age was obtained from the Ethics Committee of the Bavarian Medical Association. Written informed consent was obtained from all participants.

2.2. Frailty Index

To quantify deficit accumulation, we constructed a Frailty Index (FI) following established methods and using health deficits available at both KORA-Age baseline and follow-up. Deficits which are potential candidates to enter a FI include diseases, measures of functioning and signs and symptoms (Searle et al., 2008).

This KORA-Age FI includes in total 30 items, covering 10 diseases, 13 measures of functioning and seven signs and symptoms. A short description of the item selection process and item operationalizations can be found in Appendix B. A list of included FI items can be retrieved from Appendix C.

All deficit items were coded as values between 0 (deficit absent) and 1 (deficit fully present). The FI for a person results as the number of the person-specific deficits divided by the total number of listed deficits. Thus, FI scores range from 0 (= no deficits present) to 1 (= all deficits present). If a participant scored missing on one or more of the deficit items, the denominator of the FI was reduced accordingly. If a participant scored missing on >20% of the items, the FI value was set to missing (Yang and Lee, 2009).

2.3. DA trajectories

Throughout this text, we refer with the term "DA trajectory" to the change in FI levels between baseline and follow-up measurement.

2.4. DA patterns

Four DA patterns were defined: Stability, improvement, gradual decline, and abrupt decline.

In order to derive this classification, in a first step we defined DA states as non-frail (FI ≤ 0.08), pre-frail (0.08 < FI < 0.25) and frail (FI ≥ 0.25) using published threshold values (Song et al., 2010), and death as an absorbing state. Stability was subsequently defined as having remained in the same DA state at follow-up as compared to baseline. Improvement was defined as having changed from a DA state to any better DA state. Gradual decline was defined as having changed from one state to the next worse state (including from frail to death). Abrupt decline was defined as having deteriorated at follow-up skipping at least one DA state.

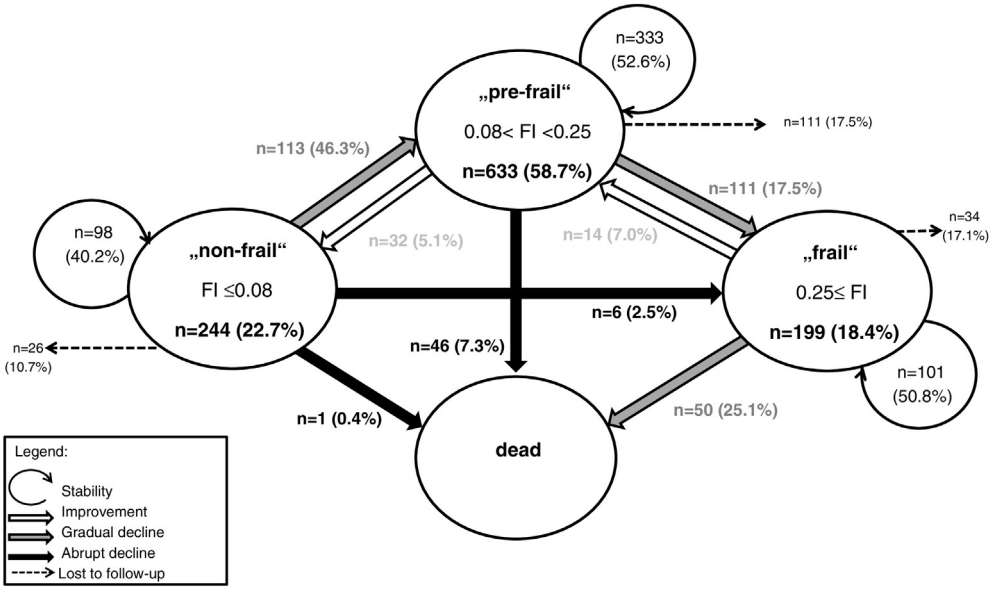


Fig. 1. Observed baseline distribution of study participants over health states and subsequent state transition frequencies. Note: DA state percentages are based on the full baseline sample of 1079 participants. Of these, three participants (0.2%) did not have enough valid deficit items for a Frailty Index value to be calculated and could thus not be classified as initially "non-frail", "pre-frail" or "frail".

2.5. Potential determinants of DA trajectories and DA patterns

We included baseline demographic (age, sex, marital status) and socio-economic (education, average household per capita income) variables as well as baseline lifestyle factors (leisure time and household physical activity, smoking status, daily alcohol intake and body mass index [BMI]) as potential predictors of DA trajectories and DA patterns. These variables were selected as they had been shown to be cross-sectionally associated with DA or one of its components. (Mello et al., 2014; Romero-Ortuno, 2014; Stenholm et al., 2014).

Age was defined as age at reference date (December 31st 2008) and categorized into five groups (<70, 70–74, 75–79, 80–84, >84). Marital status was categorized as single, married, divorced, and widowed.

Education was measured as highest level of school graduation (in ascending order: primary, secondary, and tertiary). Average household per capita income was defined as household net income (self-report through questionnaire) adjusted for household size according to the OECD-modified scale (OECD, 2009) and categorized into three groups using the poverty threshold (859 Euro for Bavaria in 2009) (Statistisches Bundesamt, 2014) as lower and the wealthiest decile as upper cut-off value.

Leisure time and household physical activity (PA) were assessed through sub-scales of the Physical Activity Scale for the Elderly (PASE) during standardized face-to-face interviews (NERI New England Research Institutes, 1991). PASE sub-scores were categorized into quartiles following previous KORA-Age research (Autenrieth et al., 2013; Stephan et al., 2016) with higher quartiles indicating more frequent/vigorous PA. We chose categorization over the continuous variable to be able to identify high risk groups and to compare groups with regard to their DA trajectories and patterns.

Participants were categorized as smokers, ex-smokers and never-smokers. Self-reported number and type of alcoholic drinks consumed during the last working-day and last weekend were transformed to grams alcohol per day. Daily alcohol intake was classified into no alcohol consumption, >0 to <20 g/day, 20 to <40 g/day, and one group consuming >40 g/day (Wellmann et al., 2004). BMI was categorized into four categories according to World Health Organization thresholds: underweight or normal weight (BMI < 25), overweight (25 ≤ BMI < 30), obesity grade I (30 ≤ BMI <35), and obesity grade II or III (BMI ≥ 35) (World Health Organization, 2000).

2.6. Statistical analyses

2.6.1. Descriptive analysis for DA trajectories: mean FI levels at baseline and follow-up

For each potential predictor category, numbers and percentages of participants as well as FI mean and standard deviation were calculated and shown separately for baseline and follow-up.

2.6.2. Descriptive analysis for DA patterns: graphical display and frequency by risk group

DA patterns were graphically displayed. Additionally, absolute and relative frequencies of the different DA patterns were calculated for socio-demographic, socio-economic and lifestyle variables.

2.6.3. Regression model for DA patterns

The effect of baseline values for income, education, age, sex, marital status, physical activity, smoking, daily alcohol intake, and BMI on resulting DA patterns was estimated controlling for baseline FI levels using multinomial regression models.

2.6.4. Regression model for DA trajectories

We analyzed the effect of baseline values for income, education, age, sex, marital status, physical activity, smoking, daily alcohol intake, and BMI on baseline FI levels and longitudinal change in FI levels after three years. Generalized linear mixed models with a log-link were applied using number of present health deficits (the FI numerator) as outcome and the logarithm of the number of potential deficits (the FI denominator) as offset term. We chose the mixed model approach because it can deal adequately with unequal numbers of observations between individuals and with autocorrelation of observations within individuals over time. Specifically, a negative binomial response distribution was chosen because the distribution of the FI scores in relatively healthy samples is expected to be right-skewed

Table 2
Distribution of DA patterns from 2009 to 2012 over baseline covariates in 2009 for study participants (excluding those lost to follow-up) from Southern Germany.

Covariates	DA patterns							
	Improvement		Stability		Gradual decline		Abrupt decline	
	N	(%)	N	(%)	N	(%)	N	(%)
All	46	(5.1)	532	(58.8)	274	(30.3)	53	(5.9)
<70	18	(8.9)	122	(60.4)	56	(27.7)	6	(3.0)
70–74	10	(4.9)	142	(68.9)	50	(24.3)	4	(1.9)
75–79	9	(4.6)	116	(60.0)	59	(30.4)	10	(5.2)
80–84	5	(2.5)	109	(55.3)	63	(32.0)	20	(10.2)
>84	4	(3.8)	43	(40.6)	46	(43.4)	13	(12.3)
Male	19	(4.1)	271	(57.3)	134	(28.7)	45	(9.6)
Female	27	(6.2)	268	(60.0)	140	(32.0)	8	(1.8)
PASE subscore leisure time[a]								
Missing values	0	–	10	(27.8)	23	(63.9)	3	(8.3)
1st quartile	13	(6.2)	114	(54.3)	64	(30.5)	19	(9.1)
2nd quartile	8	(3.8)	124	(59.3)	61	(29.2)	16	(7.7)
3rd quartile	10	(4.4)	142	(62.8)	65	(28.8)	9	(4.0)
4th quartile	15	(6.7)	142	(63.4)	61	(27.2)	6	(2.7)
PASE subscore household[b]								
Missing values	0	(−)	10	(27.8)	23	(63.9)	3	(8.3)
1st quartile	13	(6.6)	108	(54.6)	61	(30.9)	16	(8.1)
2nd quartile	12	(4.5)	158	(59.6)	79	(29.8)	16	(6.0)
3rd quartile	9	(5.4)	100	(59.9)	51	(30.5)	7	(4.2)
4th quartile	12	(5.0)	156	(65.3)	60	(25.1)	11	(4.6)
Smoking status								
Smoker	1	(2.2)	23	(51.1)	17	(37.8)	4	(8.9)
Ex-smoker	13	(3.8)	191	(56.3)	105	(31.0)	30	(8.9)
Never-smoker	32	(6.1)	318	(61.0)	152	(29.2)	19	(3.6)
Daily alcohol intake								
Missing values	0	–	1	(20.0)	4	(80.0)	0	–
0 g/day	18	(5.8)	172	(55.5)	102	(32.9)	18	(5.8)
>0 to <20 g/day	18	(5.5)	206	(62.8)	93	(28.4)	11	(3.4)
20 to <40 g/day	8	(4.4)	104	(57.1)	56	(30.8)	14	(7.7)
≥40 g/day	2	(2.5)	49	(61.3)	19	(23.8)	10	(12.5)
Marital status								
Missing values	0	–	7	(70.0)	2	(20.0)	1	(10.0)
Unmarried	1	(2.9)	21	(61.8)	8	(23.5)	4	(11.8)
Married	31	(5.3)	337	(58.1)	175	(30.2)	37	(6.4)
Divorced	1	(2.4)	25	(59.5)	16	(38.1)	0	–
Widowed	13	(5.4)	142	(59.4)	73	(30.5)	11	(4.6)
Per capita household income group								
Missing values	3	(6.3)	30	(62.5)	13	(27.1)	2	(4.2)
Highest income decile	6	(6.1)	59	(59.6)	27	(27.3)	7	(7.1)
Middle income group	32	(5.6)	335	(58.4)	183	(31.9)	24	(4.2)
Below poverty level[c]	5	(2.7)	108	(58.7)	51	(27.7)	20	(10.9)
Level of school education								
Primary	35	(5.7)	355	(57.9)	187	(30.5)	36	(5.9)
Secondary	7	(4.2)	105	(62.5)	50	(29.4)	7	(4.2)
Tertiary	4	(3.2)	72	(58.1)	38	(30.7)	10	(8.1)
BMI category								
Underweight or normal weight	8	(4.2)	113	(59.2)	59	(30.9)	11	(5.8)
Overweight	27	(6.1)	256	(57.2)	137	(31.1)	20	(4.6)
Obesity grade I	10	(4.9)	119	(57.8)	59	(28.6)	18	(8.7)
Obesity grade II or III	1	(1.5)	44	(64.7)	19	(27.9)	4	(5.9)

[a] Physical Activity Score for the Elderly (PASE): leisure time subscore. Lower quartiles indicate less frequent/vigorous activity.
[b] Physical Activity Score for the Elderly (PASE): household subscore. Lower quartiles indicate less frequent/vigorous activity.
[c] Poverty threshold: 859 Euro per person per month for Bavaria in 2009.

Table 3
Results of multinomial regression analysis on DA patterns from 2009 to 2012 in study participants from Southern Germany (n = 819).

Covariates	Adjusted[a] odds ratios of decline and improvement patterns as compared to the stability pattern								
	Abrupt decline			Improvement			Gradual decline		
	OR	(95% CL[b])		OR	(95% CL[b])		OR	(95% CL[b])	
Frailty Index score									
Increase of 0.03[c]	0.92	(0.82	1.04)	1.03	(0.94	1.14)	0.94	(0.89	0.99)
Age in years									
<70	Reference category								
70–74	0.61	(0.15	2.53)	0.51	(0.22	1.22)	0.87	(0.54	1.40)
75–79	1.98	(0.57	6.93)	0.49	(0.19	1.30)	1.36	(0.83	2.23)
80–84	4.40	(1.34	14.48)	0.31	(0.10	1.01)	1.49	(0.88	2.53)
>84	12.43	(3.13	49.29)	0.41	(0.09	1.84)	3.36	(1.65	6.82)
Sex									
Male	6.07	(2.04	18.07)	0.88	(0.39	1.98)	0.72	(0.48	1.08)
Female	Reference category								
PASE subscore household[d]									
1st quartile	1.13	(0.41	3.09)	1.97	(0.76	5.12)	1.36	(0.84	2.22)
2nd quartile	1.07	(0.42	2.75)	1.18	(0.47	2.93)	1.15	(0.74	1.77)
3rd quartile	0.51	(0.16	1.61)	1.46	(0.56	3.82)	1.25	(0.77	2.02)
4th quartile	Reference category								
PASE subscore leisure time[e]									
1st quartile	2.58	(0.87	7.64)	1.28	(0.52	3.16)	1.24	(0.75	2.0.03)
2nd quartile	2.42	(0.80	7.34)	0.70	(0.26	1.89)	1.21	(0.75	1.93)
3rd quartile	1.48	(0.46	4.75)	0.64	(0.26	1.62)	1.04	(0.67	1.63)
4th quartile	Reference category								
Smoking status									
Ex-smoker	0.52	(0.13	2.14)	1.61	(0.18	14.03)	0.55	(0.25	1.18)
Never-smoker	0.31	(0.07	1.37)	2.48	(0.29	21.46)	0.44	(0.20	0.95)
Smoker	Reference category								
Alcohol intake									
0 g/day	0.78	(0.27	2.27)	1.95	(0.39	9.73)	1.26	(0.65	2.44)
>0 to <20 g/day	0.34	(0.11	1.00)	1.48	(0.30	7.33)	1.07	(0.56	2.03)
20 to <40 g/day	0.62	(0.21	1.79)	1.73	(0.34	8.79)	1.33	(0.69	2.57)
≥40 g/day	Reference category								
Marital status									
Divorced	0	–	–	0.54	(0.06	4.79)	1.97	(0.90	4.33)
Married	1.02	(0.39	2.64)	1.00	(0.42	2.35)	1.46	(0.94	2.27)
Unmarried	5.72	(1.27	25.63)	0.55	(0.06	4.76)	0.88	(0.34	2.30)
Widowed	Reference category								
Per capita household income group									
Below poverty level[f]	3.26	(1.44	7.41)	0.44	(0.16	1.23)	0.85	(0.55	1.30)
Highest income decile	1.67	(0.57	4.94)	2.05	(0.69	6.08)	0.86	(0.48	1.53)
Middle income group	Reference category								
Education level									
Primary	0.56	(0.20	1.53)	3.29	(0.79	13.61)	0.90	(0.52	1.55)
Secondary	0.48	(0.15	1.61)	2.07	(0.45	9.44)	0.75	(0.40	1.37)
Tertiary	Reference category								
BMI category									
Obesity grade I	1.53	(0.58	4.04)	1.29	(0.45	3.69)	1.07	(0.64	1.77)
Obesity grade II	0.77	(0.16	3.67)	0.31	(0.04	2.79)	0.80	(0.39	1.66)
Overweight	0.56	(0.22	1.43)	1.59	(0.64	3.94)	1.16	(0.75	1.80)
Underweight or normal weight	Reference category								

[a] Multinomial regression analysis adjusted for baseline Frailty Index score, age category, sex, smoking, status, alcohol consumption, household physical activity, leisure time physical activity, BMI, education, income, and marital status. Covariates found to significantly improve the model according to type III test were sex, age category and income.
[b] CL: confidence limit.
[c] An increase in FI score of 0.03 approximately reflects one additional health deficit.
[d] Physical Activity Score for the Elderly (PASE): leisure time subscore. Lower quartiles indicate less frequent/vigorous activity.
[e] Physical Activity Score for the Elderly (PASE): household subscore. Lower quartiles indicate less frequent/vigorous activity.
[f] Poverty threshold: 859 Euro per person per month for Bavaria in 2009.

and over-dispersed (Rockwood et al., 2004). A scatter plot of baseline against follow-up FI scores indicated multiplicative effects rather than additive effects.

We constructed a random intercept model containing all potential predictors and their interactions with time. Exponentiated coefficients for a specific predictor category can ceteris paribus be interpreted as FI ratios in comparison to the FI in the respective predictor's reference category. Significant interactions of baseline covariates with time would indicate different changes in FI levels over time between risk groups.

For all analyses significance level was set to 5%. Analyses were performed using SAS Version 9.3 for Windows (Copyright © SAS Institute Inc., Cary, NC).

2.6.5. Sensitivity analysis: mortality

A logistic regression of baseline FI levels and all covariates used for the main analysis on survival status at follow-up was conducted. Covariates with a significant effect on survival were considered indicators of potential survivor bias.

3. Results

3.1. Study participants

FI scores were available for 1076 participants at baseline and 808 at follow-up (mean age at baseline 76 years, range 65 to 93 years, 50% female).

Complete information for the characterization of DA patterns over time (a FI value at baseline and either a FI score or information about death at follow-up) was available for 905 participants.

3.2. Descriptive analysis for DA trajectories: mean FI levels at baseline and follow-up

Table 1 shows the mean FI levels of study participants by covariate categories for baseline and follow-up. On average, FI levels were higher at follow-up than at baseline. The highest absolute changes in mean FI levels from baseline to follow-up were observed in older participants, smokers, participants with lower income and participants with obesity grade II and higher.

3.3. Descriptive analysis for DA patterns: graphical display and frequency by risk group

At baseline, 244 (22.6%) of participants were classified into a "non-frail" DA state, 633 (58.7%) into a "pre-frail" DA state, and 199 (18.4%) into a "frail" DA state.

Over three years, the most frequently observed DA patterns were gradual decline (n = 274, 30.2%) and stability (n = 532, 58.8%). Improvement occurred in n = 46 (5.1%) cases. Abrupt decline was observed in n = 53 (5.9%) cases, of which 46 (86.8%) resulted in death.

Details on DA patterns can be found in Fig. 1.

The distribution of DA patterns over baseline covariates is presented in Table 2.

3.4. Regression model for DA patterns

The number of participants with complete observations for DA patterns and all predictor variables, which could be included in the estimation of the multinomial regression model was n = 819 (76%).

The adjusted odds ratios for both gradual (OR = 3.36, CI [1.65; 6.82]) and abrupt decline including death (OR = 12.43, CI [3.13; 49.29]) as compared to stability were significantly higher for the oldest age group as compared to the youngest age group. In addition, the adjusted odds for abrupt decline as compared to stability were 6.07 times (CI [2.04; 18.07]) higher for men and 3.26 times (CI [1.44; 7.41]) higher for people living below the poverty level as compared to the middle income group. Adjusted odds ratios did not significantly differ between improvement and stability patterns with regard to any variables (all confidence intervals included 1).

For further details, see Table 3.

3.5. Regression model for DA trajectories

We included 963 (89%) participants with complete observation of all potential predictors and at least one available FI score at baseline into the regression models for DA trajectories. Baseline FI levels differed significantly by participant characteristics at baseline. While the effect of time was significant, indicating an increase of DA over time, interaction effects of covariates with time were not significant, indicating that change in FI levels over time did not vary by covariate. Results are shown in Table 4.

Exemplary estimated trajectories by age groups, sex, education level and leisure time PA, respectively, are shown in Appendix D (Fig. D.1).

3.6. Sensitivity analysis: mortality

Overall, 97 participants (60% male) died between baseline and follow-up.

Appendix D provides descriptive statistics by survival status (Table D.1) and attrition status (Table D.2) at follow-up. Drop-outs were on average less physically active, older and more often unmarried. Logistic regression on survival status revealed a higher mortality risk for older and male participants, participants with higher baseline FI levels, lower BMI (including normal BMI) and for smokers. For details, see Appendix D (Table D.3).

4. Discussion

Our analysis confirmed low physical activity (Blodgett et al., 2015; Stephan et al., 2016), obesity (Hubbard et al., 2010) and female sex (Marshall et al., 2015) as risk factors for higher baseline FI levels. However, our study is among the first to give evidence regarding the longitudinal predictors of change in FI levels and DA change patterns (Hubbard et al., 2009; Marshall et al., 2015; Wang et al., 2013; Yang and Lee, 2009).

Although many older adults in our longitudinal study gradually accumulated health deficits, we could show that men were at higher risk to experience abrupt decline, which resulted in a fatal outcome in 87% of all cases. Notably, men had overall lower FI levels at baseline, even after adjustment for potential confounders in the generalized linear mixed model. This adds evidence to the male-female health-survival paradox, with women having a higher life expectancy but experiencing higher prevalence of disease and disability at all ages as compared to men (Oksuzyan et al., 2008).

Social and behavioral explanations of this paradox include differing help-seeking patterns and social acceptability of disease and disability (Courtenay, 2000), and differing adherence to prescribed medication and therapies (Jörgensen et al., 2001). In addition, less favorable lifestyle choices have been reported for men as compared to women (Baker and Wardle, 2003).

Biomedical explanations include the protective role of estrogen in the risk for cardiovascular events (Oksuzyan et al., 2008). Likewise, genetic factors associated with the X-chromosome are hypothesized to be beneficial for survival. Following this reasoning, the higher life expectancy of women may result from their redundancy in cell lines where one X-chromosome can substitute the other in case of failure (Christensen et al., 2000).

Moreover, we found that living below poverty level additionally increased the risk of abrupt decline, which is in line with the notable life expectancy gap of >10 years for men and 8 years for women between the lowest and the highest income bracket in Germany (Lampert and Kroll, 2014). The pathways through which income may influence health and survival are both direct such as chronic psychosocial stress as a consequence of relative deprivation (Kondo, 2012) and indirect such as environmental exposures related to employment and housing, lower social capital, and lower health care utilization (Adler and Newman, 2002). The time lag between exposure to these risk factors and their effect on health combined with a cumulative effect of episodes of socioeconomic disadvantage over the life course may result in income having its greatest impact on health towards the end of life (Turrell et al., 2007), possibly after surmounting a threshold value (Kondo, 2012). This might explain the higher odds for abrupt decline which we observed for individuals from the low-income group.

Still, we could not confirm an income effect on changes in FI levels in contrast to the significant income effect we found on DA patterns, in line with previous inconclusive results on the effect of income on FI trajectories. In an US study, social status was found to influence the speed of DA with contradictory directions in different birth cohorts and overall assuming a lower growth rate for socio-economically worse-off individuals (Yang and Lee, 2009). A study from England also found a significant effect of wealth differences on DA growth rates, but with opposite results: Higher growth rates were assumed for less wealthy individuals (Marshall et al., 2015). Potential explanations may be found in the moderating effects of different health systems, the specific adjustment set for potential confounders or potential diverging effects in different birth cohorts.

In order to investigate different aspects of deficit accumulation we operationalized DA in two ways: the Frailty Index as a continuous

Table 4
Resulting DAI Ratios from the generalized linear mixed model including a random intercept and all potential predictors[a], and including all participants from Southern Germany with complete covariate information and at least one available FI value at baseline in 2009 (n = 963).

Baseline covariates		FI Ratio[b] (confidence interval)
Covariate	Risk group	
Intercept		0.06 (0.05 0.08)
Time effect		1.31 (0.97 1.77)
Age in years	<70	Reference category
	70–74	1.20 (1.06 1.36)
	75–79	1.44 (1.27 1.63)
	80–85	1.51 (1.32 1.72)
	>85	1.95 (1.67 2.28)
Interaction[c] age group and time	<70	Reference category
	70–74	1.06 (0.91 1.23)
	75–79	1.10 (0.95 1.27)
	80–85	1.15 (0.99 1.35)
	>85	1.14 (0.95 1.37)
Sex	Women	1.17 (1.06 1.29)
	Men	Reference category
Interaction[c] sex and time	Women	0.94 (0.84 1.05)
	Men	Reference category
Household physical activity	Quartile 1	1.36 (1.22 1.52)
	Quartile 2	1.09 (0.98 1.22)
	Quartile 3	1.00 (0.88 1.12)
	Quartile 4	Reference category
Interaction[c] household physical activity and time	Quartile 1	0.97 (0.85 1.10)
	Quartile 2	0.95 (0.84 1.08)
	Quartile 3	0.99 (0.85 1.14)
	Quartile 4	Reference category
Leisure time physical activity	Quartile 1	1.43 (1.27 1.61)
	Quartile 2	1.23 (1.09 1.38)
	Quartile 3	1.10 (0.98 1.24)
	Quartile 4	Reference category
Interaction[c] leisure time physical activity and time	Quartile 1	0.93 (0.82 1.07)
	Quartile 2	1.00 (0.88 1.14)
	Quartile 3	1.00 (0.88 1.15)
	Quartile 4	Reference category
Smoking status	Smoker	1.14 (0.94 1.40)
	Ex-smoker	1.07 (0.98 1.17)
	Never-smoker	Reference category
Interaction[c] smoking status and time	Smoker	1.31 (1.05 1.64)
	Ex-smoker	1.00 (0.91 1.12)
	Never-smoker	Reference category
Alcohol consumption	0 g/day	1.11 (0.95 1.31)
	>0–<20 g/day	1.21 (1.03 1.42)
	20–<40 g/day	1.07 (0.91 1.26)
	≥40 g/day	Reference category
Interaction[c] alcohol consumption and time	0 g/day	0.99 (0.81 1.20)
	>0–<20 g/day	0.96 (0.80 1.17)
	20–<40 g/day	0.94 (0.77 1.15)
	≥40 g/day	Reference category
Marital status	Unmarried	1.02 (0.84 1.23)
	Married	0.92 (0.83 1.03)
	Divorced	1.12 (0.93 1.36)
	Widowed	Reference category
Interaction[c] marital status and time	Unmarried	0.96 (0.76 1.21)
	Married	1.02 (0.91 1.14)
	Divorced	0.98 (0.79 1.22)
	Widowed	Reference category
Per capita household income group	Highest income decile	0.90 (0.78 1.03)
	Below poverty level	0.96 (0.86 1.06)
	Middle income group	Reference category
Interaction[c] per capita household income group and time	Highest income decile	0.93 (0.77 1.11)
	Below poverty level	1.09 (0.97 1.23)
	Middle income group	Reference category
Education level	Primary	1.12 (0.98 1.28)
	Secondary	1.05 (0.91 1.23)
	Tertiary	Reference category
Interaction[c] education level and time	Primary	0.98 (0.83 1.16)
	Secondary	0.96 (0.80 1.15)
	Tertiary	Reference category
BMI category	Underweight or normal weight	1.03 (0.93 1.14)
	Obesity grade I	1.07 (0.97 1.18)
	Obesity grade II or III	1.30 (1.13 1.50)
	Overweight	Reference category
Interaction[c] BMI category	Underweight or normal weight	0.93 (0.82 1.05)
and time	Obesity grade I	1.04 (0.93 1.16)
	Obesity grade II or III	1.01 (0.86 1.18)
	Overweight	Reference category

[a] Generalized linear mixed model including a random intercept and adjusted for baseline age category, sex, smoking, status, alcohol consumption, household physical activity, leisure time physical activity, BMI, education, income, and marital status. Covariates found to significantly improve the model according to type III test were the main effects for time, sex, age category, BMI, household and leisure time physical activity and alcohol consumption.

[b] Exemplary interpretation of FI Ratios for women (FI Ratio = 1.17): ceteris paribus, i.e. all other variables having the same value, women have 17% (or 1.17 times) higher FI levels than men (reference category).

[c] Since there were no significant interactions between risk groups and time, the change in FI levels over time can be considered invariant between all risk groups (FI Ratio for follow-up as compared to baseline = 1.31). In our example, this means that the estimated FI growth rate over three years is equally 31% for both men and women.

outcome and the DA patterns as categorized outcome. Whereas the continuous outcome variable allows for a more precise modeling of covariate effects, the categorization in DA patterns allowed for inclusion of deceased participants at follow-up, thus providing a more comprehensive picture of the health - deficit accumulation continuum which results in death when the body's functional redundancies are exhausted.

In our analysis of FI trajectories, none of the investigated predictors significantly explained the heterogeneity in the change in FI levels. One possible explanation may be that the rate of change cannot be modified once the DA process has started. This would be in line with the results of previous studies which have already suggested that changes in FI levels over time might be age-independent (Mitnitski and Rockwood, 2016) and comparable for men and women (Marshall et al., 2015; Yang and Lee, 2009).

However, for some high risk groups, potential survivor bias cannot fully be excluded, as male gender, low BMI and smoking were risk factors for increased mortality in our study. In these groups, the change in FI levels may have actually been higher but may have led to death before the follow-up measurement three years later.

Furthermore, differences in change in FI levels might also be too subtle to be captured in the three years' time span covered by our data.

Last, we only had a maximum of two observations per participant. Therefore, no higher-order growth curves could be fitted although they might better depict underlying trajectories. Still, the multiplicative interpretation of the coefficients in the generalized linear mixed effects model allows a more flexible interpretation of the trajectories as compared to additive growth.

A limitation of our analysis of DA patterns is the loss of information resulting from categorizing continuous outcome variables. As a result, two adjacent categories include values which are very close to each other but arbitrarily divided, while two values in the same category may show relatively large differences. This problem is exacerbated by the fact that the DA states (non-frail, pre-frail and frail) are not equidistant. Nevertheless, analysis of variance showed that absolute changes in FI levels were significantly associated with DA patterns, indicating that this categorization is indeed able to discriminate between amount and direction of absolute change in FI levels.

Although 86.8% of all observed abrupt declines resulted in death, we have reasons to assume that the identified predictors of abrupt decline are not simply predictors of survival. First, the identified predictors of abrupt decline only partly overlap with those from the sensitivity analysis on overall survival. Second, 51% of all deaths occurred following a gradual decline pattern.

In sum, our analyses indicate that higher age, female sex, lower education and lifestyle factors are associated with higher baseline FI levels. As none of the investigated factors were found to influence the three-year change in FI levels, we hypothesize that once the process of deficit

accumulation has started, it might be hard to modify. Thus, future research should investigate if the factors which cross-sectionally predict FI levels in older age are the same factors which predict the time of DA onset earlier in life.

Furthermore, our analyses suggested that towards the end of life, being male and having low income increased the risk for abrupt decline with frequent fatal outcome. Hence, for these vulnerable population groups monitoring for timely detection of abrupt decline may be advisable. Additionally, our results underline the importance of further investigating the conditions under which income may or may not influence DA. Cross-country comparisons accounting for country-specific differences in health systems may be a first step in this direction.

Conflict of interest

The authors declare there is no conflict of interest.

Funding

The project ‚Functioning and disability among aged persons' was funded by the German Research Foundation (GR 3608/1-1). The KORA-Age project was financed by the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713 and FKZ 01ET1003A, C) as part of the 'Health in old age' program. The financial sponsors played no role in the design, execution, analysis and interpretation of data, or writing of the study.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

The authors would like to thank the field staff in Augsburg who were involved in conducting the studies and the team at the Helmholtz Zentrum for data management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2017.06.032.

References

Adler, N.E., Newman, K., 2002. Socioeconomic disparities in health: pathways and policies. Health Aff. 21, 60–76.
Autenrieth, C.S., Kirchberger, I., Heier, M., Zimmermann, A.-K., Peters, A., Döring, A., Thorand, B., 2013. Physical activity is inversely associated with multimorbidity in elderly men: results from the KORA-Age Augsburg Study. Prev. Med. 57, 17–19.
Baker, A.H., Wardle, J., 2003. Sex differences in fruit and vegetable intake in older adults. Appetite 40, 269–275.
Blodgett, J., Theou, O., Kirkland, S., Andreou, P., Rockwood, K., 2015. The association between sedentary behaviour, moderate–vigorous physical activity and frailty in NHANES cohorts. Maturitas 80, 187–191.
Brothers, T.D., Theou, O., Rockwood, K., 2014. Frailty and migration in middle-aged and older Europeans. Arch. Gerontol. Geriatr. 58, 63–68.
Bundesamt, Statistisches, 2014. Armutsgefährdungsschwelle - Einpersonen-Haushalte nach Ländern, Wiesbaden.
Christensen, K., Kristiansen, M., Hagen-Larsen, H., Skytthe, A., Bathum, L., Jeune, B., Andersen-Ranberg, K., Vaupel, J.W., Ørstavik, K.H., 2000. X-linked genetic factors regulate hematopoietic stem-cell kinetics in females. Blood 95, 2449–2451.
Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381, 752–762.
Courtenay, W.H., 2000. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Soc. Sci. Med. 50, 1385–1401.
Holle, R., Happich, M., Löwel, H., Wichmann, H., Group, M.K.S., 2005. KORA-a research platform for population based health research. Das Gesundheitswesen 67, 19–25.
Hubbard, R.E., Fallah, N., Searle, S.D., Mitnitski, A., Rockwood, K., 2009. Impact of exercise in community-dwelling older adults. PLoS One 4, e6174.
Hubbard, R.E., Lang, I.A., Llewellyn, D.J., Rockwood, K., 2010. Frailty, body mass index, and abdominal obesity in older people. J. Gerontol. Ser. A Biol. Med. Sci. 65, 377–381.
Jazwinski, S.M., Kim, S., Dai, J., Li, L., Bi, X., Jiang, J.C., Arnold, J., Batzer, M.A., Walker, J.A., et al., 2010. HRAS1 and LASS1 with APOE are associated with human longevity and healthy aging. Aging Cell 9, 698–708.
Jörgensen, T., Johansson, S., Kennerfalk, A., Wallander, M.-A., Svärdsudd, K., 2001. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann. Pharmacother. 35, 1004–1009.
Kim, S., Jazwinski, S.M., 2015. Quantitative measures of healthy aging and biological age. Healthy Aging Res. 4.
Kondo, N., 2012. Socioeconomic disparities and health: impacts and pathways. J. Epidemiol. 22, 2–6.
Kulminski, A., Ukraintseva, S.V., Akushevich, I., Arbeev, K.G., Land, K., Yashin, A.I., 2007. Accelerated accumulation of health deficits as a characteristic of aging. Exp. Gerontol. 42, 963–970.
Lampert, T., Kroll, L.E., 2014. Soziale Unterschiede in der Mortalität und Lebenserwartung.
Löwel, H., Döring, A., Schneider, A., Heier, M., Thorand, B., Meisinger, C., Group, M.K.s., 2005. The MONICA Augsburg surveys-basis for prospective cohort studies. Das Gesundheitswesen 67, 13–18.
Marshall, A., Nazroo, J., Tampubolon, G., Vanhoutte, B., 2015. Cohort differences in the levels and trajectories of frailty among older people in England. J. Epidemiol. Community Health 69, 316–321.
Mello, A.d.C., Engstrom, E.M., Alves, L.C., 2014. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cad. Saude Publica 30, 1143–1168.
Mitnitski, A., Rockwood, K., 2016. The rate of aging: the rate of deficit accumulation does not change over the adult life span. Biogerontology 17, 199–204.
Mitnitski, A., Song, X., Rockwood, K., 2012. Trajectories of changes over twelve years in the health status of Canadians from late middle age. Exp. Gerontol. 47, 893–899.
Mitnitski, A., Song, X., Rockwood, K., 2013. Assessing biological aging: the origin of deficit accumulation. Biogerontology 14, 709–717.
NERI New England Research Institutes, 1991. PASE Physical Activity Scale for the Elderly - Administration and Scoring Instruction Manual.
OECD, 2009. What are Equivalence Scales?
Oksuzyan, A., Juel, K., Vaupel, J.W., Christensen, K., 2008. Men: good health and high mortality. Sex differences in health and aging. Aging Clin. Exp. Res. 20, 91–102.
Peters, A., Döring, A., Ladwig, K., Meisinger, C., Linkohr, B., Autenrieth, C., Baumeister, S., Behr, J., Bergner, A., et al., 2011. Multimorbidity and successful aging: the population-based KORA-Age study. Z. Gerontol. Geriatr. 44, 41–54.
Rockwood, K., Mogilner, A., Mitnitski, A., 2004. Changes with age in the distribution of a frailty index. Mech. Ageing Dev. 125, 517–519.
Romero-Ortuno, R., 2014. Frailty index in Europeans: association with determinants of health. Geriatr Gerontol Int 14, 420–429.
Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8, 24.
Song, X., Mitnitski, A., Rockwood, K., 2010. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J. Am. Geriatr. Soc. 58, 681–687.
Stenholm, S., Westerlund, H., Salo, P., Hyde, M., Pentti, J., Head, J., Kivimäki, M., Vahtera, J., 2014. Age-related trajectories of physical functioning in work and retirement: the role of sociodemographic factors, lifestyle and disease. J. Epidemiol. Community Health 68, 503–509.
Stephan, A.-J., Strobl, R., Müller, M., Holle, R., Autenrieth, C.S., Thorand, B., Linkohr, B., Peters, A., Grill, E., 2016. A high level of household physical activity compensates for lack of leisure time physical activity with regard to deficit accumulation: results from the KORA-Age study. Prev. Med. 86, 64–69.
Turrell, G., Lynch, J.W., Leite, C., Raghunathan, T., Kaplan, G.A., 2007. Socioeconomic disadvantage in childhood and across the life course and all-cause mortality and physical function in adulthood: evidence from the Alameda County Study. J. Epidemiol. Community Health 61, 723–730.
Wang, C., Song, X., Mitnitski, A., Yu, P., Fang, X., Tang, Z., Shi, J., Rockwood, K., 2013. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. J. Gerontol. Ser. A Biol. Med. Sci. 68, 338–346.
Wellmann, J., Heidrich, J., Berger, K., Döring, A., Heuschmann, P.U., Keil, U., 2004. Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. Eur. J. Cardiovasc. Prev. Rehabil. 11, 48–55.
Woo, J., Goggins, W., Sham, A., Ho, S.C., 2005. Social determinants of frailty. Gerontology 51, 402–408.
World Health Organization, 2000. Obesity: Preventing and Managing the Global Epidemic. World Health Organization.
Yang, Y., Lee, L.C., 2009. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the US older adult population. J. Gerontol. B Psychol. Sci. Soc. Sci. (gbp102).

2.2 Article 2: Wealth and occupation determine health deficit accumulation onset in Europe – results from the SHARE study.

Stephan A-J, Strobl R, Holle R, Grill E. Wealth and occupation determine health deficit accumulation onset in Europe – Results from the SHARE study. *Experimental Gerontology*. 2018;113:74-9. doi: 10.1016/j.exger.2018.09.021

Experimental Gerontology 113 (2018) 74–79

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Wealth and occupation determine health deficit accumulation onset in Europe – Results from the SHARE study

Anna-Janina Stephan[a,*], Ralf Strobl[a,b], Rolf Holle[c], Eva Grill[a,b,d]

[a] Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany
[b] German Center for Vertigo and Balance Disorders, University Hospital Ludwig-Maximilians-Universität München, Munich, Germany
[c] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[d] Munich Center of Health Sciences, Ludwig-Maximilians-Universität München, Munich, Germany

ARTICLE INFO

Keywords:
Health status disparities
Socioeconomic factors
Aged
Healthy aging
Frailty
Health deficit accumulation

ABSTRACT

While socio-economic characteristics have been shown to be associated with health deficit accumulation (DA) trajectories, their effect on the age at DA onset remains unclear. The objective of this study was to compare the median age at DA onset across nine European countries and to investigate the effects of income, occupation and wealth on DA onset after age 50. We used population samples aged 50 years and older from the SHARE (Survey of Health, Aging and Retirement in Europe) study. Participants from nine European countries with longitudinal data from at least three of the 2004/05, 2006/07, 2010/11, 2012/13 and 2014/15 waves were included in the analysis. A Frailty Index (FI, range 0–1) was constructed from 50 health deficits. DA onset was defined as having FI values $>$ 0.08 in at least two consecutive measurements following an initial FI value $\leq$ 0.08. We investigated the effect of income, occupation and wealth on DA onset using a random effects model for time-to-event data. Potential confounding variables were identified using directed acyclic graphs. Out of 8616 (mean age 62 years, 49.0% female) participants initially at risk, 2640 (30.6%) experienced a subsequent DA onset. Median age at onset was 71 years overall, ranging from 66 years (Germany) to 76 years (Switzerland). Wealth and occupation were found to have significant effects on DA onset which decreased with age. In sum, the median age at DA onset differs between European countries. On an individual-level, wealth and occupation, but not income influence the age at DA onset.

1. Introduction

Socio-economic characteristics such as education, income, wealth, and occupation are among the most powerful determinants of health. They may act both as direct (Kondo, 2012) and indirect determinants of health, e.g. by creating environmental hazards related to employment and housing, or by influencing health care utilization and less favourable health behaviors (Adler and Newman, 2002).

Deteriorating health in older age can be summarized using the concept of deficit accumulation (DA) (Mitnitski et al., 2001). Health effects of socio-economic risk factors may accumulate over the course of a lifetime (Ben-Shlomo and Kuh, 2002), possibly until they surmount a threshold after which the impact of external stressors is no longer as easily compensated by regenerative processes as in younger adulthood (Kondo, 2012). Failure to compensate the impact of external stressors leads to the accumulation of what is generally perceived as "age-related" chronic health deficits. Although it was recently found that a targeted intervention may reduce the number of accumulated deficits at any age (Theou et al., 2017), aging populations outside of intervention studies experience mostly stable or deteriorating health patterns (Mitnitski et al., 2007; Stephan et al., 2017). Socio-economic characteristics are associated with the onset of various degenerative health processes in older adults, such as functional limitations (Matthews et al., 2005), heart problems, diabetes, cancer, stroke (Herd et al., 2007), and depression (Koster et al., 2006). Thus, investigating the social determinants of DA onset is of high relevance.

Both socio-economic status and health expectancy vary considerably across Europe. For instance, average wealth ranges from

Abbreviations: CI, Confidence interval; DA, deficit accumulation; DAG, directed acyclic graph; FI, Frailty Index; HR, Hazard Ratio; ISCED, international standard classification of education; SHARE, Survey of Health, Aging and Retirement in Europe

* Corresponding author at: Institute for Medical Information Processing, Biometry and Epidemiology, LMU Munich, Marchioninistraße 17, 81377 Munich, Germany.
E-mail address: anna_janina.stephan@med.uni-muenchen.de (A.-J. Stephan).

https://doi.org/10.1016/j.exger.2018.09.021
Received 17 July 2018; Received in revised form 6 September 2018; Accepted 24 September 2018
Available online 25 September 2018
0531-5565/

below 40.000 Euro (Netherlands) to over 280.000 Euro (Switzerland) (Christelis et al., 2009), and healthy life expectancy at the age of 50 ranges from 14 years in Germany to 24 years in Denmark (Jagger et al., 2009). The difference in health expectancy between the lowest and highest educational level has been reported to vary between 2 years in Italy and 5.3 years in Austria (Mäki et al., 2013). For other constituents of socio-economic position, such as income, wealth, or occupation, comparative studies between countries are largely missing.

Therefore, the objective of this study was to investigate the effect of socioeconomic characteristics, especially income, wealth, and occupation on DA onset in people aged 50 years and older in nine European countries.

2. Methods

2.1. Study design, participants and data collection procedures

Data originates from the Survey of Health, Aging and Retirement in Europe (SHARE), which includes representative samples of the populations aged 50 years and older from 20 European countries and Israel.

All SHARE participants are asked to complete a multi-module computer-assisted personal interview. Details about study design, sampling methods and data collection for SHARE can be found elsewhere (Alcser et al., 2005; Börsch-Supan et al., 2013; Börsch-Supan et al., 2008; Malter and Börsch-Supan, 2013; Malter and Börsch-Supan, 2015). Approval for SHARE was obtained from the Ethics Committee of the University of Mannheim until 2011 and from the Ethics Council of the Max-Planck-Society for the Advancement of Science from 2011 onwards. Written informed consent was obtained from all participants.

To obtain a sample with a maximum of follow-ups for longitudinal analysis, we used data from those nine countries (Austria, Belgium, Switzerland, Germany, Denmark, Italy, Spain, France, and Sweden) participating in all five SHARE waves conducted in 2004/05 (wave 1), 2006/07 (wave 2), 2010/11 (wave 4), 2012/13 (wave 5) and 2014/15 (wave 6) [dataset](Börsch-Supan, 2017a; Börsch-Supan, 2017b; Börsch-Supan, 2017c; Börsch-Supan, 2017d; Börsch-Supan, 2017e) and only from participants who had participated in at least three out of the five waves.

2.2. Outcome

2.2.1. Frailty Index

To measure deficit accumulation, we constructed a Frailty Index (FI) following established methods and procedures (Searle et al., 2008). The FI for this study includes in total 50 items, covering 10 diseases, 21 measures of functioning and 19 signs and symptoms. Candidate item were taken into consideration based on two criteria: Use in earlier FIs created for analyses of SHARE data (Romero-Ortuno, 2014; Theou et al., 2013) and being available in all five SHARE waves used for the current analysis. This approach was chosen as previously developed SHARE FIs were based solely on the first two waves of SHARE. As a consequence, neither all items used in the previously published 40-item nor all items used in the previously published 70-item SHARE FI were available in all five SHARE waves used in this analysis. Definite item selection was based on the following standard inclusion criteria: Prevalence increase with age, late saturation (i.e. no prevalence > 80% in any age group) and coverage of different body structures and systems (Searle et al., 2008). The FI for a person results as the number of the person-specific deficits divided by the total number of listed deficits, ranging from 0 (=no deficits present) to 1 (=all deficits present). If information on more than 10 items (20%) were missing for a participant, the FI value was set to missing (Yang and Lee, 2009). For a list of the included and excluded FI candidate items and details on the item selection process see Appendix A.

2.2.2. Definition of onset of DA

Onset of the DA process was defined as having a FI value ≤ 0.08 followed by FI values > 0.08 in at least two consecutive measurements. Thus, to establish a confirmed DA onset, at least three measurements were needed.

The threshold of ≤ 0.08 corresponds to a maximum of four health deficits. It was chosen following published FI thresholds (Song et al., 2010).

2.3. Exposures: Income, wealth and (last) occupation

The total annual household income before tax in euros (Alcser et al., 2005) was adjusted for the square root of household size (OECD, 2013). This adjusted value was then dichotomized using country-specific poverty thresholds according to Eurostat (Eurostat, 2017). Where poverty thresholds for a specific year were unavailable, the threshold of the next available year for this country was applied.

Wealth was measured in euros as the sum of all financial and real household assets minus debts, adjusted for OECD purchasing power parity exchange rates (Organisation for Economic Co-operation and Development, 2012) and recoded into tertiles.

Occupation was measured as the respondent's last job according to the International Standard Classification of Occupations (ISCO-88) by the International Labour Organization (International Labour Office, 1990) in ten major groups of occupation. Under the assumption that elementary occupations include physical strain and may specifically increase the risk for DA onset, we dichotomized the groups into those indicating elementary occupations as compared to all others (International Labour Office, 1990).

2.4. Covariates

2.4.1. Covariate selection

While it is widely known that neglecting important covariates can induce spurious associations in regression analysis (confounding), it is less well-known that covariate over-adjustment in turn increases the risk for collider bias (Shrier and Platt, 2008), i.e. increasing bias by adjustment instead of decreasing it. To avoid both types of bias, we used directed acyclic graphs (DAGs) as covariate selection method. DAGs are constructed based on existing literature and contain the known or assumed associations among all covariates considered for a specific analysis. Ultimately, the DAG also gives the minimal adjustment set, i.e. the most parsimonious set of covariates needed for estimating an unbiased effect (Stang and Knüppel, 2010). Covariates which were entered into the DAG were selected based on their reported association with the exposures or the outcome of interest in the literature. The resulting minimal adjustment set for estimating the total effect of income, wealth and occupation on hazard of DA onset, identified through the program DAGitty, a browser based environment for creating, editing, and analyzing causal models (Textor et al., 2011), included sex, education, marital status, place of living, welfare regime and two interaction terms of income with welfare regime and wealth, respectively. The interaction terms were chosen based on the assumption that both the country-specific welfare regime and individual wealth might buffer the effect of income on DA (see Appendix B for the DAG and its references).

2.4.2. Covariate measurement

Education was measured according to the international standard classification of education (ISCED) (UNESCO, 1997). We collapsed the seven categories into three levels: lower secondary education or less (ISCED levels 0–2), upper secondary education (ISCED level 3) and post-secondary education (ISCED levels 4–6).

Welfare regimes were defined as “conservative” (Germany, Belgium, France, Switzerland, Austria), “Scandinavian” (Sweden, Denmark), or “southern” (Italy, Spain) (Dragano et al., 2011).

2.4.3. Missing values

For income, wealth, marital status and education, five imputed data sets based on multivariable fully conditional specification are provided by the SHARE team. This allows using the available information from incomplete cases and thus increases precision, while the uncertainty of the imputed values is reflected by the variance between imputed values in the different data sets (White et al., 2011).

While imputing missing covariate values increases precision of model estimation, it is generally not recommended to impute outcomes, as this increases noise in the data (White et al., 2011). Thus, we did not impute items used for construction of the FI.

2.5. Statistical methods

2.5.1. Dealing with left truncation

For all time-to event analyses, we used age as opposed to time under observation as time variable. This is generally recommended for time-to-event analyses if study entry does not represent a meaningful predictor of risk (Sperrin and Buchan, 2013).

To avoid bias by left-truncation while simultaneously keeping age as time variable, study participants contributed only time at risk for those age intervals to the likelihood estimation during which they were actually observed in SHARE (Foreman et al., 2008).This was necessary because not all participants entered the study at the same age (Cain et al., 2011) and can be ensured with the entry option in SAS proc. phreg (Foreman et al., 2008). For an explanatory example how bias by left-truncation would have affected the analysis if it had not been controlled for, see Supplemental Appendix C.

2.5.2. Non-parametric analysis: Median age at DA onset

The median age at DA onset including 95% confidence intervals was estimated for the overall sample, and stratified by all selected covariates, respectively. For details on estimation of confidence intervals see Appendix C. Estimates for age-specific hazards of DA onset were generated using the procedures phreg and mianalyze in SAS Version 9.3 for Windows (Copyright © SAS Institute Inc., Cary, NC). Plots of age at DA onset and median estimates were based on these results and generated using the procedure sgplot. Log-rank tests for difference in the distributions of age at DA onset between subgroups were calculated separately for each imputed data set.

2.5.3. Regression models and predictors

We investigated the effect of income, wealth and occupation on hazard of DA onset using a Cox-proportional hazards model with country as random effect and controlling for the minimal sufficient covariate adjustment set as identified by the DAG. All predictors were included as time-independent variables, using values of the first available wave, as we wanted to be able to draw causal inferences with a longitudinal perspective and avoid introducing unnecessary complexity (for details see Appendix C).

The proportional hazards assumption was checked by successively including time-covariate interaction terms into the model. Covariates whose interaction with time was significant were included as time-varying effects. Analyses were conducted separately in the five imputed datasets and the resulting effect estimates were subsequently combined using the SAS procedure proc. mianalyze.

For all analyses significance level was set to 5%. Analyses were performed using SAS Version 9.3 for Windows (Copyright © SAS Institute Inc., Cary, NC).

2.5.4. Sensitivity analyses

The non-parametric analysis as well as the regression analysis was repeated using FI > 0.04, FI > 0.06 and FI > 0.10 as alternative thresholds for the definition of DA onset. Additionally, we performed a sensitivity analysis which included the baseline FI value as a covariate using the FI > 0.08 threshold.

3. Results

3.1. Study participants

Longitudinal DA data from at least three waves were available for n = 21,154 participants from the nine selected countries. Mean age at study entry was 64.7 years (range: 50–98 years, 55.4% female). Of these, n = 8616 participants (40.7%) had a FI value ≤ 0.08 and were therefore at risk for DA onset (mean age 61.9 years, range 50–93 years, 49.1% female). Of the initial risk set, 2640 (30.6%, mean age 63.5 years, 50.5% female) experienced a subsequent confirmed DA onset within a median follow-up time of 7 years (range: 2–11 years). For the study participant flow chart and further descriptive statistics on the study data see Appendices D and E.

3.2. Non-parametric analysis: Median age at DA onset

Log-rank tests showed significant differences in the distribution of age at DA onset between subgroups for countries, wealth, education, occupation, income, sex and welfare regime, but not for marital status and place of living (Appendix F.1–F3).

Median age at DA onset overall was 71 years (95% CI: 70–72 years), with a range between countries from 66 years (Germany) to 76 years (Switzerland).

With regard to the main exposures, the largest univariate differences were found for wealth and occupation: Participants in the lowest wealth tertile (median age at DA onset 68 years, 95% CI [66–70]) experienced a DA onset on average 5 years earlier than persons in the highest wealth tertile (median age at DA onset 73 years, 95% CI [72–74]). Participants with elementary occupations (median age at DA onset 67 years, 95% CI [65–69]) experienced a DA onset 5 years earlier than persons with non-elementary occupations (median age at DA onset 72 years, 95% CI [71–73]).

For further details see Table 1. For plots of time to DA onset see Appendix F.1–F3.

3.3. Regression model

There were significant interaction effects of observation time with occupation and wealth, respectively, leading to an inclusion of these variables as time-varying effects in the final model.

Out of the 8616 at-risk observations, 5242 including 1596 confirmed onsets had complete covariate information.

After combining estimates from all imputed data sets, income below the poverty threshold had no significant effect on age at DA onset. Persons in the lowest wealth tertile (combined HR: 1.58, 95% CI [1.15; 2.16]), with elementary (last) occupation (combined HR: 1.79, 95% CI [1.20; 2.67]) and women (combined HR: 1.16, 95% CI [1.04; 1.28]) had a significantly higher risk for DA onset. Higher education significantly reduced the risk for DA onset. The effects of wealth and occupation were found to be age-dependent and decreased by a factor of 0.99 (95% CI [0.97; 1.00]) for wealth and 0.97 (95% CI [0.95; 0.99]) for occupation with each additional life year (Table 2).

3.4. Sensitivity analyses

3.4.1. Non-parametric analysis: Median age at DA onset

Median age at DA onset increased strictly, but for some countries slightly non-linearly with increased FI threshold values for onset definition. While for the thresholds 0.06, 0.08 and 0.10 most countries retained their relative rank with regard to median age at DA onset, ranks were slightly less stable for the 0.04 threshold. For the threshold 0.04 as compared to 0.06, Belgium (1 rank), Germany (2 ranks) and Spain (3 ranks) changed their relative position. In contrast, for the threshold 0.06 as compared to 0.08, only Austria changed its relative position by two ranks and for the threshold 0.08 as compared to 0.1,

Table 1
Median age at DA onset (in years) after age 50 with 95% confidence limits.

		Median	95% confidence limits
Overall		71	(70; 72)
By country	Germany	66	(64; 68)
	Spain	68	(66; 70)
	Austria	69	(67; 71)
	Italy	69	(67; 71)
	Belgium	70	(69; 71)
	France	71	(69; 73)
	Sweden	73	(71; 75)
	Denmark	75	(73; 77)
	Switzerland	76	(74; 78)
By wealth tertile	Lowest	68	(66; 70)
	Middle	70	(69; 71)
	Highest	73	(72; 74)
By income	Below poverty threshold	68	(66; 70)
	Above poverty threshold	71	(70; 72)
By (last) occupation[a]	Elementary	67	(65; 69)
	Non-elementary	72	(71; 73)
By sex	Female	70	(69; 71)
	Male	72	(71; 73)
By place of living[b]	A small town	70	(69; 71)
	A big city	71	(68; 74)
	A rural area or village	71	(70; 72)
	The sub urbs or outskirts of a big city	72	(70; 74)
	A large town	73	(71; 75)
By education	None or primary	67	(65; 69)
	Secondary	70	(69; 71)
	Post-secondary and tertiary	73	(72; 74)
By marital status	Never married	69	(66; 72)
	Widowed	70	(67; 73)
	Married or in a registered partnership	71	(70; 72)
	Divorced	71	(68; 74)
By welfare regime type	Southern	68	(67; 69)
	Conservative	70	(69; 71)
	Scandinavian	74	(73; 75)

Note. If not indicated otherwise, complete information or imputations were available and the full data set (n = 8616) could be used. Results are then presented for the pooled estimates of median age at DA onset.
[a] Number of participants used: n = 7951.
[b] Number of participants used: n = 5559.

only Spain changed its relative position by one rank. For a graphical display see Appendix F.4.

3.4.2. Regression model

The sensitivity analyses using FI > 0.04 and FI > 0.06 as thresholds for DA onset resulted in considerably lower numbers of eligible observations (n = 1853 (n = 3564) at risk with full covariate information including n = 916 (n = 1394) confirmed onsets for FI > 0.04 and FI > 0.06, respectively). Point estimates were comparable in size and direction, but only higher education (and, for FI > 0.06, elementary occupation) remained a significant predictor (Appendices G and H).

The sensitivity analysis using FI > 0.10 as threshold for DA onset resulted in a higher number of eligible observations (n = 6973 at risk including n = 1655 confirmed onsets), and confirmed the results of the main analysis (Appendix I).

Adjustment for baseline FI values resulted in a significant HR for this variable (HR: 1.14, 95% CI [1.01; 1.28]) without changing the estimated effects for any of the other covariates (Appendix J).

4. Discussion

Our results show for nine European countries that a person from the highest wealth tertile who was still healthy at the age of 50 could expect to live significantly longer without health deficits than a person from the lowest wealth tertile. The same applied to persons who did not work in elementary occupations. These effects were independent of the country-specific welfare regime, and also independent of individual income and education.

The strength of our study is threefold: one, we included both measures of income (the incoming stream of economic resources) and measures of wealth (the available stock of accumulated economic resources). This is important because, with increasing age and during retirement, accumulated assets may become more relevant for well-being and health than income (Pollack et al., 2007). Second, we could rely on longitudinal data from SHARE, a study that has repeatedly proven its value and validity, to define DA onset without major risk of misclassification. The third strength of our analysis was the systematic selection of potential confounders based on directed acyclic graphs. We used DAGs to select an unbiased set of covariates. Interestingly, this set confirms the choice of covariates made for earlier analyses on health effects of socio-economic determinants (Herd et al., 2007; Matthews et al., 2005).

In our study, wealth and occupation rather than income emerged as significant factors that decelerated the onset of DA. We found that these effects decreased with age. This provides further evidence that health inequalities of groups with different risks are most pronounced in middle and early older age and subsequently level out (House et al., 2005).

In conjunction with other studies, our results suggest that different components of socioeconomic position affect different parts of DA trajectories: While education (Herd et al., 2007; House et al., 2005), and according to our analysis also occupation and wealth, seem to play a role in determining the age at DA onset, income has been found to impact DA progression after DA onset (Herd et al., 2007; House et al., 2005; Stephan et al., 2017). This is also coherent with different suggested pathways: Education and health literacy seem to primarily influence health through health behaviors, wealth through living conditions and psychosocial factors, and occupation through a cumulative effect of strenuous work on homeostasis while income might provide the means to disease control once health deficits are present (House et al., 2005).

Being female was an additional independent risk factor for DA onset in our study, adding evidence to the male-female health-survival paradox, with women having a higher life expectancy although experiencing higher prevalence of disease and disability at all ages as compared to men (Oksuzyan et al., 2008; Stephan et al., 2017). Social and behavioral explanations include earlier help-seeking behavior due to higher social acceptability of disease and disability for women and biomedical explanations such as the protective role of estrogen in the risk for cardiovascular events (Oksuzyan et al., 2008).

We found considerable differences in median age at health deficit accumulation onset after age 50 between countries, with Germany showing the lowest and Switzerland the highest median age at DA onset. These estimates are well in line with previously published results on differences in healthy life expectancy after age 50 (Jagger et al., 2009), which were based on a different methodological approach: the calculation of healthy life expectancy based on cross-sectional data according to the Sullivan method (Jagger et al., 1999). Jagger et al., 2009 suggested a difference of nine years in healthy life expectancy between Germany and Denmark, a result which was exactly replicated by our time-to event analysis using longitudinal data. This strengthens the face validity of our results, as there is a considerable conceptual overlap between healthy life expectancy and time lived without DA onset, with the advantage that healthy life expectancy can be estimated on a population-level only, whereas age at DA onset can be measured on an individual level.

The order of countries with regard to median age at DA onset was generally stable even when different FI values were used for definition of DA onset, with the threshold 0.04 (corresponding to two health

Table 2
Results of the Cox-proportional hazards model with random effects for country (n = 5242, 1596 events, pooled results from five imputed datasets).

Covariates		Hazard Ratio	95% confidence limits	Significant Type III p-values[a]
Wealth tertile	Lowest	1.58	(1.15, 2.16)	5
	Middle	1.02	(0.75, 1.38)	
	Highest	Reference		
Interaction lowest wealth rank and age	Factor for each additional life year	0.99	(0.97, 1.00)	0
Interaction middle wealth rank and age	Factor for each additional life year	1.00	(0.99, 1.02)	0
Income	Below poverty threshold	0.77	(0.34, 1.75)	1
	Above poverty threshold	Reference		
(Last) occupation	Elementary occupations	1.79	(1.20, 2.67)	5
	Non-elementary occupations	Reference		
Interaction elementary occupation and age	Factor for each additional life year	0.97	(0.95, 0.99)	5
Welfare regime	Conservative	1.24	(0.88, 1.74)	0
	Southern	1.18	(0.77, 1.80)	
	Scandinavian	Reference		
Marital status	Divorced	0.96	(0.78, 1.19)	0
	Married or in a registered partnership	0.94	(0.80, 1.11)	
	Never married	1.08	(0.85, 1.36)	
	Widowed	Reference		
Education	Post-secondary and tertiary	0.76	(0.65, 0.90)	5
	Secondary	0.89	(0.78, 1.03)	
	None or primary	Reference		
Sex	Female	1.16	(1.04, 1.28)	5
	Male	Reference		
Interaction wealth tertile and income below poverty threshold	Lowest wealth tertile	1.10	(0.71, 1.70)	1
	Middle wealth tertile	1.14	(0.62, 2.11)	
	Highest wealth tertile	Reference		
Interaction welfare regime and income below poverty threshold	Conservative	1.42	(0.71, 2.83)	0
	Southern	1.28	(0.67, 2.47)	
	Scandinavian	Reference		
Place of living	A large town	0.95	(0.79, 1.14)	0
	A rural area or village	1.05	(0.88, 1.25)	
	A small town	1.05	(0.88, 1.25)	
	The sub-urbs or outskirts of a big city	1.00	(0.83, 1.22)	
	A big city	Reference		

[a] Number of imputed data sets with significant p-value according to Type III test of fixed effects (range: 0–5).

deficits) providing less stable results. This may on the one hand be due to lower numbers at risk (smaller sample size) for this threshold. It may also, on the other hand, suggest that two health deficits are not enough to reliably determine if a DA onset has occurred, because of more frequent recoveries resulting in a rather fluctuating order of countries for very low thresholds. This view is also supported by the fact that the difference in median age at onset between countries was lower for the lowest threshold (8 years) and larger (11 years) and stable for the 0.08 and 0.1 thresholds.

It has to be kept in mind that our results of both the non-parametric and the semi-parametric analyses are to be interpreted as conditional on not having experienced a DA onset before age 50. Although our results cannot necessarily be transferred to the less healthy half of the population, descriptive comparisons suggested that the same factors might play a role in DA onset at earlier ages as well.

Our major challenge was that observational studies currently do not allow for a complete follow-up of an individual's DA trajectory from birth to death. Instead, participants were included in SHARE at different ages. To minimize potential bias introduced by the study design, we took into account age at study entry in all calculations (Cain et al., 2011). As over half of all SHARE participants had experienced their DA onset already before their first participation in SHARE, DA onset did not seem to constitute a barrier for study participation. We thus assumed that censoring and DA onset were unrelated (uninformative censoring).

Also, the selected cut-off for DA onset (a FI-value > 0.08, i.e. at least 4 health deficits) can be criticized as arbitrarily chosen, although it has been previously used in the literature (Song et al., 2010; Stephan et al., 2017). To account for this, we ran sensitivity analyses with thresholds of 0.04, 0.06 and 0.10, respectively, which essentially confirmed the results of our main analysis, showing that the choice of the exact threshold for DA onset did not exert undue influence. Also, potential improvements or further deterioration after DA onset (i.e. after at least two FI measurements > 0.08 over a time period of at least two years) were not further considered for this analysis, as our focus was on DA onset, and not DA trajectories thereafter. This does not preclude improvement.

Last, as most cross-country analyses, we cannot fully exclude cultural differences in subjectively reported health deficits. Further research is required to be able to fully account for it in the future.

The results of our analysis can be interpreted in the context of current European and national-level policies: It is questionable if further increases in retirement age are feasible and desirable for all occupational classes, as this may not only further decrease health expectancy in population groups with elementary occupations, but also increase their subsequent health care costs. Our results also point to the importance of occupational health and safety measures at the work place and corporate health promotion in preventing accumulated health damage during working age, especially for elementary occupations.

In addition, governments should support provisions made in younger age to increase wealth (e.g. through acquisition of residential property and personal pension schemes). In this light, the current low interest rates might be of advantage for future generations, if they encourage people to take on loans for property acquisition.

On the other hand, low interest rates and rising life expectancy have increasingly pushed insurers to shift the risk of financial products to their customers (The Economist, 2017). This in turn may decrease consumer confidence in the usefulness of long-term investment strategies and thus dissuade people from accumulating financial assets. Governments might need to consider new incentives to citizens or regulations of the insurance market in order to stimulate the accumulation of wealth.

In conclusion, next to education, also wealth and occupation deserve a more prominent focus in studies and policies targeting DA onset

after age 50 in Europe.

Funding

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft) through the project 'Determinants and Trajectories of healthy life expectancy and deficit accumulation' (GR3608/3-1). The financial sponsors played no role in the design, execution, analysis and interpretation of data, or writing of the study.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors would like to express their special thanks to Prof. Dr. Martin Müller and Dr. Michael Lauseker for their valuable input regarding the analysis and the final version of the paper.

This paper uses data from SHARE Waves 1, 2, 4, 5 and 6 (DOIs: https://doi.org/10.6103/SHARE.w1.600, https://doi.org/10.6103/SHARE.w2.600, https://doi.org/10.6103/SHARE.w4.600, https://doi.org/10.6103/SHARE.w5.600, https://doi.org/10.6103/SHARE.w6.600), see (Börsch-Supan et al., 2013) for methodological details.

The SHARE data collection has been primarily funded by the European Commission through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812) and FP7 (SHARE-PREP: N°211909, SHARE-LEAP: N°227822, SHARE M4: N°261982). Additional funding from the German Ministry of Education and Research, the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, HHSN271201300071C) and from various national funding sources is gratefully acknowledged (see www.share-project.org).

Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2018.09.021.

References

Adler, N.E., Newman, K., 2002. Socioeconomic disparities in health: pathways and policies. Health Aff. 21, 60–76.
Alcser, K.H., Benson, G., Börsch-Supan, A., Brugiavini, A., Christelis, D., Croda, E., Das, M., de Luca, G., Harkness, J., Hesselius, P., 2005. In: Börsch-Supan, A., Jürges, H. (Eds.), The Survey of Health, Aging, and Retirement in Europe - Methodology. Mannheim Research Institute for the Economics of Aging (MEA).
Ben-Shlomo, Y., Kuh, D., 2002. A Life Course Approach to Chronic Disease Epidemiology: Conceptual Models, Empirical Challenges and Interdisciplinary Perspectives. Oxford University Press.
Börsch-Supan, A., 2017a. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 1.
Börsch-Supan, A., 2017b. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 2.
Börsch-Supan, A., 2017c. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 4.
Börsch-Supan, A., 2017d. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 5.
Börsch-Supan, A., 2017e. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 6.
Börsch-Supan, A., Brugiavini, A., Jürges, H., Kapteyn, A., Mackenbach, J., Siegrist, J., Weber, G., 2008. First results from the Survey of Health, Ageing and Retirement in Europe (2004–2007). In: Starting the Longitudinal Dimension Mannheim. MEA.
Börsch-Supan, A., Brandt, M., Hunkler, C., Kneip, T., Korbmacher, J., Malter, F., ... Zuber, S., 2013. Data resource profile: the Survey of Health, Ageing and Retirement in Europe (SHARE). Int. J. Epidemiol. 42 (4), 992–1001.
Cain, K.C., Harlow, S.D., Little, R.J., Nan, B., Yosef, M., Taffe, J.R., Elliott, M.R., 2011. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. Am. J. Epidemiol. 173 (9), 1078–1084.
Christelis, D., Jappelli, T., Paccagnella, O., Weber, G., 2009. Income, wealth and financial fragility in Europe. J. Eur. Soc. Policy 19, 359–376.
Dragano, N., Siegrist, J., Wahrendorf, M., 2011. Welfare regimes, labour policies and unhealthy psychosocial working conditions: a comparative study with 9917 older employees from 12 European countries. J. Epidemiol. Community Health 65, 793–799.
Eurostat, 2017. At-risk-of-poverty thresholds. In: EU-SILC Survey Eurostat.
Foreman, A.J., Lai, G.P., Miller, D.P., 2008. Surviving left truncation using PROC PHREG. In: Western Users of SAS Software Meeting, University City, CA.
Herd, P., Goesling, B., House, J.S., 2007. Socioeconomic position and health: the differential effects of education versus income on the onset versus progression of health problems. J. Health Soc. Behav. 48, 223–238.
House, J.S., Lantz, P.M., Herd, P., 2005. Continuity and change in the social stratification of aging and health over the life course: evidence from a nationally representative longitudinal study from 1986 to 2001/2002 (Americans' Changing Lives Study). J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 60, S15–S26.
International Labour Office, 1990. International Standard Classification of Occupations: ISCO-88. International Labour Office, Geneva.
Jagger, C., Hauet, E., Brouard, N., 1999. Health Expectancy Calculation by the Sullivan Method: A Practical Guide. Nihon University, Population Research Institute Tokyo.
Jagger, C., Gillies, C., Moscone, F., Cambois, E., Van Oyen, H., Nusselder, W., Robine, J.-M., 2009. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. Lancet 372, 2124–2131.
Kondo, N., 2012. Socioeconomic disparities and health: impacts and pathways. J. Epidemiol. 22, 2–6.
Koster, A., Bosma, H., Kempen, G.I.J.M., Penninx, B.W.J.H., Beekman, A.T.F., Deeg, D.J.H., van Eijk, J.T.M., 2006. Socioeconomic differences in incident depression in older adults: the role of psychosocial factors, physical health status, and behavioral factors. J. Psychosom. Res. 61, 619–627.
Mäki, N., Martikainen, P., Eikemo, T., Menvielle, G., Lundberg, O., Östergren, O., Jasilionis, D., Mackenbach, J.P., 2013. Educational differences in disability-free life expectancy: a comparative study of long-standing activity limitation in eight European countries. Soc. Sci. Med. 94, 1–8.
Malter, F., Börsch-Supan, A., 2013. SHARE Wave 4: Innovations & Methodology. Munich, MEA, Max Planck Institute for Social Law and Social Policy.
Malter, F., Börsch-Supan, A. (Eds.), 2015. SHARE Wave 5: Innovations & Methodology. Munich, MEA, Max Planck Institute for Social Law and Social Policy.
Matthews, R.J., Smith, L.K., Hancock, R.M., Jagger, C., Spiers, N.A., 2005. Socioeconomic factors associated with the onset of disability in older age: a longitudinal study of people aged 75 years and over. Soc. Sci. Med. 61, 1567–1575.
Mitnitski, A.B., Mogilner, A.J., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. Sci. World J. 1, 323–336.
Mitnitski, A., Song, X., Rockwood, K., 2007. Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. Exp. Gerontol. 42, 1109–1115.
OECD, 2013. Framework for integrated analysis. In: OECD Framework for Statistics on the Distribution of Household Income, Consumption and Wealth.
Oksuzyan, A., Juel, K., Vaupel, J.W., Christensen, K., 2008. Men: good health and high mortality. Sex differences in health and aging. Aging Clin. Exp. Res. 20, 91.
Organisation for Economic Co-operation and Development, 2012. Eurostat-OECD Methodological Manual on Purchasing Power Parities. OECD Publishing.
Pollack, C.E., Chideya, S., Cubbin, C., Williams, B., Dekker, M., Braveman, P., 2007. Should health studies measure wealth?: A systematic review. Am. J. Prev. Med. 33 (3), 250–264.
Romero-Ortuno, R., 2014. Frailty Index in Europeans: association with determinants of health. Geriatr Gerontol Int 14, 420–429.
Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8 (1).
Shrier, I., Platt, R.W., 2008. Reducing bias through directed acyclic graphs. BMC Med. Res. Methodol. 8, 70.
Song, X., Mitnitski, A., Rockwood, K., 2010. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J. Am. Geriatr. Soc. 58, 681–687.
Sperrin, M., Buchan, I., 2013. Modelling time to event with observations made at arbitrary times. Stat. Med. 32, 99–109.
Stang, A., Knüppel, S., 2010. Identifying minimal sufficient adjustment sets. Epidemiology 21.
Stephan, A.J., Strobl, R., Holle, R., Meisinger, C., Schulz, H., Ladwig, K.H., ... Grill, E., 2017. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. Prev. Med. 102, 31–38.
Textor, J., Hardt, J., Knüppel, S., 2011. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology 22, 745.
The Economist (Ed.), 2017. Your money and your life - as lives get longer, financial models will have to change. The Economist.
Theou, O., Brothers, T.D., Rockwood, M.R., Haardt, D., Mitnitski, A., Rockwood, K., 2013. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. Age Ageing 42 (5), 614–619.
Theou, O., Park, G.H., Garm, A., Song, X., Clarke, B., Rockwood, K., 2017. Reversing frailty levels in primary care using the CARES model. Canadian Geriatrics Journal. 20, 105.
UNESCO, 1997. International standard classification of education 1997. ISCED.
White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: issues and guidance for practice. Stat. Med. 30, 377–399.
Yang, Y., Lee, L.C., 2009. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the US older adult population. J. Gerontol. B Psychol. Sci. Soc. Sci. 65 (2), 246–255.

2.3 Article 3: Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age: results from the KORA-Age study.

Stephan A-J, Strobl R, Schwettmann L,· Meisinger C, Ladwig K-H, Linkohr B, Thorand B, Peters A, Grill E. Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age: results from the KORA-Age study. *European Journal of Epidemiology*. 2019:34(7):675-687. doi: 10.1007/s10654-019-00515-4

Available at http://link.springer.com/article/10.1007/s10654-019-00515-4

This is a post-peer-review, pre-copyedit version of an article published in European Journal of Epidemiology. The final authenticated version is available online at: https://doi.org/10.1007/s10654-019-00515-4

Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age - Results from the KORA-Age study

Anna-Janina Stephan[1§], Ralf Strobl[1,2], Lars Schwettmann[3], Christa Meisinger[4,5], Karl-Heinz Ladwig[6,7], Birgit Linkohr[6], Barbara Thorand[6], Annette Peters[6a], Eva Grill[1,2,8a]

[a] Shared senior authorship

[1]Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany.

[2]German Center for Vertigo and Balance Disorders, Klinikum der Universität München, Munich, Germany

[3]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

[4]Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

[5]Chair of Epidemiology, Ludwig-Maximilians-Universität München at UNIKA-T Augsburg, Augsburg, Germany

[6]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany.

[7]Department for Psychosomatic Medicine and Psychotherapy, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany

[8]Munich Center of Health Sciences, Ludwig-Maximilians-Universität München, Munich, Germany

[§] Corresponding author

Anna-Janina Stephan, MPH

Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistraße 17, 81377 Munich, Germany

Tel.: + 49 89 2180 78219; Fax: + 49 89 2180 78230

Email: anna_janina.stephan@med.uni-muenchen.de

ORCID: 0000-0002-6438-2058

Funding

The KORA research platform (KORA, Cooperative Health Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. The KORA-Age project was financed by the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713 and 01ET1003A, C) as part of the 'Health in old age' program. 'Functioning and disability among aged persons' was funded by the German Research Foundation (GR 3608/1-1). 'Determinants and trajectories of healthy life expectancy and deficit accumulation' was funded by the German Research Foundation (GR3608/3-1).

The financial sponsors played no role in the design, execution, analysis, and interpretation of data, or writing of the study.

Abstract

Introduction

Morbidity trends may result from cohort experiences in critical developmental age. Our objective was to compare the health status of 65-71 year-olds who were in critical developmental age before (1937-June 1945), during (June 1945-June 1948) and after (June 1948-1950) the early reconstruction and food crisis (ERFC) period in Germany following World War II.

Methods

Data originate from the KORA (Cooperative Health Research in the Region of Augsburg)-Age study in Southern Germany. We used the 2008 baseline sample born 1937-43 and the 2015 enrichment sample born 1944-50.
Health status was assessed as the number of accumulated health deficits using a Frailty Index (FI). Cohorts were defined based on co-occurrence of critical developmental age (gestation and the first 2 years of life) and the ERFC period. Cohort, age and sex effects on older-age health status were analyzed using generalized linear models.

Results

We included 590 (53% male) pre-war and war (PWW), 475 (51% male) ERFC and 171 post-currency reform (PCR) cohort participants (46% male).
Adjusted for covariates, FI levels were significantly higher for the ERFC (Ratio 1.14, CL: [1.06; 1.23]) but not for the PCR (Ratio 1.06, CL: [0.94; 1.20]) as compared to the PWW cohort.

Conclusion

Being in critical developmental age during the ERFC period increased FI levels in adults aged 65-71 years. Covariates did not explain these effects, suggesting a direct detrimental effect from being in critical developmental age during the ERFC period on older-age health. This expansion of morbidity in Germany was not detected in the PCR cohort.

Key Words: *Aged, Health Status, deficit accumulation, Frailty Index, birth cohorts, morbidity trends*

Introduction

It is currently highly debated if morbidity in European populations generally remains stable across generations or if there are trends towards compression or expansion of morbidity [1-3]. As morbidity trends can hardly be measured directly, various measures of healthy life expectancy (HLE) are used as indicators. Already today, healthy life expectancy varies largely across European countries, with Germany being below the European average [4]. Analyses comparing German birth cohorts from 1911 to 1926 and 1917 to 1932 found a decrease of healthy life expectancy from the older to the younger age cohort [5]. While this indicates an expansion of morbidity, which, combined with slowing birth rates, would be a substantial organizational and financial challenge to modern societies, the underlying mechanisms are still incompletely understood. As a consequence, it is still unclear if the potential expansion of morbidity in Germany between 1911 and 1932 should be seen as part of a continued trend which accompanies the rise in life expectancy throughout the 20th century, or if historical developments interfered with these trends. For example, the expansion of *morbidity* in the first third of the 20th century may have resulted from progress in treatment of formerly fatal diseases without progress in preventing their onset ("compression of *mortality"*) [6]. Both quantitative and qualitative trend changes further along the 20th century are conceivable, such as an intensified expansion of morbidity due to adverse political and economic conditions related to World War II on the one hand, or a compression of morbidity due to progress in prevention and postponed disease onset on the other hand.

Explanations for morbidity trends have also drawn on the *critical* and *sensitive* periods model of life course epidemiology [7]. The model posits that there are periods in life that are most relevant for the development of health deficits in older age, such as gestation or early life. During a critical period, the developing organism adapts especially well to its environment. From a biological perspective, this may result in epigenetic changes such as susceptibility to inflammatory processes which contribute to allostatic load in late life. From a social-behavioral perspective, lasting behavioral patterns (e.g. eating habits) are developed in these periods of life [8, 9]. Sensitive periods, like critical periods, are times of rapid adaptations of the body system to the environment, but as opposed to critical periods, changes in sensitive periods are less likely to be irreversible. Although critical and sensitive developmental periods are not limited to gestation and early childhood, and may also vary depending on the outcome of interest, it is uncontroversial that gestation and early childhood represent some of the most critical developmental periods over the life course [7, 10, 11].

When testing the critical period model in European countries, it may be useful to keep in mind that older adults in Europe are heterogeneous regarding their life experiences. The experience of children born during or shortly after World War II was dramatically different from those born earlier or later regarding trauma from migration and loss, famine and poor living conditions in many European countries [12]. Some of the most severe famines of the 20th century in Europe, included those in the

Soviet Union during the siege of Leningrad in 1941-44, in Greece during the German occupation with a peak in 1941-42 [8] and the Dutch Hunger Winter in the Western Netherlands caused by a blockade by the German army in 1944-45 [13]. In Germany, the nutritional situation did not deteriorate until after the end of World War II, when the formerly centralized food production and distribution system collapsed, leading to a severe food crisis [13]. The average energy intake per person in Germany, which had been kept at about 2,500 calories until 1944, dropped to 2,000 calories in spring 1945 and subsequently to 1,550 calories, further decreasing to its lowest level of around 1,050 - 1,250 calories in 1946. Thereafter, average official rations remained at about 1,550 calories per day [14]. The nutritional situation improved markedly after June 1948 with a currency reform accompanied by a good harvest and the uptake of the Marshall Plan, with average energy intake rising back to over 1,800 calories [8]. In contrast, the recommended daily energy intake at the lowest physical activity level is at least 2,450 (1,950) calories for 30-59 year-old men (women) with population-average height and weight. Higher physical activity levels, pregnancy, lactation and growth elicit higher energy requirements [15]. Apart from the food crisis, many other structural and societal challenges were associated with this early reconstruction period on the way to democracy, for example the arrival of almost 10 million refugees until October 1946 at the four occupation zones that comprised the later West and East Germany.

In sum, it remains unclear how much of the currently observed association of health status with age [16] is actually due to age effects and how much is contributed by specific cohort effects.

Adults born in Germany between 1937 and 1950, who have only recently reached retirement age, cover cohorts who were relatively well-supplied during their critical developmental age before and during World War II (i.e. up to June 1945). In addition, these adults comprise cohorts which were heavily undersupplied during their critical developmental age during the early reconstruction and food crisis (ERFC) period (June 1945 to June 1948) and (after 1948) the again well-supplied post currency reform birth cohorts. These differences in exposure to unique circumstances during critical developmental age [12] make them specifically interesting to investigate questions on future health trends in older adults in Germany.

Following the critical period model, we hypothesize that the cohort which was in critical developmental age during the ERFC period has on average worse age-specific health status in older age than a birth cohort which experienced their critical developmental age before this period. Secondly, we hypothesize that cohorts with critical developmental age before and after this period are on average comparable regarding their age-specific health status.

The objective of this study was to compare the health status of older adults at the ages of 65-71 years born before, during and after the early reconstruction and food crisis period after World War II in Germany (adjusted for later-life demographic or socio-economic characteristics or health behaviors).

Methods

Study design, participants, and data collection procedures

Data for this study originates from two independent assessments of participants from the KORA (Cooperative Health Research in the Region of Augsburg)-Age study in Southern Germany. Participants for the KORA-Age study were drawn from the population representative samples of four surveys conducted between 1984-2000 in the city of Augsburg and two surrounding counties: The first three of these former surveys were conducted in 1984/85 (S1), 1989/90 (S2) and 1994/95 (S3) as part of the WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Diseases) project. In 1999/2000, after the MONICA project had officially concluded, an additional survey (S4) using the same population-representative sampling mechanisms was conducted under the name of KORA by the Helmholtz Zentrum München. For the KORA-Age baseline assessment in 2008, all former MONICA/KORA participants aged 65 years and older (i.e. born 1943 or earlier) were invited. In 2015, a younger enrichment sample (all former MONICA/KORA participants aged 65-71 years in 2015, i.e. born 1944 to 1950) was added to the KORA-Age study population.

For the KORA-Age assessment in 2008, of the 5,990 eligible former MONICA/KORA participants, 4,123 persons (response rate: 68.8%) completed a self-administered health questionnaire and participated in a structured telephone interview. For the 2015 enrichment sample, 1,929 former MONICA/KORA participants born between 1944 and 1950 were eligible. Of these, 1,457 participated in the structured telephone interview and returned the paper-based questionnaire (response rate: 75.5%).

This paper is based on all KORA-Age participants who were aged 65-71 years either in 2008 or in 2015 and thus born between 1937 and 1950.

For the main analysis of this paper we included a sub-group of participants for whom information on place of birth was available, effectively excluding participants who may have been born outside of Germany and of whom exposure to the ERFC period in critical developmental age could thus not be ascertained. Information on birth place for former MONICA S1 (1984/85), S2 (1989/90) and S3 (1994/95) participants derived from the following question which was included in these previous studies: “How long have you lived at your current place of residence?”. Only those participants who indicated the response option “since birth” were included in the main analysis. In the MONICA/KORA survey S4 (1999/2001) the same question was not asked, but information on place of birth could be derived from the following question: “Were you born within the current defined borders of Germany?”. From this survey, only those participants who indicated the response option “yes” were included in the main analysis. The larger data set which also comprised participants for whom place of birth in Germany was possible but not ascertained was additionally used for sensitivity analyses.

Further details about study design, sampling method, data collection and response rates for the MONICA/KORA and KORA-Age studies can be found elsewhere [17-19]. A flow chart of participant recruitment for this analysis can be found in Online Resource 1.

Approval for KORA-Age was obtained from the Ethics Committee of the Bavarian Medical Association (No. 08064). Written informed consent was obtained from all participants.

With study participants aged 65-71 in 2015 and the enrichment sample aged 65 years and older in 2008, KORA-Age offers the first opportunity in Germany to simultaneously compare health status in older age across pre-war and war, early reconstruction and food crisis as well as post currency reform birth cohorts in Germany.

Health status

To measure health status, we constructed a Frailty Index (FI) following established methods using deficit variables collected in both relevant KORA-Age waves. Deficits which are potential candidates to enter a FI include diseases, measures of functioning and (pre-)clinical signs and symptoms [20].

This KORA-Age FI includes in total 33 items, covering 10 diseases, 13 measures of functioning and 10 signs and symptoms. Details on the FI item selection process can be found elsewhere [21, 22]. An updated list of included FI items and their cut-offs for deficit definition can be found in Online Resource 2.

The FI for a person results as the number of the person-specific deficits divided by the total number of listed deficits. The respective FI scores range from 0 (= no deficits present) to 1 (= all deficits present). If a participant scored missing on one or more of the deficit items, the denominator of the FI was reduced accordingly. If information on more than 20% of the FI items were missing for a participant, the FI value was set to missing [23].

Exposures: Age, cohort, and sex

Three cohorts were defined based on being in critical developmental age during the early reconstruction and food crisis period in Germany, which occurred from June 1945 until June 1948 [14]. Following literature, critical developmental age was defined as including the prenatal 9-month gestation period and birth until the age of 2 years [11, 10].

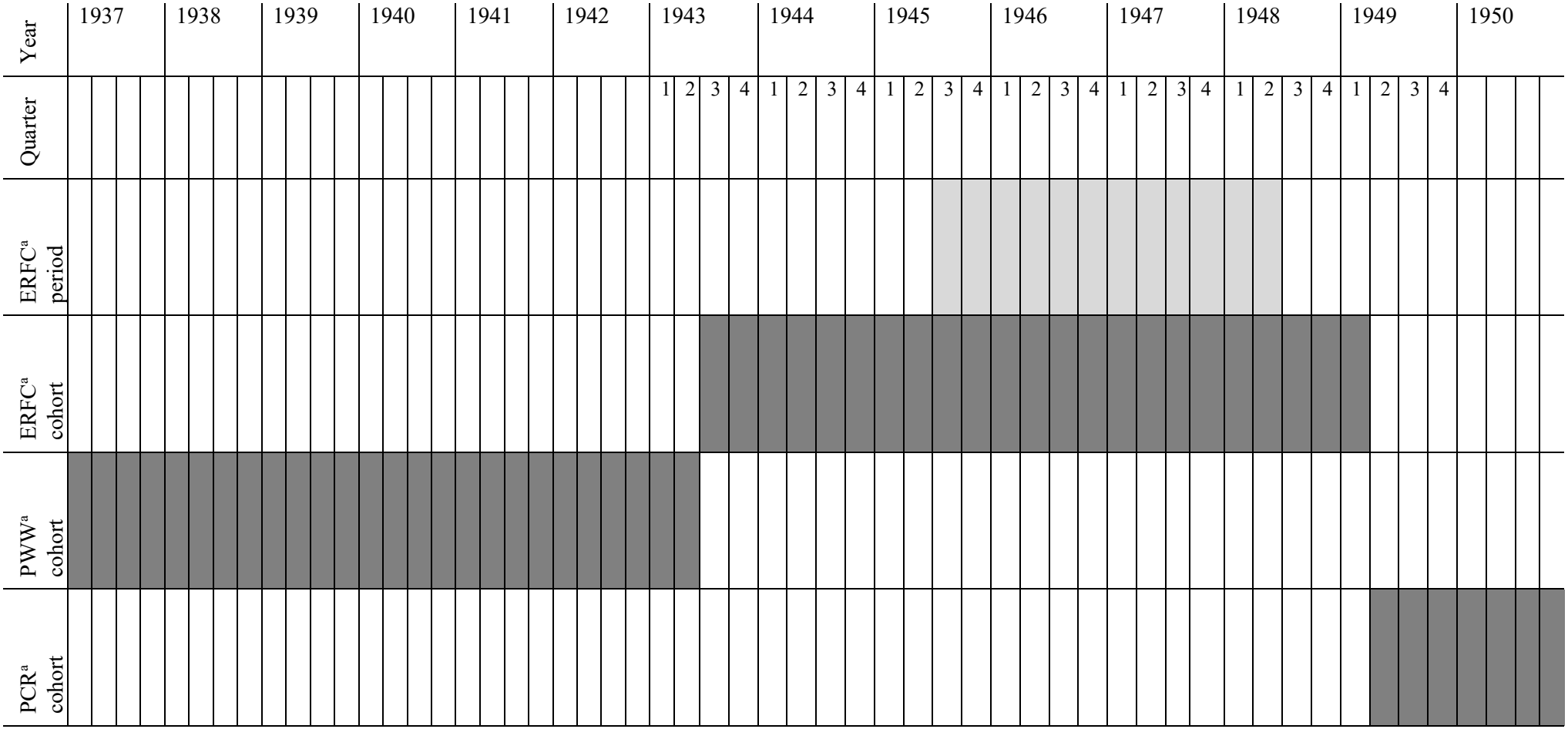
Time of birth was measured by birth quarter of the year (1, 2, 3, or 4), and gestation period was defined as including the quarter of birth plus the two preceding quarters. Exact birth dates were unavailable for analysis due to data protection considerations. Time of birth in quarter years was calculated based on age at reference date (December 31st 2008 for those born ≤1943 and December 31st 2015 for those born 1944-1950). In combination with information on the exact quarter of the

respective birth year, time of birth was calculated as year of data collection minus age at reference date minus (1-0.25 times the quarter of birth).

Thus, participants from the *pre-war and war (PWW) cohort* were older than two (up to eight) years (i.e. already past critical developmental age) at the beginning of the early reconstruction and food crisis period in June 1945, including all participants born between Q1 in 1937 and Q2 in 1943.

The *early reconstruction and food crisis (ERFC) cohort* was defined as those participants for whom the ERFC period occurred during gestation or the first two years of life, including participants born between Q3 in 1943 and Q1 in 1949.

The *post currency reform (PCR) cohort* was defined as those who were conceived and born after the currency reform in June 1948, which marked the end of the ERFC period. This cohort thus included participants born in Q2 in 1949 and thereafter (see Fig. 1).



[a]PWW: pre-war and war; ERFC: early reconstruction and food crisis; PCR: post currency reform. Cohorts were defined based on co-occurrence of critical developmental age (gestation and first 2 years of life) and the ERFC period.

Fig.1 Graphical display of the quarter-based birth cohort categorization for main analysis**.**

This exposure definition did not imply a minimum exposure time. Thus, on the one hand, it covered participants who may have been exposed the ERFC period only for one day during their critical developmental age (which could be either the first day of gestation or the last day of their second life year) as well as, on the other hand, participants who were exposed to the ERFC period throughout gestation and their first two years of life. Therefore, we developed several alternative exposure operationalizations for sensitivity analyses: a minimum exposure of 3 months, a minimum exposure of 6 months and a subdivision of exposure in three dummy variables (exposure during gestation, during the first year of life, during the second year of life). For an additional sensitivity analysis, the PWW cohort was additionally sub-divided in a war cohort (i.e. participants born between Q4 1937 and Q2 1943, who had been exposed during their critical developmental age to the war period starting in Q4 1939, but not to the ERFC period) and a pre-war cohort (i.e. those born between Q1 and Q3 in 1937 who had completed their critical developmental age before the start of World War II). For a graphical display of these categorizations see Online Resource 3.

Age at data collection was used as continuous variable centered around the mean (68 years) [21].

Covariate Selection

Covariates were selected based on their respective associations with the exposure of interest, i.e. cohort membership, in either the sensitivity or main analysis data set, in separate multinomial generalized linear models controlling for age.

We tested adult-life demographic (marital status) and socioeconomic (education) variables as well as health risk behaviors (physical activity, smoking status, alcohol intake and body mass index [BMI]) as potential predictors of cohort membership [9]. These variables were selected as they had also been shown previously to be associated with health status as measured by the FI or one of its components such as functioning, age-related diseases or signs and symptoms [24-26] and might thus be able to explain part of the association between cohort membership and older-age health status.

Education was measured as a combination of years spent at school and years spent in vocational training (resulting values: 8, 10, 11, 15, 16, 17 years). We defined a maximum of eight educational years as “low education”, 10 or 11 years as “lower intermediate education”, 12 or 13 years as “higher intermediate education” and 15 to 17 years as “high education”. Information on this variable was carried over from earlier MONICA/KORA surveys, and was assumed to have remained stable throughout adult life. All other covariates except for education were measured in 2008 (for participants born ≤1943) or 2015 (for participants born 1944-1950).

Marital status was categorized as single, married, divorced, and widowed.

Physical activity (PA) was estimated by means of two separate four-category interview questions asking about the time per week spent on sports activities during leisure time (including cycling) in summer and winter (0, <1, 1 to 2, and >2 h sport/week). The winter and summer responses were

combined to create one variable of leisure time physical activity. “No activity” was defined as less than 1h sports in summer or winter; “low activity” was irregular participation in sports for about 1h per week in at least one season; ‘moderate activity’ was defined as regular participation in sports for about 1 h per week in at least one season; and ‘high activity’ was defined as regular sports in summer and winter for more than 2h per week in both seasons [27]. Participants were classified according to their smoking habits as smokers, ex-smokers, and never-smokers and according to their alcohol consumption frequency as “daily or nearly daily”, “several times a week”, “once a week”, “less than once a week” or “hardly ever or never”.

BMI was categorized into four categories according to World Health Organization (WHO) thresholds: underweight or normal weight (BMI <25 kg/m^2), overweight (25≤ BMI <30 kg/m^2), obesity grade I (30≤ BMI <35 kg/m^2), and obesity grade II or III (BMI ≥35 kg/m^2) [28].

Descriptive Statistics

The three cohorts (PWW, ERFC, and PCR) were compared with regard to their categorical covariate characteristics in the main and sensitivity analysis data sets using absolute and relative frequencies and a chi-squared test for differences between cohorts. For continuous variables, mean scores and standard deviations were calculated for each cohort and compared by a Kruskal-Wallis test. Additionally, the distribution of single health deficit items over cohorts was described using absolute and relative frequencies.

Time-Lag Analysis

Age-specific mean FI scores with confidence intervals were graphically presented separately for the three cohorts stratified by sex. Differences in age- and sex-specific mean FI scores between cohorts were assessed visually.

Regression Model

The effects of cohort membership, age, and sex on Frailty Index in adults aged 65-71 years old were analyzed using negative binomial generalized linear models (GLMs) with a log-link, the number of present health deficits as outcome and the number of possible deficits as offset term. Resulting effect estimates were presented as Frailty Index Ratios. Additional covariates were added to the model in a second step. We used a complete case analysis. All analyses were computed using R Studio Version 1.1.423 [29]. For all analyses, significance level was set to 0.05.

Sensitivity analyses

To verify if cohort effects were actually due to differences between cohorts and not due to period effects (i.e. measurement in 2008 or 2015), and if the linearity assumption for cohort effects was reasonable, we conducted two sensitivity analyses using generalized linear mixed models (GLMMs), one with cohort membership as a random effect, and one with cohort membership as a random effect nested in period. An additional sensitivity analysis was done with the PWW cohort further divided into a pre-war and a war cohort. Due to sample size considerations, all abovementioned models were conducted in the larger data set including those participants for whom place of birth in Germany could not be ascertained. The GLMMs were also repeated in the (smaller) main analysis data set, but without adjustment for additional covariates due to power considerations.

Furthermore, we repeated the main analysis both in the smaller and the larger data set using the three abovementioned alternative exposure operationalizations: a minimum exposure of 3 and 6 months, respectively and three dummy variables capturing age at exposure more precisely (gestation, first year of life, second year of life).

Results

Study participants

FI values were available for 1,800 PWW cohort participants (48% male), 1,168 ERFC cohort participants (47% male) and for 407 (47% male) PCR cohort participants (Online Resource 1). Of these, 1,774 PWW cohort participants (48% male), 1,149 ERFC cohort participants (47% male) and 404 (47% male) PCR cohort participants had complete covariate information. Place of birth in Germany could be ascertained for 590 PWW, 475 ERFC and 171 PCR cohort participants. Thus, the sample size for the main analysis was 1,236 and the sample size for sensitivity analysis was 3,327 participants.

Descriptive statistics

The three cohorts (PWW, ERFC, and PCR) differed significantly in mean FI values, sex, mean age, marital status, education, BMI, and smoking status. No differences were found with regard to physical activity, and alcohol consumption (table 1). For descriptive statistics on the complete sample (including participants for whom place of birth could not be ascertained) see Online Resource 4. On the level of single deficit items and after adjustment for age, cohort differences seemed to be significantly driven by deficits in arising, dressing, walking, taking stairs, stooping, lung and joint diseases, anxiety, fatigue and pain (Online Resource 5).

Table 1: Descriptive statistics by birth cohort for the smaller data set including only participants for whom place of birth in Germany could be ascertained[a] (n=1,236)

		Birth Cohort[b]			
Covariates		**PWW**	**ERFC**	**PCR**	**p-value[c]**
N		590	475	171	
Frailty Index, mean (sd)		0.13 (0.09)	0.15 (0.11)	0.13 (0.08)	0.002
Age, mean (sd)		68.16 (1.85)	68.30 (1.84)	65.44 (0.5)	<0.001
Age, n (%)					
	65	42 (7.1%)	45 (9.5%)	96 (56.1%)	<0.001
	66	90 (15.3%)	30 (6.3%)	75 (43.9%)	
	67	114 (19.3%)	95 (20%)	0 (0%)	
	68	80 (13.6%)	88 (18.5%)	0 (0%)	
	69	96 (16.3%)	79 (16.6%)	0 (0%)	
	70	85 (14.4%)	60 (12.6%)	0 (0%)	
	71	83 (14.1%)	78 (16.4%)	0 (0%)	
Measurement period, n (%)					
	2008	590 (100%)	45 (9.5%)	0 (0%)	<0.001
	2015	0 (0%)	430 (90.5%)	171 (100%)	
Sex, n (%)					
	male	314 (53.2%)	242 (50.9%)	78 (45.6%)	0.211
	female	276 (46.8%)	233 (49.1%)	93 (54.4%)	
Marital status, n (%)					
	married	446 (75.6%)	347 (73.1%)	129 (75.4%)	0.667
	single	34 (5.8%)	28 (5.9%)	11 (6.4%)	
	divorced	37 (6.3%)	42 (8.8%)	15 (8.8%)	
	widowed	73 (12.4%)	58 (12.2%)	16 (9.4%)	
Educational years, mean (sd)		10.62 (2.09)	11.48 (2.52)	11.42 (2.41)	<0.001
Education, n (%)					
	low education	95 (16.1%)	30 (6.3%)	8 (4.7%)	<0.001
	lower intermediate education	359 (60.8%)	274 (57.7%)	106 (62%)	
	higher intermediate education	97 (16.4%)	99 (20.8%)	34 (19.9%)	
	high education	39 (6.6%)	72 (15.2%)	23 (13.5%)	
BMI, n (%)					
	underweight or normal weight	152 (25.8%)	141 (29.7%)	49 (28.7%)	0.001
	overweight	294 (49.8%)	198 (41.7%)	75 (43.9%)	
	obesity grade I	122 (20.7%)	88 (18.5%)	31 (18.1%)	
	obesity grade II or III	22 (3.7%)	48 (10.1%)	16 (9.4%)	
Smoking status, n (%)					

never-smoker	295 (50%)	218 (45.9%)	74 (43.3%)	0.034
ex-smoker	246 (41.7%)	204 (42.9%)	69 (40.4%)	
smoker	49 (8.3%)	53 (11.2%)	28 (16.4%)	
Alcohol consumption, n (%)				
(almost) daily	192 (32.5%)	144 (30.3%)	42 (24.6%)	0.318
multiple times a week	101 (17.1%)	92 (19.4%)	34 (19.9%)	
once a week	87 (14.7%)	66 (13.9%)	33 (19.3%)	
less than once a week	140 (23.7%)	109 (22.9%)	47 (27.5%)	
(almost) never	70 (11.9%)	62 (13.1%)	15 (8.8%)	
missing values	0 (0%)	2 (0.4%)	0 (0%)	
Physical activity, n (%)				
> 2h / week, regularly	178 (30.2%)	154 (32.4%)	59 (34.5%)	0.205
1h / week, regularly	204 (34.6%)	152 (32%)	54 (31.6%)	
1h / week, irregularly	102 (17.3%)	66 (13.9%)	33 (19.3%)	
(almost) no physical activity	106 (18%)	103 (21.7%)	25 (14.6%)	
ERFC period exposure in utero				
no	590 (100%)	158 (33.3%)	171 (100%)	<0.001
yes	0 (0%)	317 (66.7%)	0 (0%)	
in the first year of life				
no	590 (100%)	190 (40%)	171 (100%)	<0.001
yes	0 (0%)	285 (60%)	0 (0%)	
in the second year of life				
no	590 (100%)	173 (36.4%)	171 (100%)	<0.001
yes	0 (0%)	302 (63.6%)	0 (0%)	
Cohort in four categories[a]				
pre-war	69 (11.7%)	0 (0%)	0 (0%)	<0.001
war	521 (88.3%)	0 (0%)	0 (0%)	
ERFC	0 (0%)	475 (100%)	0 (0%)	
PCR	0 (0%)	0 (0%)	171 (100%)	

[a]Confirmed birth place within the current defined borders of Germany or at the current place of residency at data collection (i.e., in Augsburg, Germany or surrounding counties). Note that participants for whom birth place within the current defined borders of Germany was not ascertained may still have been born in Germany.
[b]PWW: pre-war and war; ERFC: early reconstruction and food crisis; PCR: post currency reform. Cohorts were defined based on co-occurrence of critical developmental age (gestation and first 2 years of life) and the ERFC period.
[c]p-value from Chi^2-test for categorical variables and from Kruskal-Wallis test for continuous variables

Time-Lag Analysis

Descriptive plots revealed that age- and sex-specific FI values were higher for women than for men in the PWW and ERFC cohorts. For participants from the PCR period cohort there was no clear visual difference. In addition, age- and sex-specific FI values were slightly higher for the ERFC as compared to the PWW cohort, with the highest visual discrepancy for women born in 1944 and 1945 and to a lesser extent for men born 1944-1947 (see Fig. 2 and Online Resource 6).

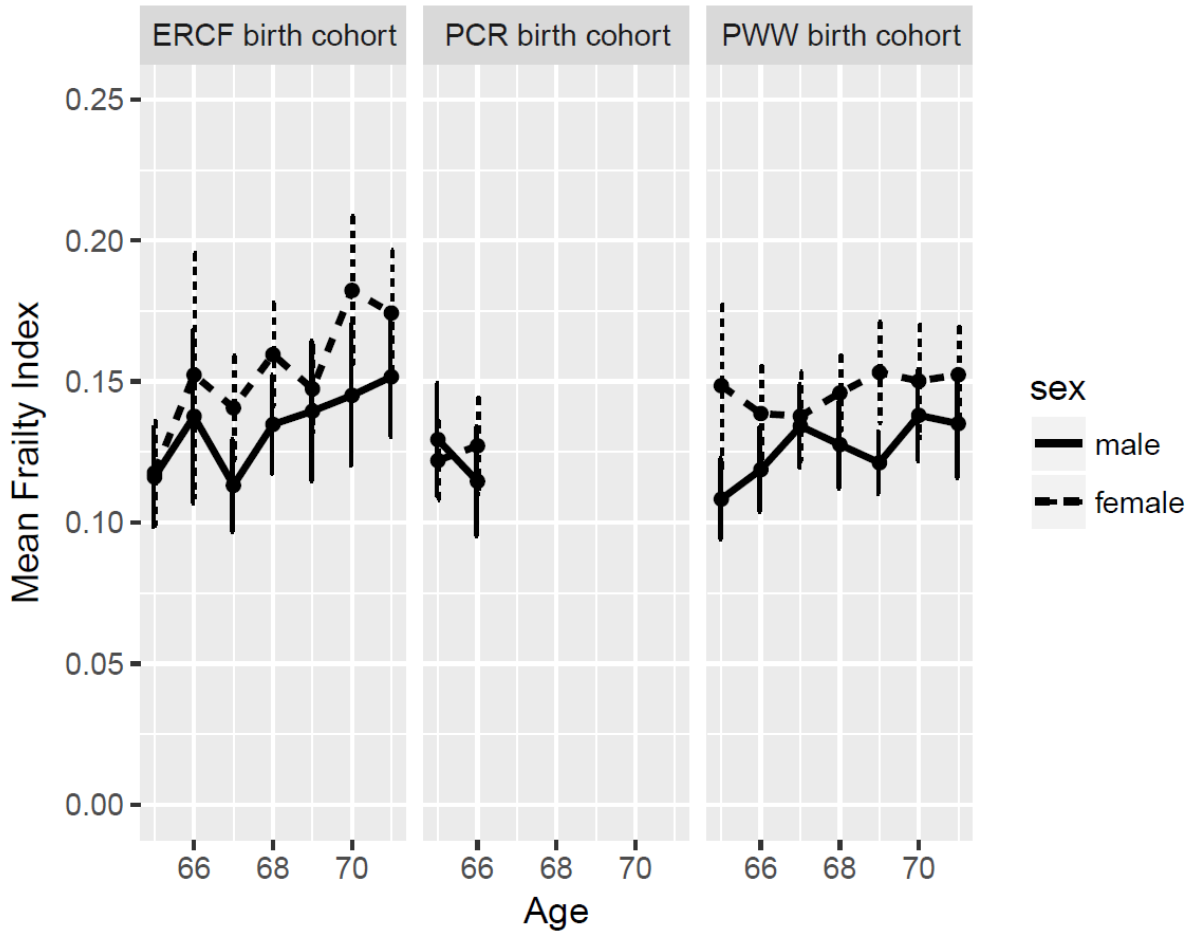


Fig.2 Mean sex- and age-specific Frailty Index values stratified by cohort

Covariate selection

Adjusted for age, cohorts differed significantly with regard to sex, education, smoking status, marital status and BMI, but not with regard to alcohol consumption and physical activity.

Regression Models

In the restricted GLM model, the FI rate ratio was significantly higher for the ERFC cohort (Ratio 1.14, CL: [1.05; 1.23] as compared to the PWW cohort. The PCR cohort was not significantly different from the PWW cohort (Ratio 1.04, CL: [0.92; 1.18]). Also, higher age (Ratio per additional life year 1.04; CL: [1.02; 1.06]) and female sex (Ratio 1.13; CL: [1.05; 1.22]) were independently and significantly associated with higher FI values.

When adjusting for the pre-selected covariates correlated to cohort membership, both age and ERFC cohort effects remained the same, and the sex effect estimate was reduced to 1.09 (CL: [1.00; 1.17]). For more details, see table 2.

Table 2: Resulting Frailty Index Ratios from the negative binomial models with complete covariate information for restricted and comprehensive covariate adjustment sets including all 65-71-year-old participants for whom birth in Germany could be ascertained[a], measured in 2008 or 2015 (depending on cohort membership) with full covariate information (n=1,236).

Covariates		Frailty Index Ratios	
		restricted covariate adustment set	comprehensive covariate adustment set
Intercept		0.124 (0.117, 0.133)	0.129 (0.111, 0.149)
Age in years (centered at the mean)		1.038 (1.017, 1.060)	1.043 (1.023, 1.064)
Sex	Male	Reference	
	Female	1.130 (1.052, 1.215)	1.085 (1.003, 1.173)
Cohort[b]	PWW	Reference	
	ERFC	1.137 (1.053, 1.229)	1.142 (1.057, 1.233)
	PCR	1.039 (0.915, 1.179)	1.062 (0.939, 1.201)
BMI	Underweight or normal weight	Reference	
	Overweight		1.020 (0.934, 1.113)
	Obesity grade I		1.252 (1.129, 1.390)
	Obesity grade II or III		1.622 (1.415, 1.859)
Smoking status	Never-smoker	Reference	
	Ex-smoker		1.132 (1.047, 1.223)
	Smoker		1.106 (0.981, 1.247)
Education	low	Reference	
	lower intermediate		0.846 (0.755, 0.948)
	higher intermediate		0.760 (0.661, 0.873)
	high		0.657 (0.557, 0.774)
Marital status	married	Reference	
	single		1.001 (0.862, 1.162)
	divorced		1.187 (1.044, 1.348)
	widowed		0.986 (0.884, 1.100)

[a]Confirmed birth place within the current defined borders of Germany or at the current place of residency at data collection (i.e., in Augsburg, Germany or surrounding counties). Note that participants for whom birth place within the current defined borders of Germany was not ascertained may still have been born in Germany.
[b]PWW: pre-war and war; ERFC: early reconstruction and food crisis; PCR: post currency reform. Cohorts were defined based on co-occurrence of critical developmental age (gestation and first 2 years of life) and the ERFC period.

Sensitivity analyses

Taking into account potential period random effects in addition to random effects for cohort membership did not significantly improve model fit as compared to a model with only cohort membership as random effect. Also, there was no considerable change in effect estimates for covariates when comparing the GLMs using cohort membership as fixed effect and the GLMM using cohort membership as random effect. Thus, we decided to keep the GLMs as final models.

When using the variable with a minimum exposure of 3 months or 6 months, respectively, effect estimates for the ERFC cohort as compared to the PWW cohort remained significant and comparable in effect size (1.15, CL: [1.07, 1.25] and 1.13, CL: [1.04, 1.23], respectively). In the overall sample including participants for whom birth in Germany could not be ascertained, the ERFC cohort effect was reduced to 1.06 (CL: [1.01, 1.11] but remained significant. Covariate effect estimates generally remained stable in size, significance and direction in all sensitivity analyses, with the exception of education (stronger protective effects in the main analysis sample) and being widowed (significant risk factor only in the larger overall KORA-Age sample).

When we used the exposure dummy variables representing age at exposure (ERFC period in utero, ERFC period in the first year of life, ERFC period in the second year of life), only exposure in the first year of life showed a significant effect, and only in the overall sample including participants for whom birth in Germany could not be ascertained (Ratio 1.12, CL: [1.02, 1.22]). For more details, see table 3 and Online Resources 7 and 8.

Table 3: Resulting Frailty Index Ratios from negative binomial models with restricted covariate adjustment sets, including participants with complete covariate information measured in 2008 or 2015 (depending on birth cohort): Sensitivity analyses using different parametrizations of ERFC period exposure in the smaller data set including only participants for whom place of birth in Germany could be ascertained[a] (n=1,236).

	Frailty Index Ratios				
	generalized linear mixed-effects models			generalized linear models	
Covariates	with random effects for cohort nested in period	with random effects for cohort	exposure in three dummy variables (during gestation, first year of life, second year of life)	with minimum exposure 3 months	with minimum exposure 6 months
Intercept	0.131 (0.115, 0.149)	0.132 (0.119, 0.145)	0.130 (0.112, 0.151)	0.129 (0.111, 0.149)	0.129 (0.111, 0.150)
Age in years	1.036 (1.014, 1.059)	1.039 (1.019, 1.060)	1.036 (1.016, 1.056)	1.041 (1.020, 1.063)	1.044 (1.022, 1.067)
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	1.128 (1.049, 1.213)	1.131 (1.052, 1.215)	1.090 (1.008, 1.179)	1.080 (0.999, 1.168)	1.080 (1.998, 1.168)
Cohort[b]					
PWW	Random effect		-	Reference	Reference
ERFC	Random effect		-	1.154 (1.066, 1.249)	1.134 (1.043, 1.232)
PCR	Random effect		-	1.080 (0.962, 1.211)	1.111 (0.998, 1.238)
Exposure in … utero					
no	-		Reference	-	-
yes	-		1.017 (0.915, 1.130)	-	-
... 1st year of life					
no	-		Reference	-	-
yes	-		1.083 (0.947, 1.240)	-	-
… 2nd year of life					
no	-		Reference	-	-

yes	-		1.042 (0.935, 1.160)	-	-
BMI					
underweight or normal weight	-	-	Reference	Reference	Reference
overweight	-	-	1.023 (0.937, 1.117)	1.020 (0.935, 1.113)	1.020 (1.934, 1.113)
obesity grade I	-	-	1.252 (1.128, 1.390)	1.251 (1.127, 1.388)	1.250 (1.127, 1.388)
obesity grade II or III	-	-	1.639 (1.430, 1.880)	1.619 (1.413, 1.856)	1.622 (1.415, 1.859)
Smoking status					
never-smoker	-	-	Reference	Reference	Reference
ex-smoker	-	-	1.129 (1.045, 1.220)	1.131 (1.047, 1.222)	1.131 (1.047, 1.222)
smoker	-	-	1.111 (0.985, 1.253)	1.105 (0.980, 1.246)	1.104 (0.979, 1.245)
Education					
low	-	-	Reference	Reference	Reference
lower intermediate	-	-	0.854 (0.762, 0.956)	0.843 (0.752, 0.944)	0.845 (0.754, 0.947)
higher intermediate	-	-	0.770 (0.670, 0.884)	0.758 (0.659, 0.870)	0.759 (0.661, 0.872)
high	-	-	0.671 (0.570, 0.789)	0.655 (0.556, 0.771)	0.659 (0.560, 0.776)
Marital status					
married	-	-	Reference	Reference	Reference
single	-	-	1.001 (0.861, 1.161)	0.999 (0.860, 1.159)	1.000 (0.861, 1.160)
divorced	-	-	1.187 (1.044, 1.348)	1.191 (1.048, 1.352)	1.190 (1.048, 1.352)
widowed	-	-	0.985 (1.882, 1.099)	0.988 (0.885, 1.102)	0.989 (0.887, 1.104)

[a]Confirmed birth place within the current defined borders of Germany or at the current place of residency at data collection (i.e., in Augsburg, Germany or surrounding counties). Note that participants for whom birth place within the current defined borders of Germany was not ascertained may still have been born in Germany.
[b]PWW: pre-war and war; ERFC: early reconstruction and food crisis; PCR: post currency reform. Cohorts were defined based on co-occurrence of critical developmental age (gestation and first 2 years of life) and the ERFC period.

Discussion

Our analysis is among the first to explore the effects of exposure to the German early reconstruction and food crisis period after World War II in early childhood on health status in older age. We found that, when taking into account both age and cohort effects for health status in adults aged 65-71 years, age remained the most influential factor. On the one hand, co-occurrence of the ERFC period with gestation period or the first two years of life further increased the number of accumulated health deficits in older age as compared to co-occurrence of the food crisis with age above 24 months. These differences between cohorts could not be explained by differences in socio-economic or socio-demographic status or health behaviors in older age, indicating a direct effect from co-occurrence of critical developmental age and the ERFC period on older-age health. On the other hand, the accumulated health deficit levels of participants born after the currency reform in June 1948 did not differ significantly from those who were already older than 24 months during early reconstruction and food crisis. Our results were significant independently of duration of exposure to the ERFC period during critical developmental age. The ERFC period effect was stronger in the main analysis sample which comprised only those participants for whom place of birth in Germany could be ascertained.

For health projections in Germany, this may indicate that an expansion of morbidity which has been reported earlier for 1911-1932 birth cohorts [5] and which our analysis additionally suggested for cohorts born between 1937 and the first quarter of 1949 (the PWW and ERFC cohorts) cannot simply be extrapolated to post war generations (such as the PCR cohort). Also the determinants leading to the two instances of morbidity expansion may be different: Whereas the first expansion of morbidity from 1911-1932 may have resulted from increased life expectancy combined with stable disease onset, the results of our analysis may be a result of a shift towards earlier disease onset from the 1937-1943 to the 1943-1949 cohorts.

Plots of age- and sex-specific mean FI values by cohort suggested that the detrimental effect of being born in the aftermath of World War II on health status was especially pronounced for women born in 1944 and 1945. Potential explanations are that these cohorts suffered some of the longest exposures to the food crisis (i.e. from birth or age 1 until age 3 or age 4, respectively). In addition, their birth years coincide with the peak of reported hunger prevalence in the German population (close to 25% in 1945) [8]. Although these birth cohorts were not exposed to the food crisis during gestation, our results are in line with the results of previous research suggesting that undersupply in infancy and childhood has a higher impact on health in older age than undersupply in utero [10].

At first sight, these findings seem to contradict the literature on fetal programming, i.e. the negative health effects of adverse exposures during gestation [30, 13]. This apparent discrepancy may be explained by differential fertility in parents and differential mortality in children [31]. Studies investigating older-age outcomes of war-related in-utero famine exposure during shorter famines, such as the six-month Dutch Hunger Winter 1944/45 where no impact on fertility is assumed, do report

significant effects for in utero exposure [13]. These effects are less stable when there is reason to believe that fertility effects may have occurred (as in Greece) [10]. For the ERFC period in Germany, fertility effects have been ascertained: The adverse living conditions in the three-year aftermath of World War II resulted in lower birth rates, higher numbers of miscarriages and increased infant mortality [32]. Thus, it can be expected that the 2008 and 2015 survivors from the early reconstruction and food crisis (ERFC) cohort are generally healthier and more resilient than the average pre-war and war (PWW) or post-currency reform (PCR) cohorts. Consequently, our results on the effect of the post-World War II turbulences on older-age health may even be biased downwards [10, 33] and may have produced the non-significant effect of in-utero-exposure. Selection effects, especially the so-called "male vulnerability" (boys seem to be more strongly affected by adverse early-life conditions) [8] and the male-female health survival paradox (men die earlier in a better health state whereas women live longer, even though in worse health) [34] may also explain why we found outliers only in women and not in men born 1944 to 1945.

A second reason why our results may be biased downwards is that during war-induced famines only a fraction of the population is exposed to adverse living conditions, with populations in large urban areas being usually more affected than those in smaller cities such as Augsburg and its surrounding rural counties. Thus, one can assume that the effect would have been stronger if all actually non-exposed individuals from the ERFC cohort (e.g. those better off because of collaborations with the allied forces or those living in rural areas with access to self-produced food) could have been singled out from the data set [8].

We are confident that the effect of age and cohort membership on health in older age was not confounded by period effects, as taking measurement period into account did not significantly improve the model nor change the results. In other words, being aged 65-71 years and interviewed in 2008 did not have a significantly different health effect than being aged 65-71 years and interviewed in 2015.

As the KORA-Age participants were sampled during their adult life and no information on place of birth or place of residence during the first two years of life was available, some of them may have moved to Germany after the food crisis period. Thus, we ran our main analysis using only those participants for whom the information was available that they were born in Germany. Nevertheless, the results were also supported by our sensitivity analyses in the larger data set including participants for whom information on place of birth was not available.

Our study has the following limitations: First, we had no individual-level data neither on the participants' mothers' exposure to hunger or other war- or early reconstruction related stressful life events, morbidities and living conditions during gestation, nor on perinatal outcomes such as birthweight or preterm deliveries. On a macro level, though, it can be confirmed that these conditions were far more frequent during the ERFC period than before and thereafter: For example, birth rates in the city of Dresden dropped from 5,100 to 1,900 in 1945, with a slow increasing trend starting again

only after 1949. Low weight births (<2,500g) in the city of Leipzig increased by 57% in 1946 as compared to the previous year, reaching earlier low levels again only after 1950. Also congenital malformations such as neural tube defects were more frequent in the ERFC period, more than doubling in Berlin in the ERFC period as compared to the PWW period [32]. The ERFC period also coincides with the period where the largest share of respondents recalls having suffered from hunger [8, 12]. In addition, we did not have information on the participants own respective experience between birth and 24 months of age. Even if information on this question had been collected, it would have been subject to information bias, as it is improbable that participants would have remembered the presence of these conditions in their first years of life. In this situation, it has been postulated that the best way to define exposure in critical developmental periods may be to rely on macro-level information [13]. We chose to use the German early reconstruction and food crisis period as indicator for the most formative period in Germany related to the aftermath of World War II, as it has a well-defined start and end date and affected a large share of the population. These characteristics apply only to a much smaller extent to bombings (different timing in different places) and separation from family members or absence of fathers (different timing, independent of place). Still, when interpreting our results, it should be taken into account that the effects of what we called "early reconstruction and food crisis period" are potentially combined effects of hunger and other experiences introduced by the aftermath of World War II such as psychological stress, displacement, poverty, separation from close family members, and interrupted education [8], all of which may also have affected our participants' parents and thus have had epigenetic effects on older-age health [35].

In conclusion, co-occurrence of critical developmental age with the early reconstruction period and the associated food crisis in Germany increased the risk for higher numbers of accumulated health deficits in adults aged 65-71 years. These effects were not explained by selected covariates and could not be found in a cohort born after 1949, suggesting a direct link from the experience of early childhood adversities to older-age health and the potential for a change in morbidity trends towards the second half of the 20th century. Thus, it is imperative that research on future morbidity trends continuously reviews its conclusions based on data from the most recent birth cohorts. At the same time, historical circumstances such as war and famine have to be taken into account, as they may excert their negative effects well into subsequent generations.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Acknowledgments: The authors would like to thank the members of the field staff in Augsburg who were involved in conducting the studies and the team at the Helmholtz Zentrum München for maintaining this complex data.

References

1. Crimmins EM, Beltrán-Sánchez H. Mortality and morbidity trends: is there compression of morbidity? J Gerontol B Psychol Sci Soc Sci. 2011;66(1):75-86.
2. Doblhammer G, Kytir J. Compression or expansion of morbidity? Trends in healthy-life expectancy in the elderly Austrian population between 1978 and 1998. Soc Sci Med. 2001;52(3):385-91.
3. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. J Epidemiol Community Health. 2015;69(4):316-21.
4. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. Lancet. 2008;372(9656):2124-31.
5. Mergenthaler A. Die Entwicklung der gesunden Lebenserwartung im Alter. Ein Kohortenvergleich auf der Grundlage des deutschen Alterssurveys. [The development of healthy life expectancy in older age. A cohort comparison based on the German Ageing Survey]. Bevölkerungsforschung Aktuell. 2011;32:2-7.
6. Kalache A, Aboderin I, Hoskins I. Compression of morbidity and active ageing: key priorities for public health policy in the 21st century. Bulletin of the world health organization. 2002;80:243-4.
7. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285-93.
8. Schoch J. Empirical Essays on the Effects of Early Life Conditions on Health Later in Life 2014.
9. Kesternich I, Siflinger B, Smith JP, Winter JK. Individual Behaviour as a Pathway between Early-life Shocks and Adult Health: Evidence from Hunger Episodes in Post-war Germany. Econ J. 2015;125(588).
10. Neelsen S, Stratmann T. Effects of prenatal and early life malnutrition: Evidence from the Greek famine. J Health Econ. 2011;30(3):479-88.
11. Bryce J, Coitinho D, Darnton-Hill I, Pelletier D, Pinstrup-Andersen P, Maternal et al. Maternal and child undernutrition: effective action at national level. Lancet. 2008;371(9611):510-26.
12. Kesternich I, Siflinger B, Smith JP, Winter JK. The effects of World War II on economic and health outcomes across Europe. Rev Econ Stat. 2014;96(1):103-18.
13. Lumey LH, Stein AD, Susser E. Prenatal famine and adult health. Annu Rev Public Health. 2011;32:237-62.
14. Klatt W. Food and farming in Germany: I. food and nutrition. Int Aff. 1950;26(1):45-58.
15. FaAOotU N. Human energy requirements: report of a joint FAO/WHO/UNU expert consultation. FAO food and nutrition technical report series, Rome. 2004.
16. Mitnitski A, Song X, Rockwood K. Trajectories of changes over twelve years in the health status of Canadians from late middle age. Exp Gerontol. 2012;47(12):893-9.

17. Holle R, Happich M, Löwel H, Wichmann H-E, Group nftMKS. KORA-a research platform for population based health research. Gesundheitswesen. 2005;67(S 01):19-25.

18. Peters A, Döring A, Ladwig K, Meisinger C, Linkohr B, Autenrieth C et al. Multimorbidity and successful aging: the population-based KORA-Age study. Z Gerontol Geriatr. 2011;44:41-54.

19. Löwel H, Döring A, Schneider A, Heier M, Thorand B, Meisinger C et al. The MONICA Augsburg surveys-basis for prospective cohort studies. Gesundheitswesen. 2005;67(S 01):13-8.

20. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8(1):24. doi:10.1186/1471-2318-8-24.

21. Stephan A-J, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig K-H et al. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. Prev Med. 2017;102:31-8.

22. Stephan A-J, Strobl R, Müller M, Holle R, Autenrieth CS, Thorand B et al. A high level of household physical activity compensates for lack of leisure time physical activity with regard to deficit accumulation: Results from the KORA-Age study. Prev Med. 2016;86:64-9.

23. Yang Y, Lee LC. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the US older adult population. J Gerontol B Psychol Sci Soc Sci. 2009;65(2):246-55.

24. Romero-Ortuno R. Frailty Index in Europeans: Association with determinants of health. Geriatr Gerontol Int. 2014;14(2):420-9.

25. Stenholm S, Westerlund H, Salo P, Hyde M, Pentti J, Head J et al. Age-related trajectories of physical functioning in work and retirement: the role of sociodemographic factors, lifestyle and disease. J Epidemiol Community Health. 2014:jech-2013-203555.

26. Mello AdC, Engstrom EM, Alves LC. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cad Saude Publica. 2014;30(6):1143-68.

27. Meisinger C, Löwel H, Thorand B, Döring A. Leisure time physical activity and the risk of type 2 diabetes in men and women from the general population. Diabetologia. 2005;48(1):27-34. doi:10.1007/s00125-004-1604-3.

28. World Health Organization. Obesity: preventing and managing the global epidemic. vol 894. World Health Organization; 2000.

29. Rstudio Team. RStudio: Integrated Development for R. . Boston, MA: RStudio, Inc.; 2016.

30. Barker DJ. In utero programming of chronic disease. Clin Sci. 1998;95(2):115-28.

31. Van Ewijk R, Lindeboom M. Why people born during World War II are healthier. 2017.

32. Wynn A, Wynn M. The effects of food shortage on human reproduction. Nutr Health. 1993;9(1):43-52.

33. Jürges H. Collateral damage: The German food crisis, educational attainment and labor market outcomes of German post-war cohorts. J Health Econ. 2013;32(1):286-303.

34. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. Aging Clin Exp Res. 2008;20(2):91-102.

35. Devakumar D, Birch M, Osrin D, Sondorp E, Wells JC. The intergenerational effects of war on the health of children. BMC Medicine. 2014;12(1):57. doi:10.1186/1741-7015-12-57.

Online resources

Online Resource 1: Study participants flow chart

Online Resource 2: Deficit items included in the modified KORA-Age Frailty Index

Online Resource 3: Graphical display of the quarter-based cohort categorization for sensitivity analyses

Online Resource 4: Descriptive statistics by birth cohort for the larger data set including participants for whom information on place of birth was not available (n=3,327)

Online Resource 5: Health deficit distributions by birth cohort for the smaller data set including only participants for whom place of birth in Germany could be ascertained (n=1,236)

Online Resource 6: Mean age-specific Frailty Index values stratified by cohort and sex

Online Resource 7: Resulting Frailty Index Ratios from the negative binomial models: Sensitivity analysis repeating the main analysis models in the larger data set including participants for whom information on place of birth was not available (n=3,327)

Online Resource 8: Resulting Frailty Index Ratios from negative binomial models: Sensitivity analyses using different parametrizations of ERFC period exposure in the larger data set including participants for whom information on place of birth was not available (n=3,327)

3. Scientific publications

3.1 Peer reviewed publications

Stephan A-J, Strobl R, Schwettmann L, Meisinger C, Ladwig K-H, Linkohr B, Thorand B, Peters A, Grill E. Being born in the aftermath of World War II increases the risk for health deficit accumulation in older age: results from the KORA-Age study. *European Journal of Epidemiology*. 2019.

Stephan A-J, Strobl R, Holle R, Grill E. Wealth and occupation determine health deficit accumulation onset in Europe – Results from the SHARE study. *Experimental Gerontology*. 2018;113:74-9.

Kovacs E, Strobl R, Phillips A, **Stephan A-J**, Müller M, Gensichen J, et al. Systematic review and meta-analysis of the effectiveness of implementation strategies for non-communicable disease guidelines in primary health care. *Journal of general internal medicine*. 2018:1-13.

Kovacs E, **Stephan A-J**, Phillips A, Schelling J, Strobl R, Grill E. Pilot cluster randomized controlled trial of a complex intervention to improve management of vertigo in primary care (PRIMA-Vertigo): study protocol. *Current medical research and opinion.* 2018;34(10):1819-1828.

Stephan A-J, Kovacs E, Phillips A, Schelling J, Ulrich SM, Grill E. Barriers and facilitators for the management of vertigo: a qualitative study with primary care providers. *Implementation Science*. 2018;13(1):25.

Saal S, Meyer G, Beutner K, Klingshirn H, Strobl R, Grill E, Mann E, Köpke S, Bleijlevens M H C, Bartoszek G, **Stephan A-J**, Hirt J, Müller M. Development of a complex intervention to improve participation of nursing home residents with joint contractures: a mixed-method study. *BMC Geriatrics*. 2018;18(1):61.

Stephan A-J, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig K-H, et al. Male sex and poverty predict abrupt health decline: Deficit accumulation patterns and trajectories in the KORA-Age cohort study. *Preventive Medicine*. 2017;102:31-8.

Stephan A-J, Strobl R, Müller M, Holle R, Autenrieth CS, Thorand B, et al. A high level of household physical activity compensates for lack of leisure time physical activity with regard to deficit accumulation: Results from the KORA-Age study. *Preventive Medicine*. 2016;86:64-9.

Müller M, Bartoszek G, Beutner K, Klingshirn H, Saal S, **Stephan A-J**, et al. Developing and piloting a multifactorial intervention to address participation and quality of life in nursing home residents with joint contractures (JointConImprove): study protocol. *GMS German Medical*

Science. 2015;13.

3.2 Conference Contributions

Stephan A-J, Koller D, Phillips A, Grill E. Steckbrief: Netzwerk für Partizipation durch Mobilität im Alter (MobilE-Net). Oral presentation at *DKVF 2018. 17. Deutscher Kongress für Versorgungsforschung.* 2018 October 10-12, Berlin, Germany.

Stephan A-J, Strobl R, Schwettmann L, Meisinger C, Ladwig K-H, Linkohr B, Thorand B, Peters A, Grill E. Does being born during a hunger period make a difference for deficit accumulation in older age? Results from the KORA-Age study. Oral presentation at *DGEpi 2018. 13th annual conference of the German Society for Epidemiology.* 2018 Sept 26-28; Bremen, Germany.

Stephan A-J, Strobl R, Holle R, Meisinger C, Ladwig KH, Linkohr B, Thorand B, Peters A**,** Grill E. Do birth cohorts make a difference for deficit accumulation in older age? First results from the KORA-Age study. Oral presentation at *IEA European Congress of Epidemiology (EuroEpi) 2018*. 2018 July 04-06; Lyon, France.

Albertsmeier M, Riedl K, **Stephan A-J**, Angele M, Werner J, Guba M. Resektion kolorektaler Lebermetastasen in Gegenwart nicht resezierter Lungenmetastasen. Oral presentation at *Viszeralmedizin 2018. 73. Jahrestagung der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten mit Sektion Endoskopie und 12. Herbsttagung der Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie gemeinsam mit den Arbeitsgemeinschaften der DGAV*. 2018 September 12-15, Munich, Germany.

Stephan A-J. Gesundheit im Alter - Epidemiologische Konzepte und Forschungsbeispiele. Oral presentation at *Fachtag der Landeszentrale für Gesundheit in Bayern (LZG) „Gesundheit im Herbst des Lebens - Psychosoziale Aspekte der Gesundheit im Alter“ 2017*. 2017 December 06; Munich, Germany.

Kovacs E, **Stephan A-J**, Phillips A, Schelling J, Grill E, Koller D. Primary care providers' perspective on challenges in management of patients with dizziness and vertigo. Poster presented at: *DKVF 2016. 16. Deutscher Kongress für Versorgungsforschung*. 2017 Oct 4-6; Berlin, Germany.

Stephan AJ, Strobl R, Grill E. The effect of income and wealth on the onset of health deficit accumulation in older adults in Europe – results from the SHARE study. Oral presentation at *DGEpi 2017. 12th annual conference of the German Society for Epidemiology*. 2017 Sept 05-08; Lübeck, Germany.

Stephan AJ, Strobl R, Grill E. Deficit accumulation in older adults: Predictors of late deficit accumulation onset in older adults in Europe – results from the SHARE study. Oral presentation at: *IEA World Congress of Epidemiology(WCE) 2017*; 2017 Aug 19-22;

Saitama, Japan.

Stephan AJ, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig KH, Thorand B, Peters A, Grill E. Deficit accumulation in older adults: Older men with lower income may experience faster decline in health status - Results from the KORA-Age study. Oral presentation at: *International Conference on Frailty & Sarcopenia Research (ICFSR) 2017*. 2017 Apr 27-29; Barcelona, Spain.

Stephan AJ, Strobl R, Holle R, Meisinger C, Schulz H, Ladwig KH, Thorand B, Peters A, Grill E. 3-Year trajectories and predictors of deficit accumulation in older people: results from the KORA-Age cohort study. Poster presentation at: *HEC 2016. GMDS & DGEpi & IEA-EEF annual meeting, Medical Informatics Europe – MIE 2016*; 2016 Aug 28 - Sep 2; Munich, Germany.

Klingshirn H, Saal S, Bartoszek G, Beutner K, Hirt J, **Stephan A-J**, Strobl R, Grill E, Meyer G, Müller M. Developing a complex intervention to improve participation and quality of life in nursing home residents with joint contractures (JointConImprove). Poster presentation at: *HEC 2016. GMDS & DGEpi & IEA-EEF annual meeting, Medical Informatics Europe – MIE 2016*; 2016 Aug 28 - Sep 2; Munich, Germany.

Stephan AJ, Strobl R, Müller M, Holle R, Autenrieth CS, Thorand B, Linkohr B, Peters A, Grill E. Association of leisure time and household physical activity with deficit accumulation in older adults: Results from the cross-sectional KORA-Age study. Oral presentation at *DGEpi 2015. 10th annual conference of the German Society for Epidemiology*. 2015 Sep 30 – Oct 2; Potsdam, Germany.

Strobl R, **Stephan A-J**, Müller M, Holle R, Thorand B, Linkohr B, Peters A, Grill E. Physical activity is inversely associated with deficit accumulation in older adults - Results from the KORA-Age study. Poster presented at: *IEA European Congress of Epidemiology (EuroEpi) 2015*. 2015 Jun 25-27; Maastricht, the Netherlands.

4. Acknowledgements

I am deeply grateful to Eva Grill for her trust in my abilities and her continuous support and for challenging and encouraging me to push my own boundaries. I would also like to acknowledge the other two members of my thesis advisory committee, Prof. Dr. Rolf Holle and Prof. Dr. Martin Müller for their thorough thoughts and critical comments which improved my work. Likewise, I would like to thank all my coauthors for their valuable input. All publications included in this thesis are the result of excellent cooperations, and I would like to express my gratitude to all parties involved. In this context, I would like to acknowledge the institutions that made this thesis possible, particularly the IBE at LMU and the Helmholtz Zentrum München. I would like also to thank the MMRS PhD coordination team for their support.

I owe gratitude to Amanda Phillips for being the best work companion and PhD teammate I could imagine, and to Ralf Strobl for offering both chocolate and statistical advice when needed. Another sincere thank you goes to all my colleagues in Eva Grill's working group. I could not have imagined being part of a better team.

I would like to take the opportunity and thank the following people who make my life worthwhile and supported me on my PhD journey:

My husband Matthias Lissek for being my best friend, and for all the small and big things he provided me with throughout the last years, including but not limited to emotional and practical support, home-made dinners, speech rehearsals and bans on working on weekends.

My mother, Christine Stephan, to whom I am indefinitely grateful for having raised me, being proud of me and for believing in my abilities. I am so lucky to be your daughter.

Christine Stephan, Valeska Stephan and Ulrich and Karin Westholt for their unconditional support and for proving that patchwork is an amazing family constellation.

My oldest friend Julia Plappert, for exhaustive telephone calls and for the recurrent feeling whenever we meet, that the last time we met was just yesterday.

I would also like to take this opportunity and thank all my friends for their support throughout this journey, and for the passionate discussions and wonderful times we have together.