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Multimorbidity and Mortality: Evidence from Epidemiological Studies in Older Adults

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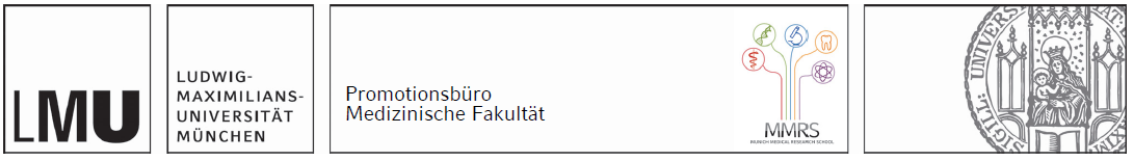
“Dedicated to my beloved Son”

Affidavit



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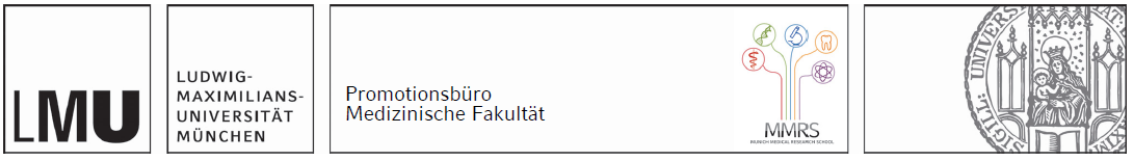

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List of abbreviations

BMI Body mass index

CI Confidence intervals

ICD International Classification of Diseases

IQR Interquartile range

GLMM Generalized Linear Mixed Models

HR Hazard ratios

KORA Cooperative Health Research in the Region of Augsburg

MM Multimorbidity

OR Odds ratios

WHR Waist-to-hip ratios.

List of publications

1. *"Ava Arshadipour, Birgit Linkohr, Barbara Thorand, Karl-Heinz Ladwig, Margit Heier, Susanne Rospleszcz, and Annette Peters, Impact of prenatal and childhood adversity affects around World War II on MM: results from the KORA-Age study. BMC Geriatrics (2022) 22:115,"*
   https://doi.org/10.1186/s12877-022-02793-2
2. *"Ava Arshadipour,, Birgit Linkohr, Barbara Thorand, Margit Heier, Karl-Heinz Ladwig and Annette Peters, MM patterns and mortality in older adults: Results from the KORA-Age study. Frontiers, Front. Nutr. (2023), 10:1146442,"*
   https://doi: 10.3389/fnut.2023.1146442.

1. Contribution to the publications

1.1 Contribution to publication I

I am the first author of paper I, and I was involved in developing the research questions under the supervision of my doctoral supervisor, Prof. Annette Peters. I performed all conceptualization, statistical analyses, interpretation, and drafting of the papers under the supervision of Prof. Annette Peters, and Prof. Barbara Thorand as the members of my Thesis Advisory Committee and Dr. Birgit Linkohr as my mentor. Moreover, I have written all manuscript drafts, incorporated co-authors' comments, finalized the manuscripts based on reviewers' comments, and coordinated the communication between co-authors and editors from the journal.

1.2 Contribution to publication II

I am the first author of paper II, and I was involved in developing the research questions under the supervision of my doctoral supervisor, Prof. Annette Peters. I performed all conceptualization, statistical analyses, interpretation, and drafting of the papers under the supervision of Prof. Annette Peters, and Prof. Barbara Thorand as the members of my Thesis Advisory Committee and Dr. Birgit Linkohr as my mentor. Moreover, I have written all manuscript drafts, incorporated co-authors' comments, finalized the manuscripts based on reviewers' comments, and coordinated the communication between co-authors and editors from the journal.

2. Introductory summary

2.1 Problem statement

Multimorbidity (MM), as the presence of multiple chronic diseases simultaneously in one person, is a significant global public health issue, particularly among the elderly population, and its prevalence is increasing [1]. It has the potential to place a considerable limitation for both the healthcare system and the individual. The presence of MM can result in higher risk of hospitalization, polypharmacy and healthcare and society costs [2-4]. In addition, MM has been associated with decline in quality of life and functional abilities (5). It can also increase the mortality risk, based on a meta-analysis of 26 articles (6). Overall, the burden of MM is a significant public health concern that requires attention from healthcare providers and policymakers. The increasing prevalence of MM and its associated healthcare costs, functional impairment and mortality, necessitates the development of effective prevention and management strategies to decrease the problem of the healthcare system and to enhance the quality of life of individuals affected by this condition.

Depending on the number of included diseases, data, and measurement methods, the prevalence of MM among adults 65 years and older ranged from 55% to 98%, according to a systematic evaluation of 41 articles conducted in different countries [7]. As per one cross-sectional study conducted in Germany (2012-2013), the prevalence of MM was 61.7% amongst individuals aged 60-69 years old and 72.9% amongst those who were 70-79 years old [8]. Moreover, based on the data from KORA (Cooperative Health Research in the Region of Augsburg)-Age study performed in 2008 till 2009, the MM prevalence in southern Germany was 58.6% among individuals aged 65 to 94 [9].

Longer life expectancies and epidemiologic disease shifts in industrialized countries, as well as more recently in less developed countries, are the main causes of the global increase in the prevalence of chronic diseases and MM correspondingly. A large demographic shift brought on by population aging can provide new problems for governments, healthcare systems, and society worldwide. By the year 2050, the proportion of adults aged 60 years old and above is expected to rise from approximately 12% (equivalent to around 900 million) in 2015 to approximately 22% (corresponding to about 2.1 billion) globally. Moreover, the global population who are at least 80 years old

will be almost triple in the world and reach to 426 million by 2050 [10]. In Germany, the percentage of people over 60 years old will rise to 40.8% by 2060 (currently ~40.8%) [11]. The epidemiological transition, which describes how chronic diseases over time have replaced infectious diseases because of better medical care and disease prevention, is another significant factor contributing to the rising prevalence of chronic disease and MM [12].

In addition, improvements in healthcare, sanitation, and vaccination programs have contributed to the decline in infectious diseases [13]. However, lifestyle factors, including poor nutrition, being physically inactive, overweight, living alone, excessive alcohol, and tobacco consumption, and socioeconomic factors including education, occupation, and life pass exposure [14-17], have led to an increase in chronic diseases.

MM can result in a higher mortality risk. According to one study combined with the results of 26 PUBMED studies, the hazard ratio (HR) for the association between mortality and MM was found to be 1.44 (HR: 1.44, 95% CI: 1.34, 1.55) for individuals who were 60 years old and above. With a greater number of included chronic diseases, there was a higher mortality risk (HR: 1.20, 95% CI: 1.10, 1.30). Compared to people without MM, individuals who had two or more diseases experienced a 1.73 times higher mortality risk (HR: 1.73, 95% CI: 1.41, 2.13), while those with three or more diseases had a 2.72 times higher risk (HR: 2.72, 95% CI: 1.81, 4.08) [18].

Various factors influence the risk of mortality such as the disease types in the MM definition, the considered age groups, the number of participants, and the chronic disease risk factors [19-24]. A longitudinal observational study was conducted in Germany with a focus on individuals older than 65 years old. They examined the association between MM (based on 46 chronic diseases) and mortality. It revealed that women had an all-cause mortality hazard ratios of 1.02 (HR: 1.02, 95% CI: 1.01, 1.02), while men had a ratio of 1.04 (HR: 1.04, 95% CI: 1.03, 1.04). Various disease clusters may exhibit distinct levels of mortality risk. The study also revealed that the cluster of neuropsychiatric disorders (such as dementia, Parkinson disease, urinary issues, etc.) was significantly associated with an increased mortality risk of 1.33 (HR: 1.33, 95% CI: 1.30, 1.36) in women and 1.46 (HR: 1.46, 95% CI: 1.43, 1.50) in men. Furthermore, cardiovascular, and metabolic disorders (e.g. hypertension, diabetes, kidney and liver insufficiency, heart disease, and so on) had inconsistent risk in women (HR: 0.99, 95% CI: 0.97, 1.01) and (HR: 1.08, 95% CI: 1.07, 1.09) in men. Additionally, psychiatric, psychosomatic, and

pain-related disorders (e.g. hypotension, migraine, anxiety, asthma, joint arthrosis and so on) were related to significantly lower mortality risk in women (HR: 0.87, 95% CI: 0.86, 0.89) and men (HR: 0.88, 95% CI: 0.87, 0.90) [25].

Even though MM is becoming more common and poses significant difficulties, the studies on the MM prevalence, potential diseases associations, and relationship between MM patterns and mortality in Germany are limited [25]. Then, with an expanding population of senior citizens in the coming decades in Germany [11], substantial prospective studies are required to offer evidence for program planning, treatments, and management of MM. This would aid in the development of medical services and treatment protocols to satisfy the needs of Germans with multiple diseases.

2.2 Research questions and objectives

The current cumulative doctoral thesis aims to investigate the following questions:

2.2.1 Publication I:

1a) What percentage of individuals aged 65 to 71 years old have MM?

1b) Did prior exposure to early age hardship, during and after World War II (for individuals born between 1937 and 1950) influence the development of MM in individuals aged 65 to 71 years old?

1c) Which chronic diseases cluster together for the age group 65 to 71 years old?

2.2.2 Publication II:

2a) What percentage of individuals aged 65 years old and above were affected by MM?

2b) Which typical characteristics distinguish elderly adults with MM from those without MM in the KORA-Age database?

2c) What are the common patterns of multiple chronic disease combinations (stratified by sex), along with their respective mortality risks?

2d) How strong is the longitudinal relationship of MM and mortality in older Germans, stratified by sex?

2.3 Overview of the doctoral thesis

This cumulative Ph.D. thesis incorporates the following two scientific articles that have been published in reputable international journals:

1. *"Ava Arshadipour, Birgit Linkohr, Barbara Thorand, Karl-Heinz Ladwig, Margit Heier, Susanne Rospleszcz, and Annette Peters, Impact of prenatal and childhood adversity affects around World War II on MM: results from the KORA-Age study. BMC Geriatrics (2022) 22:115,"* *https://doi.org/10.1186/s12877-022-02793-2*
2. *"Ava Arshadipour,, Birgit Linkohr, Barbara Thorand, Margit Heier, Karl-Heinz Ladwig and Annette Peters, MM patterns and mortality in older adults: Results from the KORA-Age study. Frontiers, Front. Nutr. (2023), 10:1146442,"* *https://doi: 10.3389/fnut.2023.1146442.*

Four years of research went into these two papers to address the above-mentioned questions.

2.4 Study design and population

The study was conducted based on the data from two population-based studies conducted under the name of KORA. KORA-Age was a subset of the KORA study focusing on individuals who were aged 65 years and older. KORA-Age1 (01.12.2008 to 06.11.2009) and KORA-Age3 (01.02.2016 to 07.10.2016) studies were the follow-up of the S1 till S4 studies conducted from 1984 until 2001 in southern Germany.

Publication I of this thesis was based on individuals who were 65 to 71 years old. 1920 participants came from the KORA-Age 1 (born between 1937 and 1943) and 1444 participants from the KORA-Age 3 (born between 1944 and 1950) (Figure 1).

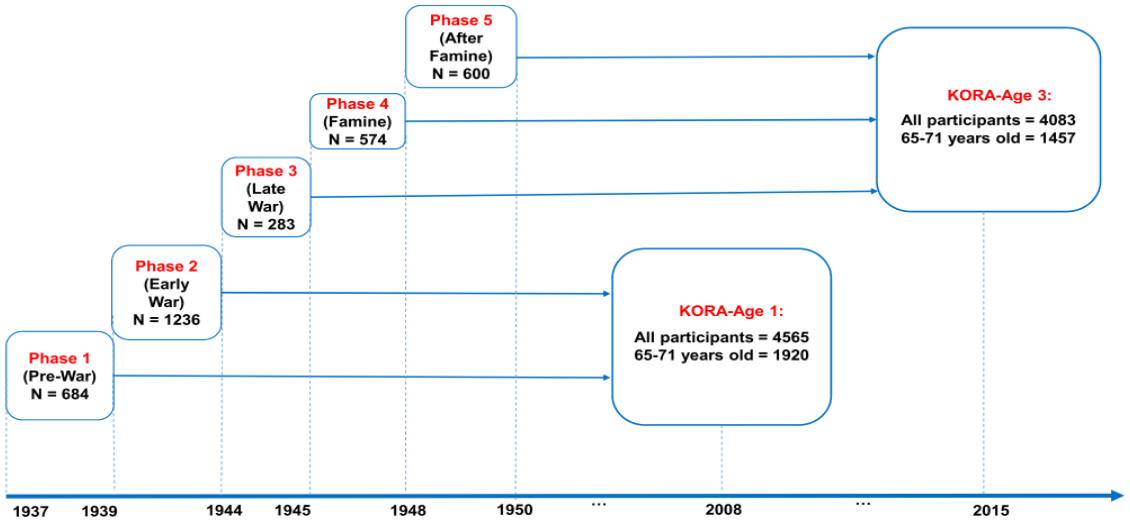

Figure. 1 Study design, Participant of the KORA-Age 1 and KORA-Age 3. Combined study population (*N*=3,377) and birth phases. 2008 and 2015 referred to the years for the age calculation in two studies. Phases were defined based on the participant's critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany [26].

Publication II was based on the health information of 4127 participants (2015 men and 2112 women) from KORA-Age 1 and the mortality status of these individuals was followed until 2016. The study was conducted under the Helsinki Declaration. KORA study has been approved by the "Bavarian Ethics Committee" (EC No. 08084). Additional information about the KORA-Age is available in other sources [27].

2.4.1 Exploratory variable

Sex, age, alcohol consumption, exercising, education, body mass index (BMI), smoking habit, and cognitive level are considered as covariates for analysis. More details about these exploratory variables definition and their values are presented in the publications in the method section.

2.4.2 Multimorbidity definition

MM is considered as the existence of at least two chronic diseases simultaneously in one individual [9]. Heart disease, stroke, eye disease, joint disease, liver diseases, gastrointestinal disease, diabetes, cancer, kidney diseases, lung disease, depression, neurological diseases, anxiety, and hypertension have been considered as important chronic diseases for the MM definition. These fourteen diseases were collected based on telephone interviews or questionnaires. More information about these diseases and their definition can be found in the method section of the publications.

2.4.3 Mortality assessment

All participants of the first arm, KORA-Age 1, followed for cause-related (cancer, cardiovascular, and other disease-related) mortality and all-cause mortality according to the death participants certificate. The death certificate was coded based on the "International Classification of Diseases (originally ICD-9, translated to ICD-10)". Follow-up median time of mortality was 6.7 years with 25% and 75% quartile of 7.07 and 6.74 years respectively. More details about all-cause mortality and cause-specific mortality can be found in publication II.

2.5 Statistical methods

In publication I, Chi-squared tests were used to check the differences between sex and birth phases of baseline characteristics. Odds ratios (OR) were used with multivariate logistic regression analysis while adjusting for potential confounder to check the association between MM and born phases during World War II. The unsupervised clustering machine learning approach was used to identify associated diseases as clusters. For the sensitivity analysis part, hypertension was excluded from MM definition and analysis performed without it. Moreover, other linkage methods in the clustering approach for clustering have been used for checking the robustness of the method. "Generalized Linear Mixed Models (GLMM)" have been used for checking the effect of the time point collection data in two different arms of the KORA-Age.

In publication II, Chi-squared and Wilcoxon rank-sum tests were used to check the association between mortality outcome variable and baseline characteristics. The Kaplan-Meier curve estimator displayed to show the survival function of individuals with and without MM. Moreover, using log-rank test the hypothesis of difference between two groups in death probability has been checked. "Cox Proportional-Hazards" analysis was used to calculate the hazard ratios (HR). These estimations were performed to assess the mortality risk associated with MM in both men and women.

Furthermore, the most common combinations of diseases, along with their associated HR were calculated. As part of sensitivity analyses, the Cox proportional models were performed with waist-to-hip ratio instead of BMI.

RStudio 2021.09.1 and R 4.1.2 used for analysis and all plots display (https://www.r-project.org). P-values < 0.05 were considered statistically significant test results.

2.6 Key findings publication I

2.6.1 Multimorbidity and chronic diseases prevalence

For adult participants aged 65 to 71 years old, the prevalence of MM was 49.4% and no significant difference in statistical prevalence between men (48.8%) and women (49.9%) was detected.

In general, hypertension, eye diseases, and cardiovascular diseases exhibited the highest occurrence rates among males and females, respectively. While women exhibited significantly higher rates of occurrence of joints, eye, anxiety and gastrointestinal diseases, men demonstrated a greater incidence of cardiovascular diseases, diabetes, and strokes.

2.6.2 Born in different phases of World War II and multimorbidity development

Individuals born in the period of late World War II in south Germany exhibited the highest MM prevalence compared to those born in other World War II periods. Furthermore, being born in various phases of the World War II demonstrated a significant statistical difference in the development of single chronic diseases and MM accordingly during age 65 to 71 among KORA-Age participants. More details about the odds ratios of MM and single chronic disease can be found in publication I.

Education level, alcohol consumption, BMI, smoking, and cognitive status had a significant association with birth in different phases of World War II.

2.6.3 Chronic disease clusters

Using the agglomerative hierarchical clustering method on fourteen chronic diseases, we found three main clusters of disease for individuals who were 65 to 71 years old. The first cluster included depression, anxiety, neurological and joint diseases. The second cluster consisted of hypertension, stroke, diabetes, and heart diseases. The third cluster is composed of gastrointestinal, kidney, lung, and liver diseases.

The scientific contribution of publication I is summarized in Box 1.

- For all individuals aged 65 to 71 years old, no significant difference in MM prevalence has been specified.

- Early year life hardship during the late World War II phase significantly increased the MM risk at age 65 to 71 years old.
- For the age group 65 to 71 years old, hypertension, eye diseases, and heart diseases were the most prevalent chronic diseases in both sexes.
- The most prevalent chronic diseases among women aged 65 to 71 were joint, eye, gastrointestinal disease, and anxiety. However, within the same age range, males exhibited higher prevalence of heart disease, diabetes, and stroke.
- Three primary clusters of chronic diseases have been identified for this age group.

2.7 Key findings publication II

2.7.1 Multimorbidity and all-cause mortality association

In both sexes, individuals without MM had greater survival probabilities in comparison to those with MM. Furthermore, MM exhibited a significant positive association with all-cause mortality in both men and women.

2.7.2 Multimorbidity and cause-related mortality association

The risk of cardiovascular-related mortality was found to be 83% higher among men with MM compared to those without MM, while in women, this risk was elevated by 27%. The risk of mortality due to cancer was 66% higher in men with MM compared to those without MM. Likewise, in women, individuals with MM had a 76% higher risk of cancer-related mortality compared to those without MM. Additional information regarding hazard ratios for cause-specific mortality is available in publication II.

2.7.3 The most common diseases combination and their associated mortality

Hypertension, heart, eye, diabetes, lung, joint, and anxiety were the most common diseases in both sexes. In terms of the most frequently occurring combinations of diseases, men displayed pairs such as hypertension-heart disease, hypertension-eye disease, hypertension-diabetes, eye-heart disease, and hypertension-joint disease. In contrast, women exhibited pairs including hypertension-heart disease, hypertension-eye disease, hypertension-diabetes, hypertension-joint disease, and eye-heart disease. More

details about HR and confidence intervals associated with these common combinations can be found in publication II.

The scientific contribution of publication II is summarized in Box 2.

- Participants with MM had a significantly less probability of survival in both sexes compared with those without MM.
- MM can significantly increase the mortality risk in all participants older than 65 years old for both sexes.
- Cardiovascular-related death risk was significantly higher for participants with MM in comparison with those without MM in men, however it was not significant in women.
- Individuals with MM had significantly higher cancer-related mortality risk in both sexes.
- Hypertension, heart, lung, diabetes, and joint disease were specified as prevalent diseases in 65 years old and older individuals.
- Different disease clusters can present different amounts of mortality risk in men and women.

2.8 Strengths and limitations

This study encompasses several strengths and limitations.

2.8.1 Strengths

This thesis has some strengths. First, two KORA-Age cohort studies were high-quality population-based samples. They were performed in 2008 and 2015 and consisted of individuals aged 65 and above who were born before, during and after World War II. These two informative similar samples facilitated the examination of MM development across various cohorts. We were able to conduct a longitudinal study to look at the impact of MM on mortality while adjusting for sociodemographic characteristics because KORA in 2015 was a follow-up of KORA in 2008. We were able to reduce the population bias thanks to this. Additionally, the large sample size gave us the power to study the interactions between MM and other factors like age and BMI. Another strength is that the same interview tools were used in both cross-sectional KORA-Age investigations, reducing the likelihood of biased results [28]. The large sample size helped us to explore the common disease combination and their corresponding mortality risks.

2.8.2 Limitations

Our study also had some limitations. While reporting the height and weight by individuals was more practical, it may potentially lead to an underestimation of the actual BMI values. Participants often report lower weights, which can result in a significant discrepancy between the reported BMI and the actual value. This phenomenon may be susceptible to recall bias [29]. Another possible study limitation is the reliance on disease information obtained through telephone interviews and questionnaires. This methodology might introduce information and recall biases, particularly among old individuals with severe health disease. Additionally, we lacked information regarding the chronological order of disease occurrence within individuals, which could have provided a more precise interpretation of the findings. Moreover, our research did not account for the severity of each disease or include geriatric syndromes such as functional decline, frailty, pressure ulcers, incontinence, delirium, or falls, which could have added valuable insights to our analysis. In addition, it's worth noting that the prevalence of most diseases was a bit low within the KORA-Age participants. This could potentially account for the absence of a significant association between certain diseases and their combination and the mortality risk and this can result in low power. Moreover, for the analysis of childhood adversity, we only relied on the birth year of individuals. Specifically, we lacked information pertaining to factors such as maternal health, birth weight, childhood diet, parent-child separation, exposure to adversity, and other variables that could potentially contribute to the development of MM.

2.9 Outlook of doctoral thesis

This doctoral thesis investigated the importance of MM and its relationship with mortality in older adults, utilizing evidence from epidemiological studies. The two publications included in this thesis shed light on the MM prevalence, corresponding influential factors, and its impact on mortality in individuals aged 65 and older. Considering the findings of these two publications, it can be concluded that MM poses a substantial burden on older adults, influencing both their health status and mortality outcomes. The results emphasize the need for healthcare professionals and policymakers to recognize the significance of MM and its impact on older individuals well-being. Looking ahead, future studies should be directed towards investigating the hidden structures that establish connections between prenatal and childhood adversity to increased MM prevalence in older adults. Additionally, further exploration is needed to specify the causal association of MM and

mortality, as well as to identify preventive strategies to mitigate the burden of MM and its associated mortality risks in older populations. More longitudinal studies should be conducted to provide more robust evidence in vulnerable populations, such as older individuals with MM.

In conclusion, this doctoral thesis contributes to the understanding of MM and its implications for mortality in older adults. Healthcare professionals should consider MM as a crucial factor when assessing the health status and mortality risk of older patients. Efforts should be made to incorporate routine risk assessment of MM within existing multidisciplinary healthcare services. With a global aging population and the subsequent events, it is essential to prioritize interventions that maximize the quality of life for the elderly population, with particular attention given to MM management.

3. Publications

3.1 Publication I

Arshadipour et al. BMC Geriatrics (2022) 22:115
https://doi.org/10.1186/s12877-022-02793-2

BMC Geriatrics

RESEARCH Open Access

Impact of prenatal and childhood adversity effects around World War II on multimorbidity: results from the KORA-Age study

Ava Arshadipour[1,2*], Barbara Thorand[1,3], Birgit Linkohr[1], Susanne Rospleszcz[1,2], Karl-Heinz Ladwig[1,4], Margit Heier[1,5] and Annette Peters[1,2,3,6]

Abstract

Background: While risk factors for age-related diseases may increase multimorbidity (MM), early life deprivation may also accelerate the development of chronic diseases and MM.

Methods: This study explores the prevalence and pattern of MM in 65–71 year-old individuals born before, during, and after World War II in Southern Germany based on two large cross-sectional KORA (Cooperative Health Research in the Region of Augsburg) -Age studies in 2008/9 and 2016. MM was defined as having at least two chronic diseases, and birth periods were classified into five phases: pre-war, early war, late war, famine, and after the famine period. Logistic regression models were used to analyze the effect of the birth phases on MM with adjustment for sociodemographic and lifestyle risk factors. Furthermore, we used agglomerative hierarchical clustering to investigate the co-occurrence of diseases.

Results: Participants born during the late war phase had the highest prevalence of MM (62.2%) and single chronic diseases compared to participants born during the other phases. Being born in the late war phase was significantly associated with a higher odds of MM (OR = 1.83, 95% CI: 1.15–2.91) after adjustment for sociodemographic and lifestyle factors. In women, the prevalence of joint, gastrointestinal, eye diseases, and anxiety was higher, while heart disease, stroke, and diabetes were more common in men. Moreover, three main chronic disease clusters responsible for the observed associations were identified as: joint and psychosomatic, cardiometabolic and, other internal organ diseases.

Conclusions: Our findings imply that adverse early-life exposure may increase the risk of MM in adults aged 65–71 years. Moreover, identified disease clusters are not coincidental and require more investigation.

Keywords: Chronic disease, Multimorbidity, Geriatrics, Logistic regression, Machine learning, Agglomerative hierarchical clustering

Introduction

Parallel to the worldwide increase in life expectancy in the last decades, the prevalence of age-related chronic diseases has also risen. Consequently, multimorbidity (MM), defined as the presence of at least two chronic diseases has become increasingly prevalent especially

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among older adults. MM is a major concern in the health care system since it can result in reduced quality of life, increased mortality, disability, and higher health care costs [1].

Based on a systematic literature review of 41 articles from different countries, the prevalence of MM ranges from 55 to 98% in those aged ≥ 65 years [2]. In Germany, based on the cross-sectional national telephone health interview survey "German Health Update" (GEDA 2012–2013), the MM prevalence ranged from 61.7% (95% CI: 59.3 -64.1) for 60 to 69 year-old to 72.9% (95% CI: 70.4–75.2) for 70 to 79 year-old individuals [3]. Others reported a 62% MM prevalence for those aged ≥ 65 years in the German population [4]. In Augsburg, MM prevalence was 58.6% for individuals aged 65–94 years based on the KORA-Age 1 data in 2008/9 [5]. Various studies have assessed the association of MM with sociodemographic and lifestyle factors, which indicated MM has been mainly associated with age, sex, educational level, income, physical activity, smoking, and alcohol consumption [6, 7].

The potential clustering of chronic diseases is in particular relevant for prevention, diagnosis, and treatment. Various studies have explored different approaches to determine the co-occurrence of chronic diseases, such as analyzing the prevalence of specific disease combinations, network analysis, factor analysis, and multiple correspondence analysis [8]. Kirchberger et al. [5] used factor analysis based on the Tetrachoric correlation matrix for 4127 persons. They identified four main comorbidity patterns: metabolic/cardiovascular diseases, liver/lung/joint/eye diseases, anxiety/depression/neurological diseases, and cancer/gastrointestinal problems. To specify the chronic diseases clustering, only a few studies to date used clustering as an unsupervised machine learning algorithm, which has some advantages: No initial assumption on data distribution, the number of clusters or cluster structure is needed in most algorithms and the results are very informative by using dendrograms for visualization [8].

Childhood adversity and malnutrition have been identified in studies as a possible source of chronic disease risk and then MM in later life [9]. In addition, socioeconomic hardship and traumatic events such as abuse and neglect during early life stages can contribute to chronic diseases progression [10, 11]. Regarding the early life experience, it is also worth noting that there were widespread food shortages during World War II, especially in the Soviet Union, India, China, Java, Vietnam, Greece, Austria, and The Netherlands. However, in Germany, food shortages mainly occurred at the end of World War II due to the destruction of agricultural land, livestock, machinery, and labor shortages. In Germany, adults aged 65–71 years who born or were in their crucial developmental age during the famine period and the early reconstruction after World War II had increased risk of health deficit accumulation including chronic diseases, disability and frailty. The average energy consumption per person in Germany decreased from about 2500 cal in 1944 to 1050–1250 cal in 1946, and after June 1948, it increased to 1800 cal again due to the currency reform [12]. Since aged adults in our sample born in Germany from 1937 to 1950 were exposed to this crucial period in their early phases of life, it offers the opportunity to study how the adversity of Word War II affected the prevalence of MM and chronic diseases later in life.

Therefore, we aimed to determine the effect of adverse developmental age situations on MM development and single chronic diseases in older individuals aged 65–71 years. In addition, we explored the pattern of chronic diseases to specify the clusters of these chronic diseases for this age group.

Methods

Data collection and study sample

Data originated from two population-based cross-sectional KORA-Age study arms: KORA-Age 1 conducted from 01.12.2008 to 06.11.2009 and KORA-Age 3 conducted from 01.02.2016 to 07.10.2016, which are follow-ups of four independent cross-sectional studies (S1 1984/5, S2 1989/90, S3 1994/5, and S4 1999- 2001). Both studies focused on the health of participants aged 65 and older in Augsburg and the two adjacent regions in Southern Germany based on questionnaires and telephone interviews. The KORA-Age study is described in detail elsewhere [13]. In short, 4,565 out of 5991 eligible individuals (response rate: 76.2%) participated in the KORA-Age 1 survey, and 1920 were between 65 and 71 years old on 31.12.2008 (born between 1937–1943). The KORA-Age 3 survey consisted of 4,083 out of 6051 eligible individuals (response rate: 67.5%), of whom 1444 participants were in the same age range on 31.12.2015 (born between 1944–1950). The present analysis combines these two similar KORA-Age study arms, which were completely independent because of the different birth years of the participants (Fig. 1).

Exposure: birth phases

Since malnutrition during pregnancy and early childhood can have a negative impact on metabolism, growth and development of chronic diseases later in life [9], the exposure variable was defined based on the participants' crucial developmental age during prenatal gestation or the first two years of life. Based on the World War II situation and the famine period which occurred afterwards roughly until June 1948 in Germany, individuals

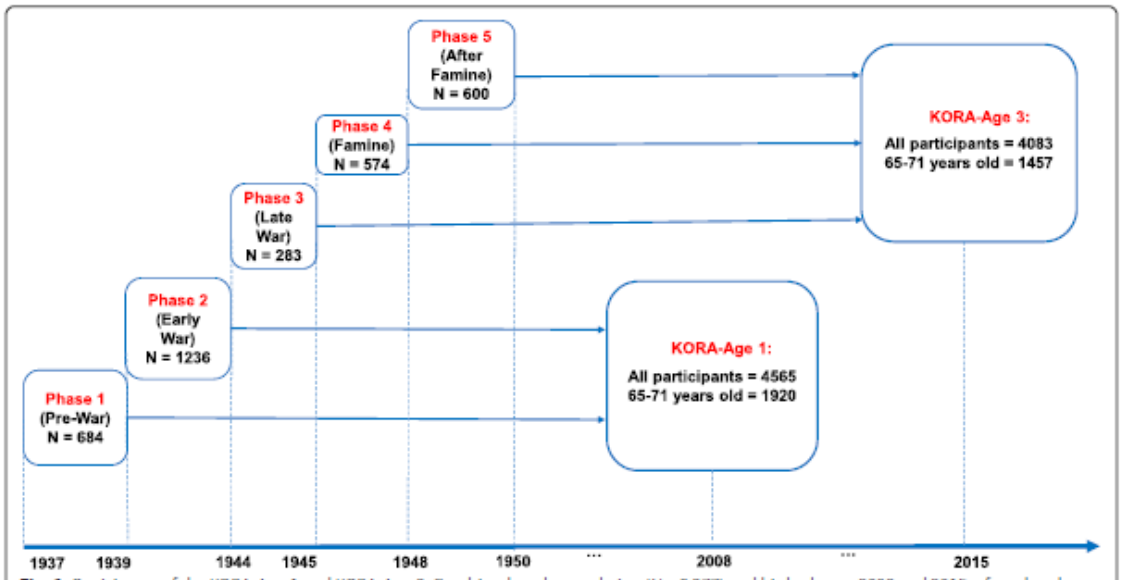

Fig. 1 Participants of the KORA-Age 1 and KORA-Age 3. Combined study population ($N = 3,377$) and birth phases. 2008 and 2015 referred to the years for the age calculation in two studies. Phases were defined based on participants critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany

were divided into five independent birth phases: pre-war (January 1937-August 1939), early war (September 1939-December 1943), late war (January 1944-April 1945), famine period after the war (May 1945- Jun 1948) and after famine period and reconstruction (July 1948-Dec 1950) [12].

Outcome: multimorbidity

The primary outcome was MM, defined as the presence of two or more concomitant chronic diseases in individuals [5]. We considered fourteen major chronic diseases, including hypertension, eye disease, heart diseases, diabetes, joint disease, lung disease, gastrointestinal disease, stroke, cancer, kidney diseases, liver diseases, neurological diseases, depression, and anxiety. All disease variables were defined as life-time diagnoses except for cancer diagnosed within the last three years. Hypertension, diabetes, cancer, stroke, heart diseases (myocardial infarction and coronary artery disease) were assessed based on the questionnaire. All other diseases were identified in a telephone interview based on the Charlson Comorbidity Index [14]. Participants were asked whether they suffer from kidney, liver, lung diseases (e.g., asthma, chronic bronchitis, and emphysema), inflammatory joint problems (e.g., arthritis or rheumatism), gastrointestinal diseases (e.g., colitis, cholecystic, gastric, or ulcer), heart diseases (e.g., congestive heart failure, coronary heart failure, or angina), eye problem (e.g., cataract, retinitis pigmentosa, glaucoma, macular degeneration, diabetic retinopathy). Neurological diseases were evaluated based on diseases like epilepsy, Parkinson's, or sclerosis using telephone interviews. The Geriatric Depression Scale [15] and Generalized Anxiety Disorder Scale-7 [16] were used to diagnose depression and anxiety. Individuals with scores ≥ 10 were defined as suffering from depression or anxiety.

Explanatory variables

We considered age, sex, education level, alcohol consumption, physical activity, body mass index (BMI), smoking behavior, and cognitive status as covariates. Education levels were based on the duration of education and vocational training and categorized into three groups: low (9 years or less), middle (10 or 11 years), and high (12 years or more). Body mass index (BMI), defined by the World Health Organization (WHO), was used. Participants were categorized as underweight or normal weight ($BMI < 24.99$ kg/m^2), overweight ($25 \leq BMI \leq 29.99$), obese class I ($30 \leq BMI < 34.99$), and obese class II or III ($35 \leq BMI$) [17].

Leisure time physical activity was measured from two separate questions about leisure time sports activity in winter and summer, including cycling. Possible answers were (1) > 2 h, (2) 1–2 h, (3) < 1 h and (4) none. Participants, who had a total score less than 5, obtained

by summing the numbers (1)–(4) relating to activities in winter and summer, were classified to be "physically active" [18].

Alcohol consumption was based on self-reported alcohol intake with the following five groups: "almost every day", "several times a week", "about once a week", "less than once a week", and "never or seldom" [19]. For our analysis, we categorized the first two groups as "daily use" and the last two as "never or rare use." Based on self-reported information, there are three categories for smoking status: never smokers, former smokers, and active smokers. The cognitive status is identified as dementia, mildly impaired cognitive status, and normal status based on TICS-M (Telephone Interview for Cognitive Status) score, a standard instrument for assessing cognitive impairment [20].

Statistical analysis

The frequency and prevalence of baseline characteristics were stratified by sex and birth phases, and the Chi-squared test was computed to check the differences. Overall, the stratified prevalence of MM and single diseases was calculated and tested by the Chi-squared test. Then Post-hoc tests with Bonferroni adjustment were performed for multiple comparisons. Covariates multi-collinearity was assessed using the variance inflation factors (VIF). Associations between the birth phases and MM were estimated by odds ratios (OR) in logistic regression models with different adjustment steps for risk factors. We used a standardized age variable (calculated as age minus mean age divided by the standard deviation of age) in our models because of different age distributions in the different birth phases. The modeling process started with the standardized age variable as covariate only (model 1), then birth period only (model 2), standardized age (rescaled with mean and standard deviation) and birth period together (model 3), then sex, education, alcohol use, physical activity, BMI, smoking behavior and cognitive status were added to the final model (models 4). The interaction effect of sex and birth phase variable was also checked in the final model. Agglomerative hierarchical clustering approach as an unsupervised machine learning technique was carried out to identify disease clusters so that diseases in one cluster are more similar than diseases in other clusters. This bottom-up algorithm begins with each disease as an individual cluster and merges the similar clusters until remaining only one cluster based on the proximity distance matrix. The average linkage method as proximity distance and Yule Q coefficient as similarity measurement for the binary disease variables were considered. The final cluster selection was created based on the threshold (cut-off height), corresponding to subject information, prior research, and clinical significance.

Since there is a big difference between the prevalence of hypertension and other chronic diseases, regression models and cluster analysis were performed without hypertension as a sensitivity analysis. Furthermore, the Ward and Single linkage methods, as other possible determinants for the pairwise distance between the set of observations were used to determine the robustness of agglomerative hierarchical clustering [8]. As our analysis was based on the combination of two very similar KORA-Age studies conducted in 2008/9 and 2016, we examined the effect of study period in another sensitivity analysis:. To see if the differences across phases are indeed due to differences in phases rather than a study effect, we used the generalized linear mixed models (GLMM) and created two GLMMs, one with a phase variable as a random effect only and one with a phase variable as a random effect nested in the study variable.

Results

Study population characteristics

The final sample consisted of 3377 participants aged 65 to 71 years (Fig. 1). From this population, 684 persons (52.2% female) were born during the pre-war, 1236 persons (50.8% female) in the early war, 283 persons (51.9% female) in the late war, 574 persons (53.5% female) in the famine period, and 600 persons (53.7% female) after the famine phase.

The overall baseline characteristics of the participants and their stratification by each phase are displayed in Table 1. Men were more likely to have a high educational level (45.0% versus 19.7%, $p<0.001$), drink alcohol daily (65.1% versus 29.8%, $p<0.001$), have pre-obesity (52.1% versus 38.9%, $p<0.001$) or obesity class I (20.4% versus 17.0%, $p<0.001$), be a former smoker (57.5% versus 32.2%, $p<0.001$) and have a slightly impaired cognitive status (8.7% versus 4.8%, $p<0.001$) compared with women.

Educational levels increased over time with the lowest level of high education for people born before the war (26% high education) and higher levels later (37% high education in after famine). Individuals born during and after the famine had a lower percentage (41.0% and 41.5%, $p<0.001$) of pre-obesity compared to the other phases. Participants born after the famine were more likely (15.0%) to be active smokers than people born before. Individuals born during the late war phase had a higher percentage of mildly impaired (8.1%) and impaired cognitive (2.8%) status compared with other phases (Table 1).

Table 1 Descriptive statistics percentages stratified by sex and birth phases for the whole participants (n = 3,377) from KORA-Age 1 and KORA-Age 3

Characteristic		Total (*N* = 3,377)	Sex			Birth phases					
			Male (*N* = 1,616)	Female (*N* = 1,761)	*P*-value	Pre-war (*N* = 684)	Early war (*N* = 1,236)	Late war (*N* = 283)	Famine (*N* = 574)	After famine (*N* = 600)	*P*-value
Sex	Male	47.8				47.8	49.2	48.1	46.5	46.3	0.76
	Female	52.2				52.2	50.8	51.9	53.5	53.7	
Age mean (SD)	MM = yes	68.1 (1.9)	68.1 (2.0)	68.2 (1.9)	0.325	70.1 (0.8)	66.9 (1.3)	70.7 (0.42)	68.5 (0.9)	65.9 (0.7)	0.750
	MM = no	67.7 (1.9)	67.7 (1.9)	67.7 (1.9)	0.364	70.1 (0.7)	66.8 (1.2)	70.7 (0.4)	68.5 (0.9)	65.8 (0.7)	0.734
Education	Low	10.2	3.2	16.6	< 0.001	16.5	11.6	5.6	5.4	6.7	< 0.001
	Middle	58.0	51.8	63.7		57.7	58.5	56.9	59.7	56.2	
	High	31.7	45.0	19.7		25.7	29.8	37.1	34.8	37.0	
Alcohol consumption	Never or rare use	38.5	20.9	53.8	< 0.001	38.6	37.1	38.2	40.9	36.7	0.038
	Once a week	15.1	13.9	16.3		12.4	15.1	20.5	13.7	17.2	
	Daily use	46.7	65.1	29.8		49.0	47.8	41.3	44.9	45.8	
Physical Activity	Active	66.8	69.2	64.6	0.005	64.5	66.6	63.6	67.1	71.3	0.072
	Inactive	33.2	30.8	35.4		35.5	33.3	36.4	32.7	28.7	
BMI	Underweight or normal weight	29.1	22.4	35.4	< 0.001	26.9	27.5	32.9	29.9	32.5	< 0.001
	Pre obese	45.2	52.1	38.9		48.2	47.1	46.2	41.0	41.5	
	Obese class I	18.6	20.4	17.0		19.9	19.6	12.0	19.3	17.5	
	Obesity class II or III	6.2	4.4	7.9		4.2	5.3	6.7	8.4	8.0	
Smoking behavior	Never	45.3	31.6	58	< 0.001	55.9	45.4	43.8	39.7	39.0	< 0.001
	Active smoker	10.3	10.9	9.8		7.3	10.1	10.6	9.4	15.0	
	Former smoker	44.3	57.5	32.2		36.8	44.3	45.6	50.9	46.0	
Cognitive status	Good	89.5	86.5	92.3	< 0.001	84.8	90.8	86.2	92.0	91.5	< 0.001
	Mildly impaired	6.6	8.7	4.8		10.0	5.6	8.1	5.2	5.7	
	Impaired	2.1	2.8	1.5		3.0	2.3	2.8	1.4	1.2	
Baseline Survey	S1	26.0	25.3	26.7	0.685	27.6	26.8	24.0	24.8	24.7	0.17
	S2	23.5	23.4	23.6		21.1	25.0	25.1	23.2	22.5	
	S3	25.8	25.7	25.8		28.9	24.9	26.1	24.0	25.5	
	S4	24.7	25.6	24.0		22.4	23.2	24.7	28.0	27.3	

Values represent % unless otherwise indicated. *P*-value from Chi-square test for categorical variables, from t-Test for comparing the mean of age variable and from ANOVA test for comparing the mean of multiple phases. Phases were defined based on participant's critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany

Prevalence of MM and single chronic diseases

MM prevalence was 49.4% in the total sample. There were no considerable differences in the prevalence of MM among men (48.8%) and women (49.9%) overall. MM prevalence was highest (62.2%) for individuals born during late war phase compared with the other phases (Table 2). In post hoc multiple comparisons, significant differences in MM prevalence were observed between late war and early war phase and between late war and after famine phase. There was no difference in MM between men and women (Fig. S1). Likewise, there were the same pattern in males and females and multiple comorbidities (Table S1). The prevalence of the chronic diseases stratified by sex and phases was presented in Table 2. Overall, hypertension (56.7%), eye diseases (25.6%), and heart diseases (18.9%) were the most prevalent diseases in both men and women. Although, women had significantly higher prevalence of joint (13.1% vs. 7.4%, $p<0.001$), gastrointestinal (9.1% vs. 6.7%, $p=0.01$), eye diseases (28.5% vs. 22.5%, $p<0.001$) and anxiety (7.8% vs. 3.4%, $p<0.001$), men had more heart diseases (23.0% vs. 15.1%, $p<0.001$), stroke (6.8% vs. 3.1%, $p<0.001$) and diabetes (17.1% vs. 12.9%, $p<0.001$). Furthermore, there was a significant difference in the prevalence of some single diseases according to the birth phases. For most diseases, the prevalence was highest among individuals born in late war (Table 2).

Association between birth phase and MM

In the age-adjusted logistic regression model, the odds ratio of MM in late war phase (OR = 1.69, 95% CI: 1.08–2.64) and famine phase (OR = 1.39, 95% CI: 1.04–1.87) were significantly higher compared to the reference after famine phase. After adjusting for other covariates (model 4), participants born in late war had a higher odds of MM compared with the individuals born in after famine phase (OR = 1.83, 95% CI: 1.15–2.91) (Table 3). We did not observe any significant interaction between sex and birth phase on the odds of MM (Fig. S1).

The pattern of comorbidity

Three main clusters of diseases were specified based on the agglomerative hierarchical clustering. The first cluster composed of joint and psychosomatic disorders consisted of anxiety, depression, joint and neurological diseases. The second cluster of cardio-metabolic diseases comprised of diabetes, hypertension, stroke, and heart diseases. The last one was the other internal organ diseases cluster, including the lung, gastrointestinal, kidney, and liver diseases (Fig. 2).

The number and percent of multimorbid individuals for each cluster were calculated by dividing the number of individuals who had at least two of these diseases in the cluster by the total number of multimorbid patients. In total, 1002 of the 1667 participants with MM could be assigned to at least one cluster. A high percentage (49.1%) of multimorbid participants were assigned to the cardiometabolic cluster. The other internal organ cluster had a similar prevalence in terms of sex and different phases of the birth period; however, the joint and psychosomatic diseases cluster had a more significant prevalence in women (6.4%) and pre-war phase (7.0%) and early war phase (6.1%) of birth years. Moreover, men (57.9%) and participants born in pre-war (52.7%) and late war (52.8%) had a significantly higher prevalence in the cardiometabolic disease cluster (Table 4).

Sensitivity analysis

We repeated the analysis without hypertension for MM and the findings were close to the previous model analysis including hypertension overall. Late war Phase still had the highest MM odds ratio (OR = 2.14, 95% CI: 1.29–3.52). Moreover, pre-war phase (OR = 1.64, 95% CI: 1.07–2.49) and famine phase (OR = 1.52, 95% CI: 1.08–2.14) had a bit higher odds than hypertension consideration, and they were significant (Table S2). When results from GLMM with a phase variable as random effect were compared to results from a logistic regression model with a phase variable as fixed effect, there was no significant difference in the covariates effect estimate. Moreover, considering a phase variable nested in the study did not significantly improve the model compared to considering phase as random effect only (Table S3).

Hierarchical clustering was also performed without hypertension, and the three major clusters remained as before (Fig. S5). The dendrograms of chronic diseases association based on the Single and Ward linkage approaches were also very close to the average method. The number of main clusters and included diseases also remained stable (Fig. S6, S7).

Discussion

Multimorbidity

In our study, the overall prevalence of MM was 49.4% for adults aged 65–71 years-old. The comparison of the prevalence of MM between studies is hampered by differences in the examined age groups, including diseases and study areas, even in Germany [3]. While there was no difference between men and women in the MM prevalence in the present study like in other studies [4, 7], others observed a higher prevalence in women [21]. Although men had a higher prevalence of diabetes, heart disease, and stroke relative to women, the prevalence of joint, gastrointestinal, and eye diseases and anxiety was more remarkable for women in the present study.

Table 2 Number and percentage of single diseases and multimorbidity stratified by sex and birth phases for the whole participants ($n = 3,377$) from KORA-Age 1 and KORA-Age 3

Disease	Total (3,377)	Sex			Birth phases				
		Male (1,616)	Female (1,761)	P-value	Pre-war (684)	Early war (1,236)	Late war (283)	Famine (574)	After famine (600)	P-value
Multimorbidity (MM)	1667 (49.4%)	788 (48.8%)	879 (49.9%)	0.503	370 (54.1%)	561 (45.4%)	176 (62.2%)	310 (54.0%)	250 (41.7%)	< 0.001
Lung	343 (10.2%)	157 (9.7%)	186 (10.6%)	0.415	61 (8.9%)	109 (8.8%)	35 (12.4%)	71 (12.4%)	67 (11.2%)	0.065
Joint diseases(Arthritis Rheumatic)	349 (10.3%)	119 (7.4%)	230 (13.1%)	< 0.001	74 (10.8%)	138 (11.2%)	31 (11.0%)	52 (9.1%)	54 (9.0%)	< 0.001
Cancer	145 (4.3%)	74 (4.6%)	71 (4.0%)	0.433	25 (3.7%)	55 (4.4%)	13 (4.6%)	27 (4.7%)	25 (4.2%)	0.898
Gastrointestinal	270 (8%)	109 (6.7%)	161 (9.1%)	0.0101	61 (8.9%)	97 (7.8%)	21 (7.4%)	49 (8.5%)	42 (7.0%)	0.735
Heart diseases	637 (18.9%)	371 (23%)	266 (15.1%)	< 0.001	149 (21.8%)	216 (17.5%)	65 (23.0%)	121 (21.1%)	86 (14.3%)	< 0.001
Stroke	165 (4.9%)	110 (6.8%)	55 (3.1%)	< 0.001	34 (5.0%)	52 (4.2%)	27 (9.5%)	32 (5.6%)	20 (3.3%)	< 0.001
Kidney	117 (3.5%)	62 (3.8%)	55 (3.1%)	0.257	30 (4.4%)	34 (2.8%)	18 (6.4%)	24 (4.2%)	11 (1.8%)	0.002
Liver	82 (2.4%)	43 (2.7%)	39 (2.2%)	0.400	15 (2.2%)	29 (2.3%)	9 (3.2%)	15 (2.6%)	14 (2.3%)	0.913
Diabetes mellitus	504 (14.9%)	276 (17.1%)	228 (12.9%)	< 0.001	118 (17.3%)	165 (13.3%)	48 (17.0%)	95 (16.6%)	78 (13.0%)	0.056
Neurological disease	103 (3.1%)	51 (3.2%)	52 (3.0%)	0.731	22 (3.2%)	31 (2.5%)	10 (3.5%)	20 (3.5%)	20 (3.3%)	0.727
Hypertension	1914 (56.7%)	910 (56.3%)	1004 (57.0%)	0.626	396 (57.9%)	673 (54.4%)	179 (63.3%)	344 (59.9%)	322 (53.7%)	0.013
Eye disease	866 (25.6%)	364 (22.5%)	502 (28.5%)	< 0.001	202 (29.5%)	285 (23.1%)	103 (36.4%)	164 (28.6%)	112 (18.7%)	< 0.001
Anxiety	192 (5.7%)	55 (3.4%)	137 (7.8%)	< 0.001	55 (8.0%)	87 (7.0%)	9 (3.2%)	24 (4.2%)	17 (2.8%)	< 0.001
Depression	44 (1.3%)	16 (1.0%)	28 (1.6%)	0.131	12 (1.8%)	15 (1.2%)	3 (1.1%)	9 (1.6%)	5 (0.8%)	0.616

P-value from Chi-square test for categorical variables. Phases were defined based on participant's critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany

Table 3 Odds ratios and 95% confidence intervals for multimorbidity based on hierarchical logistic regression for the whole participants ($n = 3,377$) from KORA-Age 1 and KORA-Age 3

Characteristics		model 1	model 2	model 3	model 5
Standardized age		1.12 (1.08–1.16)		1.12 (0.98–1.29)	1.11 (0.96–1.27)
Birth phases (ref: After famine)	Pre-war		1.64 (1.32–2.05)	1.26 (0.88–1.82)	1.35 (0.92–1.98)
	Early war		1.16 (0.95–1.41)	1.09 (0.88–1.34)	1.08 (0.87–1.34)
	Late war		2.3 (1.72–3.07)	1.69 (1.08–2.64)	1.83 (1.15–2.91)
	Famine		1.64 (1.30–2.07)	1.39 (1.04–1.87)	1.35 (0.99–1.84)
Female (ref: male)					0.98 (0.83–1.16)
Education (ref: low)	Middle				0.82 (0.63–1.05)
	High				0.72 (0.55–0.95)
Alcohol consumption (ref: never or rare use)	Once a week				0.99 (0.81–1.20)
	Daily use				0.76 (0.64–0.91)
Physical Activity (active)	Inactive				1.47 (1.26–1.72)
BMI (ref: underweight or normal)	Overweight				1.32 (1.11–1.57)
	Obesity class I				1.92 (1.55–2.38)
	Obesity class II or III				3.09 (2.21–4.33)
Smoking behavior (ref: never smoker)	Active smoker				1.34 (1.05–1.72)
	Ex-smoker				1.36 (1.16–1.59)
Cognitive status (ref: good)	Mildly impaired				1.43 (1.07–1.92)
	Impaired				1.32 (0.81–2.18)
AIC		4638.4	4639.0	4637.8	4373.6

Phases were defined based on participant's critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany

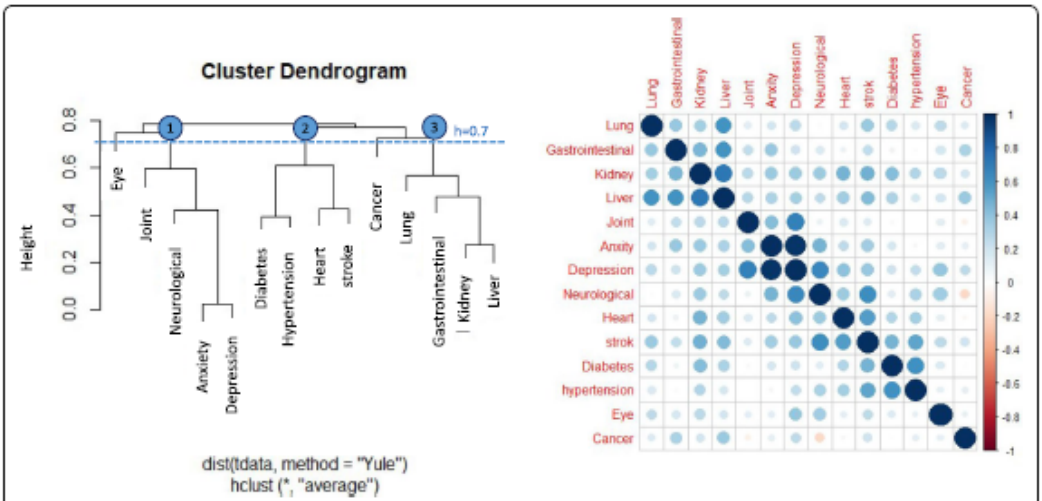

Fig. 2 *Left:* Dendrogram based on the hierarchical clustering of chronic diseases using the average linkage method and Yule-Q coefficient. The threshold (dotted line, h=0.7) was used to specify three main clusters for all participants; *Right:* Correlation matrix of chronic diseases based on Yule coefficient. Three red squared lines shows three main clusters on the matrix

Multimorbidity according to birth phases

The prevalence of MM and every single chronic disease was higher in late war phase. Since it is well known that MM and chronic diseases increase with increasing age [2], differences in the unadjusted prevalence could be biased by differences in the age distribution between birth

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Table 4 Number and percent of individuals with multimorbidity (i.e. at least two diseases) in each cluster

Cluster	Total (1,667)	Sex			Birth phases					
		Male (788)	Female (879)	*P*-value	Pre-war (370)	Early war (561)	Late war (176)	Famine (310)	After famine (250)	*P*-value
Joint. Neuro. Anxiety. Depression	78 (4.7%)	22 (2.8%)	56 (6.4%)	< 0.001	26 (7%)	34 (6.1%)	2 (1.1%)	9 (2.9%)	7 (2.8%)	0.002
Heart. Stroke. Diabetes. Hypertension	818 (49.1%)	456 (57.9%)	362 (41.2%)	< 0.001	195 (52.7%)	258 (46%)	93 (52.8%)	156 (50.3%)	116 (46.4%)	< 0.001
Lung. Gastro. Kidney. Liver	106 (6.4%)	44 (5.6%)	62 (7.1%)	0.218	20 (5.4%)	31 (5.5%)	17 (9.7%)	19 (6.1%)	19 (7.6%)	0.051

P-value from Chi-square test for categorical variables. Phases were defined based on participant's critical developmental age (prenatal gestation or the first two years of life) and the World War II situation in Germany

phases. Therefore, we also assessed the impact of the birth phase on MM in logistic regression models adjusted for age and other sociodemographic and lifestyle factors. We found that the OR of MM was significantly higher in late war compared with after famine, even after adjusting for these potential confounders. This effect could be explained by the unfavorable living conditions which were observed in the late war phase in South Germany. Large parts of the city of Augsburg were devastated during the most extensive bombing raid at the end of February 1944 [22]. Participants born during the last years of war were thus exposed to food crises and famine in Germany in 1945 during early life stages [12]. In this context, it has previously been shown that maternal and early-life malnutrition can negatively affect adults mental and physical health [23]. Individuals with low birthweight could have negative outcomes later in life. They might have poorer cognitive performance, higher blood pressure, decreased glucose tolerance, poorer functionality in lung, kidney and immune system, more diseases like coronary heart disease, chronic lung and kidney disease, diabetes and higher cardiovascular and all-cause mortality [9].

Moreover, an increased chronic health disease incidence was identified for aged individuals (born 1922–1960 in former West Germany) exposed to war during their utero and childhood [24]. These findings are important as they indicate that besides well-established risk factors in adult life, the birth phases and the living conditions during the World War II still are of concern today. Therefore, health service measures as well as individual treatment efforts may specifically need to pay attention to both men and women born between 1944 to 1945.

Clusters of chronic diseases

We identified three major clusters with the clustering approach to recognize individuals with similar MM diseases. The other internal organ cluster included illnesses involving main body organs, such as the stomach and intestines, kidneys, liver, and lung, which indicated the same co-occurrence in men and women and individuals born in different phases. Association among the lung, liver, and gastrointestinal diseases is consistent with Rodriguez-Roisin et al. [25] in adult patients based on the possible shared mechanisms. This coexistence might increase vascular diseases, such as portopulmonary hypertension and hepatopulmonary syndrome, and other chronic respiratory diseases coexisting with chronic hepatic diseases. Still, more research is warranted to corroborate our understanding of the underlying mechanisms for this cluster.

We verified the association between joint diseases and psychosomatic disorders within the second cluster, more prevalent in women. Previous studies have established links between rheumatoid arthritis, mood disturbances, and neurological diseases [26, 27]. Lee et al. [26] observed the coexistence of Parkinson's disease and rheumatics. Lwin et al. [27] also observed that depression was twice as prevalent in patients with rheumatoid arthritis as in the general population.

The cardiometabolic cluster had the highest proportion of co-occurrence of cardiovascular and metabolic diseases, typically found in aged people, and it was more prevalent in men. This relationship also has been widely illustrated in prior populations [5, 28]. Sowers et al. [28] showed that hypertension prevalence was twice as high in people with diabetes than those without diabetes. Also, individuals with hypertension experienced diabetes more frequently than persons with normal blood pressure. They also reported that hypertension could be responsible for up to 75% of CVD in diabetes.

Strengths and weaknesses

One of our analysis strengths is that it was based on two large data sets from the KORA cohort study [13] with individuals born around World War II. This enabled us to analyze comorbidity and MM in different birth phases. The information also came from the specific age range of individuals from two KORA-Age studies that provided uniformity in data, which is essential for exploring disease patterns. This huge database also contained information about demographic, sociodemographic, physical, and mental health factors, which helped adjust a wide range of factors associated with MM. Another strength is that both cross-sectional KORA-Age studies used the same instruments in the interview; thus the data is less likely to be biased [29]. The clustering method helped discover disease comorbidity clusters that define specific risk domains and assign individuals to subgroups with common characteristics and risks. Furthermore, using of Yule Q coefficient enabled us to measure the correlation among the binary chronic disease data.

Our study does not come without its limitations. Although using the self-reported weight and measured height in the baseline information was economical and straightforward, it might underestimate the real value for BMI. Individuals mostly tend to report less weight, then the real value for BMI goes far from the reported one which might be subject to recall bias [30]. Moreover, since chronic disease prevalence was mainly based on self-reported data, disease severity was not considered. Furthermore, we only used the birth year of individuals. We did not have any information about childhood diet, mother's health or exposure to adversity, birth weight, separation of the child from the parent, and others, which may determine MM later in life. Since we examined the

longitudinal association of birth phases with MM, we identified the temporal sequence between exposure and outcome, which might support a potential causal link. To preclude any cause and effect interpretation, other covariates were simultaneously used in model adjustment.

Moreover, although we used the standardized age variable in our models, we need to interpret our results cautiously since the prevalence and patterns of MM are influenced by age.

Conclusion

This research offers insight into differences in the MM prevalence for individuals aged 65–71 years born in different periods before, during, and after World War II. Adverse circumstances experienced during the late war period may have contributed to the higher MM prevalence in adult life. Moreover, our findings suggest three main disease clusters: i. Joint and psychosomatic diseases (joint, neurological, anxiety, depression); ii. Cardiometabolic diseases (heart, stroke, diabetes, hypertension); iii. Other internal organ diseases (lung, gastrointestinal, kidney, and liver). Although the adverse situation of World War II and famine may increase MM risk at retirement age, more comprehensive childhood and life course circumstances are required to explain long-term health consequences. Future research shall investigate potential interactions between risk factor profiles during adult life and adverse early life exposures on MM. Furthermore, our results on the diseases clustering focusing on three significant clusters of MM call for further investigation, specifically their association with genetic effects, environmental factors, and polypharmacy.

Abbreviations

MM: Multimorbidity; BMI: Body mass index; KORA: Cooperative Health Research in the Region of Augsburg.

Supplementary Information

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Additional file 1.

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Authors' contributions

Conceptualization: AA; Methodology: AA; Statistical Analyses: AA; Evaluation and Interpretation: AA, AP, BT, SR, BL; Original Paper Draft: AA; Revision and Editing: AA, AP, BT, SR, BL, MH, KHL; Main Study Design: AP, BL, MH; Data Curation and Quality Assurance: AP, BL, MH; Supervision: AP; All authors have read and approved the final manuscript.

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Availability of data and materials

Data is not openly available, and participants' data privacy is protected by data-protection standards established by the ethics committee of Bavarian Chamber of Physicians, Munich. However, data could be available upon request through a project agreement with KORA (http://epi.helmholtz-muenchen.de/koragen/) and the KORA Board approval.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Bavarian Medical Association has approved the KORA-Age study (08094). Written informed consent was obtained from all study participants according to the Helsinki Declaration.

Consent for publication

All of the study's participants gave their informed consent.

Competing interests

The authors declare that they have no competing interests.

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Multimorbidity patterns and mortality in older adults: Results from the KORA-Age study

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The coexistence of several chronic diseases is very common in older adults, making it crucial to understand multimorbidity (MM) patterns and associated mortality. We aimed to determine the prevalence of MM and common chronic disease combinations, as well as their impact on mortality in men and women aged 65years and older using the population-based KORA-Age study, based in South of Germany. The chronic disease status of the participants was determined in 2008/9, and mortality status was followed up until 2016. MM was defined as having at least two chronic diseases. We used Cox proportional hazard models to calculate the hazard ratios (HRs) and the 95% confidence intervals (CIs) for associations between MM and all-cause mortality. During the study period 495 men (24.6%) and 368 women (17.4%) died. Although the MM prevalence was almost the same in men (57.7%) and women (60.0%), the overall effect of MM on mortality was higher in men (HR: 1.81, 95% CI: 1.47–2.24) than in women (HR: 1.28, 95% CI: 1.01–1.64; *p*-value for interaction <0.001). The type of disease included in the MM patterns had a significant impact on mortality risk. For example, when both heart disease and diabetes were included in the combinations of two and three diseases, the mortality risk was highest. The risk of premature death does not only depend on the number of diseases but also on the specific disease combinations. In this study, life expectancy depended strongly on a few diseases, such as diabetes, hypertension, and heart disease.

KEYWORDS

chronic disease, multimorbidity, mortality, older people, sex differences, hazard ratios

1. Introduction

Even though life expectancy has increased in recent decades as a result of modern medicine, individuals are developing more chronic diseases, resulting in rising multimorbidity (MM) (1). According to the World Health Organization (WHO), MM has been defined as the occurrence of two or more chronic diseases in one person at the same time (2).

Based on a systematic literature review of 41 articles from different countries, the prevalence of MM ranges from 55 to 98% in those aged ≥65 years. In Germany, based on the cross-sectional national telephone health interview survey "German Health Update" (GEDA 2012–2013), the MM prevalence ranged from 61.7% (95% CI: 59.3–64.1) for 60 to 69-year-olds to 72.9% (95%

CI: 70.4–75.2) for 70 to 79-year-old individuals. Others reported a 62% MM prevalence for those aged ≥65 years in the German population. In Augsburg, MM prevalence was 58.6% for individuals aged 65–94 years based on the KORA-Age data in 2008/9 (3).

Investigating chronic illness combinations and their negative consequences on the old people and the health care system is a major concern in countries with growing aging populations nowadays. Many studies showed the association between MM and lower quality of life (4), higher health care use and cost (5), and functional decline in older adults (6).

Moreover, many studies have found a relationship between MM and an increased risk of mortality (7–12), but the value of mortality risk is not similar. One reason for these dissimilarities could be a low sample size in some studies, and another reason for the differences might be the included disease types, age groups, and risk factors (7–12).

To our knowledge, there exists only one recent study (13) in Germany exploring the association of MM patterns and mortality based on health insurance claims data. Therefore, we aimed to identify the prospective association of MM with all-cause mortality controlling for sociodemographic and lifestyle factors in men and women based on the large population-based KORA-Age study. Additionally, we specified the most prevalent combinations of disease in men and women, and their associated mortality risk.

2. Methods

2.1. Data collection and study design

The adult population-based KORA (Cooperative Health Research in the Region of Augsburg) study was conducted between 1984 and 2001 in the Region of Augsburg, Germany. In 2008/9, KORA participants who were aged 65-year-olds or older were invited for the first wave of a specific project on health in old age – the KORA-Age study. Details about the study design and data collection have been explained elsewhere (14). Briefly, 5.991 individuals from the KORA cohort who were still alive, had not moved outside the study area or had not withdrawn their consent to participate met the inclusion criteria born between 1915 and before 1944 (i.e., ≥65 years in 2009). 4,565 individuals returned a postal self-report questionnaire and 4,127 individuals (2015 men and 2,112 women) answered further questions in a 30 min standardized telephone interview. The questionnaire and interview items are based the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project of the World Health Organization or from validated instruments. For instance, the MM instruments chosen were from established questionnaires (15–17). The study was conducted by trained staff at the KORA study Center in Augsburg after an initial pilot phase. Mortality status was assessed until 2016 by official death certificates. 4,127 individuals with questionnaire and interview information were included in this analysis.

Abbreviations: MM, Multimorbidity; BMI, Body mass index; WHR, Waist to hip ratio; KORA, Cooperative Health Research in the Region of Augsburg; WHO, World Health Organization; IQR, Interquartile range; SD, Standard deviation.

2.2. Mortality

All participants of the first wave of the KORA-Age study were followed for all-cause and cause-specific (cardiovascular, cancer, and other disease-related) mortality using official death certificates, coded according to the International Classification of Diseases (ICD-10). Cardiovascular-related mortality consists of diseases of the circulatory system (ICD-9 codes 390–459, ICD-10 codes I00–I99) and sudden death with unknown cause (ICD-9 code 798, ICD-10 code R99). Cancer-related mortality consists of neoplasms (ICD-9 codes 140–208, ICD-10 codes C00–C95). Other disease-related mortality consists of the remaining causes of death, for example, pneumonia (ICD-9 code 486, ICD-10 codes J18.8, J18.9), chronic bronchitis (ICD-9 code 491, ICD-10 Codes J41, J42, J44) and dementias (ICD-9 code 290, ICD-10 Codes F03.90, F05, F01.50, F01.51) (18). Follow-up for participant's mortality status was performed until 07.10.2016 (median follow-up time: 6.97 years, interquartile range; IQR = 75th%–25th%: 7.07–6.74 years).

2.3. Multimorbidity and single chronic diseases

MM has been defined as the presence of two or more chronic diseases in one person simultaneously (2). We considered 14 major chronic diseases, including hypertension, eye disease, heart disease, diabetes, joint disease, lung disease, gastrointestinal disease, stroke, cancer, kidney diseases, liver diseases, neurological diseases, depression, and anxiety. Hypertension, diabetes, cancer (any cancer recognized within the last 3 years), stroke, and heart diseases (myocardial infarction and coronary artery disease) were assessed based on the self-report questionnaire (whether participant currently have disease). All other diseases were identified in a telephone interview based on the Charlson Comorbidity Index (15). Participants were asked whether they suffer from kidney, liver, lung diseases (e.g., asthma, chronic bronchitis, and emphysema), inflammatory joint problems (arthritis or rheumatism), gastrointestinal diseases (e.g., colitis, cholecystic, gastric, or ulcer), heart diseases (e.g., congestive heart failure, coronary heart failure, or angina), eye problems (e.g., cataract, retinitis pigmentosa, glaucoma, macular degeneration, diabetic retinopathy). Neurological diseases were evaluated based on self-reported diseases like epilepsy, Parkinson's disease, or multiple sclerosis. The Geriatric Depression Scale (16) and Generalized Anxiety Disorder Scale-7 (17) screening tools were used to diagnose depression and anxiety. Persons with scores >10 were defined as suffering from depression or anxiety.

2.4. Demographic and lifestyle measures

We considered age, family status, education level, alcohol consumption, physical activity, body mass index (BMI), and smoking behavior as covariates. Family status is a combination of the self-reported marital status and living alone or with a spouse/partner categorized in the two groups "living with a partner/spouse" and "living alone, divorced or widowed." The education level had three categories based on years of education and vocational training: low

level (9 years or less), middle (10 or 11 years), and high (12 years or more).

Alcohol consumption was based on self-reported alcohol intake with the following three groups: "Never, rare or former use," "once a week," or "daily use." Leisure time physical activity was measured from two separate questions about leisure time sports activity per week in winter and summer, including cycling. Possible answers were (1) >2 h, (2) 1–2 h, (3) <1 h, and (4) none. Participants, who had a total score of <5, obtained by summing the numbers (1)–(4) relating to activities in winter and summer, were classified to be "physically active" (19).

The BMI was computed by dividing weight in kilograms by square height in meters. Measurements of height and weight were made by trained investigators while wearing light clothes and without shoes. Based on self-reported information, there are three categories for smoking status: never smokers, former smokers, and active smokers.

2.5. Statistical analysis

We presented categorical data as percentages and continuous data as means (SD) if they were normally distributed or medians (IQR) if non-normally distributed in the descriptive analysis. To examine the differences between outcome groups (alive and dead), *t*-test for continuous variables and the Chi-squared test for categorical variables were performed. Kaplan–Meier curves and log-rank tests were presented graphically to compare the survival distributions of participants with and without MM.

Cox proportional-hazards models were used to investigate the associations between MM and specific combinations of disease with mortality by adjusting for age, education, family status, smoking habits, alcohol use, BMI, and physical activity. The combined model has been used to check the significance of sex differences and then the sex-specific models have been performed. The interaction effect of MM with age and BMI was also checked in the sex specific models. Moreover, the spline Cox proportional hazard model was used for examining the non-linear effect of BMI. The proportional hazard assumption was examined using Schoenfeld residuals. Additionally, the prevalence of every single disease in men and women was calculated. In order to check the patterns of disease combinations, all possible combinations of two and three diseases were identified and the most prevalent combinations were presented in men and women separately. Using those with no disease or just one disease as the reference group, the adjusted hazard ratios of these most common combinations were then calculated.

For sensitivity analysis, we adjusted the model examining the association between MM and mortality for waist-to-hip ratio instead of BMI. Additionally, we fitted the model without MM to check to which degree MM can explain the underlying association between risk factors and mortality. We also ran the model without BMI to evaluate how much BMI could confound the effect of MM on mortality. Statistical relationships were considered significant for *p*-values <0.05. All statistical analyses were performed using R 4.1.2 and RStudio 2021.09.1[1] and the "dplyr," "pspline," "survival" and "survminer" libraries for analysis has been used.

1 https://www.r-project.org

2.6. Ethics statement

The Ethics Committee of the Bavarian Medical Association has approved the KORA-Age study (08094). Written informed consent was obtained from all study participants according to the Helsinki Declaration.

3. Results

3.1. Study population characteristics

The prevalence of MM was 57.7 and 60.0% in men and women, respectively. Baseline characteristics of the 4,127 participants stratified by their mortality status are shown in Table 1. Out of 2015 male participants, 495 (24.5%) died (24.1% cancer related, 44.5% CVD-related and 31.4% other disease-related deaths). Out of 2,112 female participants, 368 (17.5%) died (23.1% cancer-related, 44.8% CVD-related, and 32.1% other disease-related deaths). There were statistically significant differences ($p < 0.001$) between those who survived and those who died for age, family status, education, alcohol use, physical activity, and MM status in both men and women (Table 1). Although associations of BMI and smoking habits with mortality were statistically significant in men, they were not significant in women. Individuals without MM had a significantly longer survival probability compared to those with MM in both men and women (Figure 1).

3.2. Association between multimorbidity and all-cause mortality

Based on a non-linear multivariable-adjusted model, MM status was significantly positively associated with all-cause mortality in men (HR: 1.81, 95% CI: 1.47–2.24) and women (HR: 1.28, 95% CI: 1.01–1.64; Table 2).

3.3. Risk factor profiles of all-cause mortality

Age, family status, educational attainment, physical activity, and smoking were significantly linked to increased mortality risk in males, whereas age, physical activity, and smoking were significantly linked to increased mortality risk in women (Table 2).

Since the interaction effect between age and MM was significant, we stratified our analysis by 5-year age groups.

Among men and women aged 65–79 years, MM was positively associated with all-cause mortality (Table 3; Figure 2). The interaction effect between MM and BMI was not significant, however; there were significant differences in survival probabilities of individuals with and without MM at different levels of BMI in men and women. Additionally, participants with higher BMI (BMI >25 kg/m^2) had a longer survival probability compared to lower BMI (BMI <=25 kg/m^2) both with and without MM (Figure 3). Based on the spline Cox proportional model, a curvilinear association between BMI and all-cause mortality was specified in men and women. The BMI value related to the highest mortality

TABLE 1 Baseline characteristics of the study participants were stratified by sex and mortality status.

Characteristics		Men			Women		
		Died=No	Died=Yes	Value of *p*	Died=No	Died=Yes	Value of *p*
N		1,520	495	...	1744	368	...
Age [mean (SD)]		71.85 (5.34)	77.45 (6.20)	< 0.001	72.3 (5.39)	78.3 (6.66)	<0.001
Multimorbidity (%)	Yes	799 (52.6)	364 (73.5)	< 0.001	993 (56.9)	274 (74.5)	<0.001
	No	721 (47.4)	131 (26.5)		751 (43.1)	94 (25.5)	
Family status (%)	Living alone, divorced, widowed	262 (17.2)	144 (29.1)	< 0.001	965 (55.3)	118 (32.1)	<0.001
	Living with a partner/ spouse	1,258 (82.8)	351 (70.9)		779 (44.7)	250 (67.9)	
Education (%)	Low (8–9 years)	85 (5.6)	52 (10.5)	< 0.001	466 (26.7)	138 (37.5)	< 0.001
	Medium (10–11 years)	800 (52.6)	292 (59.0)		1,012 (58.0)	182 (49.5)	
	High (12 or higher years)	635 (41.8)	151 (30.5)		266 (15.3)	48 (13.0)	
Alcohol (%)	Never, rare or former use	330 (21.7)	142 (28.7)	0.006	977 (56.0)	239 (64.9)	0.004
	Once a week	192 (12.6)	56 (11.3)		251 (14.4)	36.0 (9.8)	
	Daily use	998 (65.7)	297 (60.0)		516 (29.6)	93 (25.3)	
BMI-kg/m^2 (SD)		27.67 (3.59)	27.13 (3.81)	0.004	27.35 (4.55)	26.94 (4.98)	0.122
Smoking (%)	Never Smoker	518 (34.1)	128 (25.9)	0.003	1,231 (70.6)	262 (71.6)	0.637
	Former smoker	900 (59.3)	330 (66.7)		414 (23.7)	80 (21.9)	
	Current smoker	100 (6.6)	37 (7.5)		99 (5.7)	24 (6.6)	
Physical activity (%)	Active	993 (65.3)	201 (39.9)	< 0.001	992 (56.9)	113 (30.3)	<0.001
	Inactive	527 (34.7)	294 (60.1)		752 (43.1)	255 (69.7)	

Arithmetic means (SD) were given for age and BMI as continuous variables and frequency (percentage) for other categorical variables. *T*-test for continuous variables and the chi-squared test for categorical variables were used to check the difference between groups.

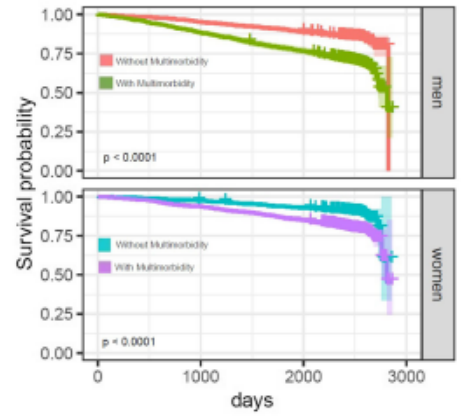

FIGURE 1
Kaplan–Meier survival curves for men and women with and without multimorbidity. Kaplan–Meier curve shows the time to death for individuals with and without MM. Censored data (vertical sign-on lines) denotes participants no longer available in KORA-Age 3 who did not experience death. There were statistically significant (p <0.0001) differences in survival probability between 2 groups in both men and women based on the log-rank test.

was for BMI lower than 25 kg/m^2 (underweight or normal BMI) in both men and women (Figure 4).

3.4. Association between multimorbidity and cause-specific mortality

In the fully adjusted models for cause-specific mortality, the risk of cancer caused mortality was 66% (HR: 1.66, 95% CI: 1.11–2.49) and 76% (HR: 1.76, 95% CI: 1.05–2.95) higher in individuals with MM compared to those without MM in men and women, respectively. In addition, compared with men without MM, the risk of mortality from cardiovascular causes was 83% (HR: 1.83, 95% CI: 1.33–2.51) higher in those who had MM. In women with MM, the hazard ratio for cardiovascular causes was 27% (HR: 1.27, 95% CI: 0.87–1.86) higher than without MM, but the HR was not significantly elevated. For other disease causes, the hazard ratios were (HR: 1.96, 95% CI: 1.32–2.92) and (HR: 1.08, 95% CI: 0.69–1.69) in men and women, respectively, (Figure 5).

3.5. Prevalence of single diseases and disease combinations

The prevalence of single and a combination of two and three diseases are shown in Table 4. The five most prevalent paired diseases

TABLE 2 Multivariate adjusted association of MM and all-cause mortality for men and women.

Characteristics		Men (*n*=2015)				Women (*n*=2,112)			
		Model 0	Model 1	Model 2	Model 3 (non-linear BMI)	Model 0	Model 1	Model 2	Model 3 (non-linear BMI)
Multimorbidity (ref: no)		2.32 (1.89,2.85)	1.84 (1.51,2.26)	1.82 (1.48,2.24)	1.81 (1.47, 2.24)	2.10 (1.66,2.66)	1.35 (1.05,1.72)	1.29 (1.01,1.65)	1.28 (1.01,1.64)
Age (per year)			1.13 (1.12,1.15)	1.12 (1.09,1.13)	1.11 (1.09, 1.12)		1.15 (1.13,1.17)	1.12 (1.10,1.15)	1.12 (1.11,1.15)
Family status (ref: Living with a partner/ spouse)	Living alone, divorced, widowed	...	...	1.36 (1.12,1.67)	1.35 (1.11,1.66)	...	...	1.27 (0.99,1.61)	1.25 (0.98,1.59)
Education (ref: 12 years or more)	8–9 years	...		1.50 (1.09,2.07)	1.49 (1.08,2.06)	...		1.15 (0.82,1.62)	1.20 (0.85,1.69)
	10–11 years			1.29 (1.05,1.57)	1.30 (1.06,1.59)			0.93 (0.67,1.28)	0.96 (0.69,1.33)
Alcohol use (ref: once a week)	Never, rare or former use	...		1.29 (1.09,2.07)	1.18 (0.85,1.64)	...		1.25 (0.87,1.79)	1.21 (0.84,1.74)
	Daily use			1.04 (0.77,1.41)	1.04 (0.76,1.40)			1.11 (0.75,1.65)	1.08 (0.73,1.61)
Physical activity (ref: active)		...		1.70 (1.40,2.04)	1.68 (1.39,2.00)	...		1.70 (1.35,2.15)	1.67 (1.32,2.11)
BMI (kg/m^2)		...		0.97 (0.94,0.99)	*	...		0.99 (0.97,1.01)	*
Smoking status (ref: never)	Former smoker	...		1.16 (0.94,1.43)	1.15 (0.93,1.42)	...		1.08 (0.83,1.39)	1.04 (0.880,1.35)
	Current smoker			1.76 (1.21,2.56)	1.73 (1.18,2.51)			1.59 (1.03,2.46)	1.54 (1.00,2.39)
AIC		7070.243	6794.823	6740.871	6730.415	5305.573	5050.834	5032.326	5026.419

Data were presented as hazard ratios with 95% confidence intervals. Model 0, model 1, and model 2 were calculated based on the Cox proportional hazard model. *In model 3, BMI was considered as the spline effect in the spline Cox proportional hazard model.

TABLE 3 Number of men and women in different age groups stratified by mortality status (alive and died).

Age groups	Men			Women		
	Total	Alive	Died	Total	Alive	Died
65–69	709	645	64	720	666	54
70–74	533	433	100	606	548	58
75–79	413	278	135	408	327	81
80–84	262	136	126	250	151	99
85+	98	28	70	128	52	76
Total	2015	1,520	495	2,112	1744	368

Number of men and women in each age groups who were alive or died until end of follow up (07.10.2016).

in men were heart-hypertension, hypertension-eye, diabetes-hypertension, heart-eye, and joint-hypertension. In women, hypertension-eye, heart-hypertension, diabetes-hypertension, joint-hypertension, and heart-eye were the most prevalent pairs.

3.6. Disease combinations and all-cause mortality

The seven most prevalent diseases in men and women (lung, joint, heart, diabetes, hypertension, eye, and anxiety) were selected to check the hazard ratio of the most prevalent combination of two and three diseases. Since the frequencies of quartets and quintets were low, we calculate the HR for the pairs and trios only.

3.6.1. Mortality and combination of two diseases

Men with heart-hypertension, diabetes-hypertension, diabetes-eye, and heart-diabetes had a significantly increased risk of mortality compared with men with one or no disease. Women with heart-hypertension, diabetes-hypertension, heart-eye, joint-hypertension, diabetes-eye, heart-diabetes, lung-hypertension, and hypertension-anxiety had a significantly higher risk of all-cause mortality compared to women with one or no disease. In women, the combination of two diseases resulted in a significantly increased risk of mortality with higher HR value than in men with the same combination (Table 4).

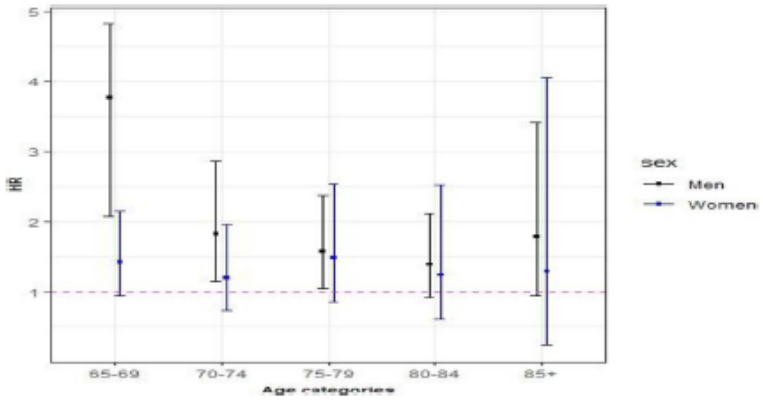

FIGURE 2
Age stratified hazard ratios for the association of multimorbidity with all-cause mortality for men and women. Hazard ratios (95% CIs) for associations of MM with all-cause mortality were calculated for each age group and adjusted for education, family status, smoking habits, alcohol use, BMI, and physical activity.

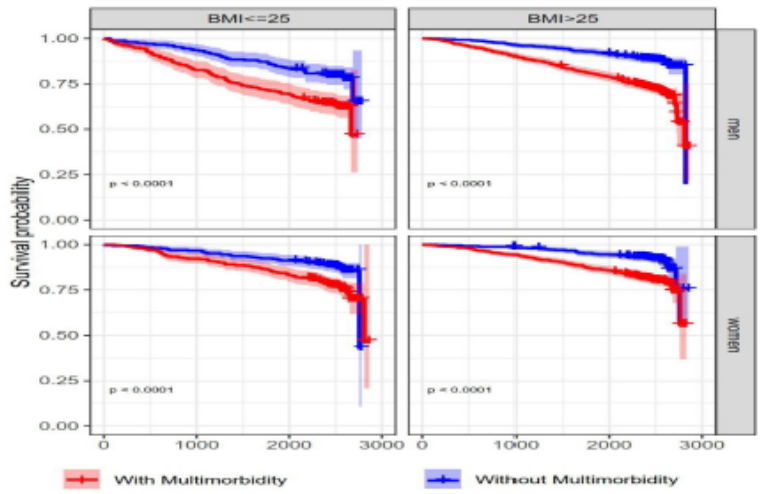

FIGURE 3
Kaplan–Meier survival curves for men and women based on BMI and multimorbidity status. Kaplan–Meier curves show the comparison of survival probability between individuals with and without MM stratified by BMI category (<=25, >25) and sex. *p*-value <0.0001 are presented for the log-rank test.

3.6.2. Mortality and combination of three diseases

Men presented significantly higher hazard ratios for individuals who had the combination of heart-diabetes-hypertension, heart-diabetes-eye, and joint-diabetes-hypertension compared with men with one or no disease. However, women showed a significantly higher risk for the combination of heart-hypertension-eye, heart-diabetes-hypertension, diabetes-hypertension-eye, lung-hypertension-eye, heart-diabetes-eye, and joint-diabetes-hypertension (Table 4).

3.7. Sensitivity analysis

There is some evidence that the waist-to-hip ratio (WHR) could be a good measure of fat distribution within the body while adjusting for the body shape (20). According to the WHO, a normal WHR range for men is 0.9 or less and 0.85 or less for women, while a WHR of >1.0 can raise the risk of chronic diseases in both male and female. Therefore, we repeated our Cox proportional models using WHR instead of BMI. We only had WHR ratio values for 1,051 participants out of 4,127. Hazard

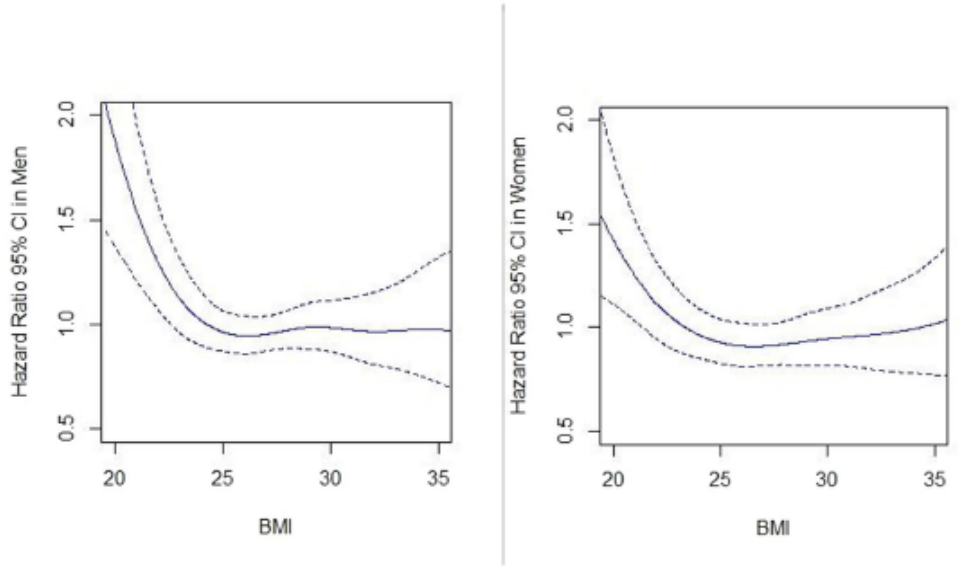

FIGURE 4
Association between BMI (kg/m²) and all-cause mortality in men and women. Hazard ratios of all-cause mortality are calculated by the spline Cox proportional hazard model. Solid lines and dash lines, respectively, represent the hazard ratios and their 95% confidence intervals after adjusting for MM, age, education, family status, smoking habit, alcohol use, and physical activity.

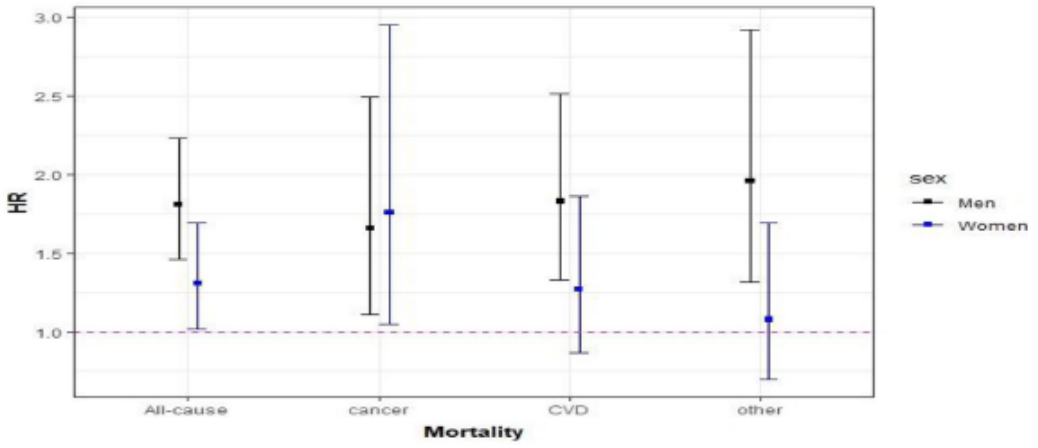

FIGURE 5
Association between multimorbidity and cause-specific mortality. Hazard ratios (95% CIs) of MM were calculated for all-cause and cause-specific mortality and adjusted for education, family status, smoking habit, alcohol use, BMI, and physical activity.

ratios of MM were (HR: 1.89, 95% CI: 1.24–2.78) in men and (HR: 1.12, 95% CI: 0.92–1.69) in women after adjusting the model for WHR instead of BMI. When WHR was used as a continuous variable in the model, a curvilinear (U-shaped) relationship between WHR and all-cause mortality was detected in both men and women (Figure 6). When the cox model was fitted without the MM, the effect estimates for age, particularly in men, increased significantly, but there was no considerable change for the other covariates. Furthermore, only the hazard ratios of MM in men were reduced by roughly 7% after fitting the model without BMI, whereas effect estimates for other covariates did not change significantly (Table 5).

TABLE 4 Frequency of single disease and the most prevalent combination of two and three diseases and their corresponding adjusted hazard ratios (95% confidence interval) for all-cause mortality stratified by sex.

Frequency (Rank) of single diseases			Combination of two diseases	Men (n =2015)		Women (n =2,112)	
Disease	Men (n =2015)	Women (n =2,112)		Frequency (Rank*)	HR (95% CIs)	Frequency (Rank)	HR (95% CIs)
Hypertension	1,086 (1)	1,206 (1)	Heart-hypertension	381 (1)	1.47 (1.15,1.71)	323 (2)	1.59 (1.17,2.16)
Eye	630 (2)	862 (2)	Hypertension-eye	378 (2)	0.87 (0.78,1.08)	542 (1)	1.25 (0.94,1.67)
Heart	555 (3)	454 (3)	Diabetes-hypertension	268 (3)	1.63 (1.31,2.04)	258 (3)	2.09 (1.52,2.89)
Diabetes	352 (4)	312 (5)	Heart-eye	203 (4)	1.15 (0.91,1.46)	241 (5)	1.52 (1.11,2.11)
Joint	227 (5)	404 (4)	Joint-hypertension	173 (5)	1.15 (0.87,1.51)	247 (4)	1.42 (1.01,2.02)
Lung	207 (6)	200 (7)	Diabetes-eye	146 (6)	1.34 (1.02,1.74)	163 (7)	1.98 (1.38,2.83)
Gastrointestinal	139 (7)	196 (8)	Heart-diabetes	134 (7)	1.87 (1.43,2.45)	108 (12)	2.87 (1.96,4.20)
Stroke	136 (8)	100 (9)	Lung-hypertension	128 (8)	1.34 (0.99,1.81)	134 (8)	1.67 (1.12,2.51)
Cancer	99 (9)	68 (11)	Joint-eye	116 (9)	1.11 (0.81,1.48)	206 (6)	1.12 (0.77–1.62)
Anxiety	90 (10)	223 (6)	Hypertension-anxiety	60 (16)	1.47 (0.95,2.27)	132 (9)	1.64 (1.06,2.55)
Kidney	81 (11)	70 (10)	Joint-heart	91 (12)	1.32 (0.94,1.85)	129 (10)	1.32 (0.86,2.03)
Neurological	60 (12)	50 (12)	**Combination of three diseases**	**Frequency (Rank)**	**HR (95% CIs)**	**Frequency (Rank)**	**HR (95% CIs)**
Liver	41 (13)	47 (14)	Heart-hypertension-eye	145 (1)	1.08 (0.82,1.43)	177 (1)	1.43 (1.00,2.03)
Depression	23 (14)	49 (13)	Heart-diabetes-hypertension	112 (2)	1.81 (1.36,4.42)	91 (4)	2.87 (1.92,4.28)
			Diabetes-hypertension-eye	111 (3)	1.34 (0.99,1.80)	135 (2)	2.61 (1.65,4.13)
			Lung-hypertension-eye	67 (4)	1.14 (0.76,1.77)	80 (6)	1.69 (1.06,2.72)
			Joint-hypertension-eye	67 (5)	1.23 (0.86,1.75)	129 (3)	1.24 (0.81,1.88)
			Joint-heart-hypertension	66 (6)	1.11 (0.73,1.67)	90 (5)	1.52 (0.95,2.43)
			Heart-diabetes-eye	60 (7)	1.69 (1.18,2.41)	63 (9)	2.61 (1.65,4.12)
			Lung-heart-hypertension	53 (8)	1.46 (0.95,2.23)	50 (13)	1.74 (0.98,3.08)
			Joint-diabetes-hypertension	49 (9)	1.61 (1.07,2.39)	51 (12)	2.09 (1.31,3.36)
			Joint-heart-eye	42 (13)	1.09 (0.69,1.72)	73 (7)	1.17 (0.69,1.98)
			Hypertension-eye-anxiety	27 (23)	1.28 (0.69,2.35)	69 (8)	1.66 (0.99,2.76)

*The Rank of disease combination shows the sorted descending rank based on the prevalence of specific combinations among all possible combinations in men and women separately. The heart-hypertension and the hypertension-eye have the highest frequency and first rank for the diseases pair in men and women, respectively. The Hazard ratios (95% CIs) of the specific combination were calculated after adjusting for age, education, family status, smoking habit, alcohol use, BMI, and physical activity. For each hazard ratio, the reference group was considered as individuals who had no or one disease.

4. Discussion

The KORA-Age study demonstrated a positive association of MM with all-cause mortality. While women had a higher MM prevalence, the HR for the association between MM and all-cause mortality was higher for men than for women. The findings of other studies confirm this finding that women live longer than men but are less healthy (21–24). We could also confirm the finding from a Bavarian Aging Study for individuals older than 65 years old that women with poorer health situations had a lower mortality rate compared to men. They showed that for all ages and morbidity definitions, women had significantly higher life expectancy than men (25).

The sex disparities in MM prevalence and impact of MM on mortality in different parts of the world suggest that there are underlying mechanisms accountable for these differences. One explanation could be that most studies use self-reported information on health status to assess chronic diseases and men prefer to report only severe health conditions. Moreover, women report their chronic diseases and symptoms with more detail and accuracy (26). For instance, a woman suffering from mild angina pectoris might claim that she has a cardiovascular illness, while a man might report it only if he had a heart attack. This reason could also explain the stronger link between MM and CVD mortality among men observed in the present study. Another possible explanation is that the mortality difference between men and women might be influenced by lifestyle factors. Although we performed our analysis after adjusting for socioeconomic factors, the confounder residuals might influence the sex differences in the effect of MM on mortality. While family status was not a significant predictor for women, males who lived alone,

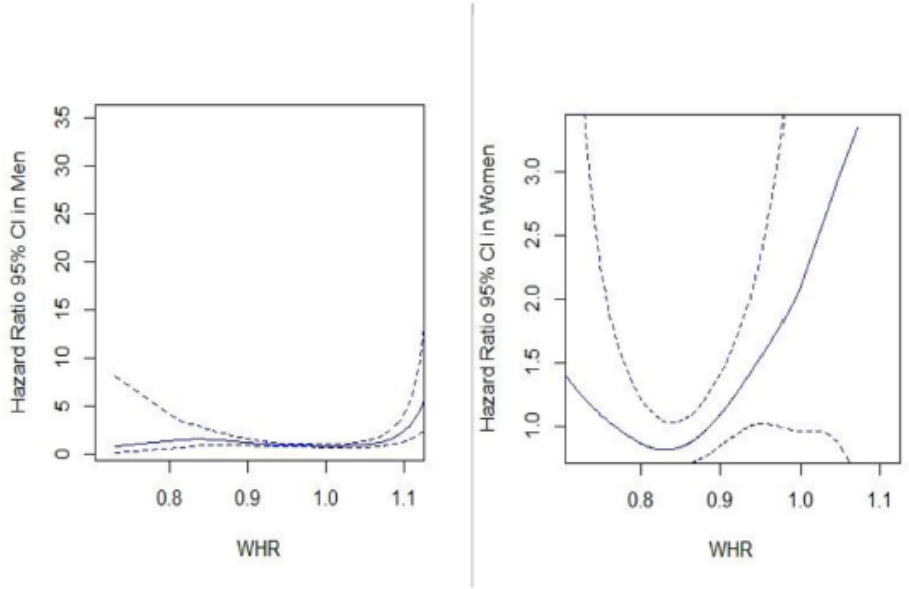

FIGURE 6
Association between waist-hip ratio (WHR) with all-cause mortality in men and women. Hazard ratios of all-cause mortality are calculated by the spline Cox proportional hazard model. Solid lines and dash lines, respectively, represent the hazard ratios and their 95% confidence intervals after adjusting for MM, age, education, family status, smoking habit, alcohol use, and physical activity.

TABLE 5 Association of multimorbidity and covariates with all-cause mortality.

Characteristics		Men			Women		
		Full model	Without MM	Without BMI	Full model	Without MM	Without BMI
Multimorbidity (ref: No)		1.82 (1.48,2.24)	…	1.77 (1.45,2.19)	1.29 (1.01,1.65)	…	1.28 (1.00,1.64)
Age (per year)		1.12 (1.09,1.13)	1.22 (1.14,1.18)	1.12 (1.10,1.13)	1.12 (1.10,1.15)	1.14 (1.11.,1.16)	1.13 (1.11,1.15)
Family status (ref: Living with a partner/spouse)	Living alone, divorced, widowed	1.36 (1.12,1.67)	1.34 (1.10,1.64)	1.27 (0.99,1.61)	1.32 (1.02,1.66)	1.26 (0.99,1.61)	1.27 (0.99,1.61)
Education (ref: 12 years or more)	8–9 years	1.50 (1.09,2.07)	1.46 (1.06,2.01)	1.15 (0.82,1.62)	1.29 (0.88,1.78)	1.16 (0.83,1.64)	1.13 (0.81,1.59)
	10–11 years	1.29 (1.05,1.57)	1.27 (1.04,1.55)	0.93 (0.67,1.28)	1.02 (0.75,1.47)	0.94 (0.68,1.30)	0.93 (0.67,1.28)
Alcohol use (ref: once a week)	Never, rare or former use	1.29 (1.09,2.07)	1.24 (0.89,1.72)	1.25 (0.87,1.79)	1.15 (0.80,1.65)	1.26 (0.88,1.82)	1.27 (0.88,1.82)
	Daily use	1.04 (0.77,1.41)	1.03 (0.76,1.39)	1.11 (0.75,1.65)	1.01 (0.68,1.51)	1.11 (0.75,1.65)	1.13 (0.76,1.67)
Physical activity (ref: active)		1.70 (1.40,2.04)	1.73 (1.43,2.09)	1.66 (1.38,2.00)	1.70 (1.35,2.15)	1.73 (1.37,2.19)	1.69 (1.34,2.14)
BMI (kg/m^2)		0.97 (0.94,0.99)	0.98 (0.95,1.01)	…	0.99 (0.97,1.01)	0.99 (0.97,1.02)	…
Smoking status (ref: never)	Former smoker	1.16 (0.94,1.43)	1.24 (1.01,1.53)	1.15 (0.93,1.42)	1.08 (0.83,1.39)	1.08 (0.84,1.41)	1.08 (0.83,1.40)
	Current smoker	1.76 (1.21,2.56)	1.81 (1.24,2.62)	1.82 (1.25,2.64)	1.59 (1.03,2.46)	1.61 (1.04,2.48)	1.62 (1.05,2.49)
AIC		6740.871	6773.993	6743.304	5032.326	5034.715	5031.005

Data were represented as hazard ratios with a 95% confidence interval. In sensitivity analyses, MM and BMI were, respectively, omitted from the models.

divorced, or widowed had a higher significant mortality risk than those who lived with a partner/spouse. Furthermore, males were more likely to use alcohol daily and less likely to be never smokers than females in our study; therefore, sex-specific differences in MM patterns and mortality could be caused by lifestyle differences. Similar results confirmed in self-reported health status that older men with poorer healthy lifestyles had increased mortality risk compared to women (27).

Our research also found that for older men and women, being overweight or obese (BMI > 25 kg/m^2) is linked to lower mortality risk than having a normal weight (BMI <= 25 kg/m^2). Although some studies showed that individuals in young or middle age who were overweight (25 < BMI < 30) or had obesity (30 > =BMI) could have an increased risk of mortality compared with normal BMI (18.5 < BMI < =25) adults, there are other studies as well which show a BMI paradox particularly for older adults (aged ≥ 65-year-olds) (24). Moreover, BMI cannot always discriminate between body fat mass and lean tissue properly (28). In sensitivity analysis, we discovered a similar relationship using the waist-to-hip ratio instead of BMI. This paradoxical relationship has been shown in various cohort studies and meta-analyses for those aged over 65 years old. They reported less (29–31) or similar (32) mortality risk for overweight or obese individuals compared to normal weight in older persons. There is still a need to explore the effect of central adiposity on MM and then mortality development in older people. Another possible explanation is that the results pointing at a paradox might mostly be a consequence of misclassification bias, reverse causation, or collider bias (33).

Interestingly, although MM is associated with a higher HR of mortality in men compared to women (based on the general definition of having two or more diseases), the risk of all significant combinations of two and three diseases is higher in women compared to men. In our study, the risk of premature mortality for diseasecombination increased with the number of diagnoses, particularly in women, which is consistent with earlier research (7). Participants with three or four chronic diseases had a 25% higher risk of premature death than those who did not have a chronic disease, and the risk jumped to 80% for those with five or more diseases (34).

According to our findings, hypertension is the most common condition, both alone and in combination, which is consistent with past research (2, 35). Hypertension is strongly associated with risk of premature mortality among individuals with diabetes (36), cardiovascular (37), rheumatoid arthritis (38), and eye disease (39). Men's mortality risk decreased or remained constant when hypertension was combined with the pairs of diseases; however, there was no specific pattern in women's risk. Other studies showed that for the old population, hypertension is four times more common in postmenopausal women than in premenopausal women, but only three times more common in age-matched males (40). This sex disparity likely contributes to the lower estrogen level in postmenopausal women since estrogen acts as a protective factor in women (41). Additionally, anxiety and depression in women can increase the risk of hypertension (41). In our study, anxiety appears in the most prevalent combination for women, but these combinations do not show a significantly elevated risk of mortality. Other underlying mechanisms, such as renin-angiotensin, the sympathetic nervous system, the immunological system, lifestyle, and environmental factors could potentially explain sex differences in the presence of hypertension and cardiovascular diseases (42). We also found the heart disease-diabetes combination as the most hazardous in both male and female and it had a higher risk in women compared to men, even when combined with other diseases. Many studies also reported the increased risk of heart failure in the presence of diabetes. This increase might happen because diabetes can raise the risk of atrial fibrillation, and coronary heart disease, which are significant risk factors for heart failure (43). When heart disease-diabetes is combined with hypertension and eye diseases, respectively in trios, the risk decreased in men but remained almost constant in women. In addition, although the joint diseases had the same prevalence in our old men and women, when added into heart-diabetes-hypertension combination, it resulted in significant mortality in women. This finding is in line with other studies that cardiovascular disease is the leading cause of death among rheumatoid arthritis patients, accounting for around 35% of all deaths (44). In contrast to our findings, other studies have found that women suffering from joint disease have less cardiovascular risk compared to men (45, 46). They discovered that, although women are three times more likely than males to have rheumatoid arthritis, they are more protected from coronary artery disease and cardiovascular disease. Different factors such as estrogen level, blood vessel situation, menopausal status, coronary calcium score (46), disability (47) and other lifestyle factors such as alcohol use (48), physical activity (49), BMI (50), and smoking behavior (51) could explain the sex difference risk in diseases combination.

5. Strengths and weaknesses

One of the study's strengths was that it included the most common chronic diseases in the age group 65 and older that might have a significant impact on mortality in older people. Being a very large and informative dataset from the population-based KORA cohort study with older participants and their follow-up information is another strength of our research. We were able to investigate not only the combination of two diseases but also multiple different combinations of diseases due to the large sample size. This database also included data on demographic, sociodemographic, physical, and mental health characteristics, which enabled us to adjust our findings for a variety of MM-related factors.

One potential limitation of this study is that our disease information was collected by questionnaires and telephone interviews, which could result in recall and information biases due to misreporting and non-response in very sick participants. Furthermore, neither the severity of each disease nor geriatric syndromes such as pressure ulcers, incontinence, frailty, falls, functional decline, or delirium were considered in our research. We also did not know which disease occurred first in one individual, which would have allowed for a more exact interpretation. Furthermore, the prevalence of most diseases was relatively low in the KORA-Age population, which could explain the lack of a significant association between some disease combinations and the risk of mortality. Therefore, some of the differences in the strength of associations between MM combinations and mortality between men and women could be explained by the low power induced by the small number of cases in particular combinations of disorders. Furthermore, the data was gathered before the Corona Pandemic and therefore obviously analysis does not take into account the cause-specific mortality by SARS-CoV2.

6. Conclusion

The effects of morbidity patterns on mortality in older men and women are highly heterogeneous and depend on the specific disease combinations. Some diseases affected the MM prevalence, but they had no substantial impact on mortality risk. We suggest that future

research should look at the morbidity patterns in men and women separately, as they showed different patterns of mortality, which might be due to differences in risk factors profileAlthough hypertension, eye, and joint disease appeared in the most common combinations, these conditions were not as strongly associated with the risk of death as other diseases. In conclusion, MM prevalence itself does not predict mortality but depends on the different disease combination. In the KORA-Age population studied here it was heart disease together with diabetes alone or in combination with other diseases was associated with mortality. Future work should however include geriatric syndromes as well as MM prevalence to add to the understanding what factors contribute to a long and healthy life.

Data availability statement

The datasets presented in this article are not readily available because there is no participant consent for public data repositories. Requests to access the datasets should be directed to kora.passt@helmholtz-muenchen.de.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Bavarian Medical Association (08094). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA: conceptualization, methodology, statistical analyses, and original paper draft. AA, AP, BT, and BL: evaluation and interpretation. AA, AP, BT, BL, and MH: revision and editing. AP, BL, BT, MH, and K-HL: main study design, data curation, and quality assurance. AP: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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