World War II Effects on Prevalence and Pattern of Multimorbidity in Older Adults: Results From the KORA-Age Study

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Abstract

While risk factors for age-related diseases may increase multimorbidity (MM), early life deprivation may also accelerate the development of chronic diseases and MM. This study explores the prevalence and pattern of MM in 65-71 year-olds individuals born before, during, and after World War II in Southern Germany based on two KORA (Cooperative Health Research in the Region of Augsburg) -Age studies. MM was defined as the presence of 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. 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 in older age (OR = 1.83, 95% CI: 1.15-2.91). In women, the prevalence of joint, gastrointestinal, eye diseases, and anxiety was higher, while in men, heart disease, stroke, and diabetes were more common. Moreover, three main chronic disease clusters responsible for the observed associations were identified: joint and psychosomatic, cardiometabolic and, internal organs diseases. Our results suggest that early life experiences may accelerate the development of MM. Moreover, the identification of disease clusters could assist in management strategies for diseases multimorbidities.

Introduction

Parallel to the worldwide increase in life expectancy in the last decades, the prevalence of age-related chronic diseases has risen as well. Consequently, multimorbidity (MM), defined as the presence of two or more than two chronic diseases, is becoming more prevalent, especially among older adults. MM is a crucial concern in the health care system since it can result in less quality of life, increased mortality, disability, and higher health care costs [1].

Based on a systematic literature review of 41 articles from different countries, MM prevalence changes from 55% to 98 % in those aged 65+ year-olds in various studies [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-olds individuals to 72.9% (95% CI: 70.4-75.2) for 70 to 79 year-olds individuals [3]. Others reported a MM prevalence of 62% for the German population aged 65+ year-olds [4]. In the Augsburg area, the MM prevalence was 58.6% for individuals aged 65-94 year-olds based on the KORA-Age 1 data in 2008 [5]. Various studies have assessed the association of MM with sociodemographic and lifestyle factors, which indicated MM is mostly associated with age, sex, educational level, income, physical activity, smoking, and alcohol consumption [6,7].

Other studies have suggested childhood adversity as a potential exposure that may increase MM risk at older age. During the first years of life, socioeconomic hardship, and traumatic events such as abuse and neglect can lead to the rise of many chronic diseases [8,9]. 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 Netherland. However, in Germany, food shortages mainly occurred during the end of World War II due to the destruction of agricultural land, livestock, machinery, and labor shortages. The average energy consumption per person decreased from about 2500 calories in 1944 to 1050-1250 calories in 1946 in Germany, and after June 1948, it increased to 1800 calories again due to the currency reform [10]. 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 this affected the prevalence of MM and chronic diseases at older age.

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 [11]. Kirchberger et al. [5] used factor analysis based on the Tetrachoric correlation matrix for 4127 persons. They identified four main comorbidity patterns, including metabolic/ cardiovascular diseases, liver/lung/joint/eye diseases, anxiety/depression/neurologic diseases, and cancer/gastrointestinal problems. To specify the groups of chronic diseases, only a few studies used clustering as an unsupervised machine learning algorithm, which has some advantages: the results are very informative by using the dendrograms for visualization and no initial assumption on data distribution, the number of clusters, or clusters structure is needed in most algorithms [11].

This study aimed to determine the effect of Birth phases on the prevalence of MM and cluster of chronic diseases for individuals aged 65-71. In addition, we explored the difference between men and women in this context.

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 in Peters et al. 2011 [12]. In short, 4,565 out of 5,991 eligible individuals (response rate: 76.2%) participated in the survey, and 1,920 were between 65 and 71 year-olds on 31.12.2008 (born between 1937-1943). The KORA-Age 3 survey consisted of 4,083 out of 6,051 eligible individuals (response rate: 67.5%), of whom 1,444 participants were in the same age range on 31.12.2015 (born between 1944-1950). The present analysis is based on combining these two KORA-Age study arms, which were completely independent because of the different birth years (Figure 1).

Birth phases

Based on the World War II situation in the Augsburg area, individuals were divided into five independent birth periods [Figure 1]: phase one (pre-war, January 1937-August 1939), phase two (early war, September 1939-December 1943), phase three (late war, January 1944-April 1945), phase four (famine period after the war, May 1945- Jun 1948) and phase five (after famine period and reconstruction, July 1948-Dec 1950) [10].

Outcome: Multimorbidity

The primary outcome was MM, defined as the presence of two or more than two chronic diseases in one person simultaneously [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. Hypertension, diabetes, cancer (any cancer recognized within the last three years), 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 [12]. Participants were asked whether they suffer from kidney, liver, lung diseases (e.g., asthma, chronic bronchitis, and emphysema), inflammatory joint problem (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). With telephone interviews, neurological diseases were evaluated based on having diseases like epilepsy, Parkinson diseases, or sclerosis. The Geriatric Depression Scale [13] and Generalized Anxiety Disorder Scale-7 [14] were used to diagnose depression and anxiety. Persons with scores greater than ten 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. 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). According to the categories for the body mass index (BMI) defined by the World Health Organization (WHO), we classified participants into underweight or normal weight ($BMI < 24.99 \text{ kg/m}^2$), overweight ($25 \leq BMI < 29.99$), obese class I ($30 \leq BMI < 34.99$) and obese class II or III ($35 \leq BMI$) [15].

Leisure time physical activity measured from two separate questions about leisure time sports activity in winter and summer, including cycling. Possible answers were (1) > 2 hours, (2) 1–2 hours, (3) <1 hour 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” [16].

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” [17]. 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 [18].

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. Covariates multi-collinearity was assessed using the variance inflation factors (VIF). Associations of the birth phases and MM were estimated by odds ratios (OR) in logistic regression models with different adjustment steps for risk factors. The Modeling process started with the 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). An agglomerative hierarchical clustering approach 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 (cutoff height), which corresponded 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 [11].

Results

Study population characteristics

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

Individuals born later were more educated so that the prevalence of a high educational level increased significantly from 25.7% to 37.1% for people born during the late war. It decreased to 34.8% during the famine phase and rose again to 37.0% in those born after the famine. Individuals born during the famine and after the famine had a lower percentage (41.0% and 41.5%, $p<0.001$) of pre-obesity compared with the other phases. Participants born after famine were more likely (15.0%) to be active smokers than people born before. For individuals born during the late war phase, the percentage of mildly impaired and impaired cognitive abilities increased to 8.1% and 2.8%, respectively, and then decreased again for the last two phases (Table 1).

Prevalence of MM and single chronic diseases

MM prevalence was 49.4% based on the total sample. There were no considerable difference in the prevalence of MM among men (48.8%) and women (49.9%) overall and in every phase. The prevalence of MM was 54.1% for individuals who were born during phase one, and it fell to 45.4% in phase two. After that, it significantly increased to 62.2% in phase three and then declined to 54.0% and 41.7% in Phase four and five, respectively. Likewise, there was the same pattern in males and females and multiple comorbidities (Additional table 1).

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% versus 7.4%, $p<0.001$), gastrointestinal (9.1% versus 6.7%, $p=0.01$), eye diseases (28.5% versus 22.5%, $p<0.001$) and anxiety (7.8% versus 3.4%, $p<0.001$), men had more heart diseases (23.0% versus 15.1%, $p<0.001$), stroke (6.8% versus 3.1%, $p<0.001$) and diabetes (17.1% versus 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 phase three (Table 2).

MM prevalence in different phases

In the age-adjusted logistic regression model, the odds ratio of MM in phase three (1.69, CI: 1.08-2.64) and phase four (1.39, CI: 1.04-1.87) were significantly higher compared to phase five. After adjusting for other covariates, the participants born in phase three (1.83, CI: 1.15-2.91) had a higher odds ratio of MM compared with the individuals born in phase five (Table 3).

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 disorder cluster consisted of anxiety, depression, joint and neurological diseases. The second cluster of cardiometabolic diseases comprised diabetes, hypertension, stroke, and heart diseases. The last one was the internal organ diseases cluster, including the lung, gastrointestinal, kidney, and liver diseases (Figure 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 whole 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 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 phase one (7.0%) and phase two (6.1%) of birth years. Moreover, men (57.9%) and participants born in phases one (52.7%) and phase three (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. Phase three still had the highest MM odds ratio (2.14, CI: 1.29-3.52). Moreover, phase one (1.64, CI: 1.07-2.49) and phase four (1.52, CI: 1.08-2.14) had a bit higher odds than hypertension consideration, and they were significant (additional table 2). Hierarchical clustering was also performed without hypertension, and the three major clusters remained as before (additional figure 4).

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 (Additional figure 5, 6).

Discussion

Multimorbidity

In our study, the overall prevalence of MM was 49.4% for adults aged 65-71 year-olds. The comparison of the prevalence of MM between studies is hampered by differences in the examined age groups, included 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 for women [19]. 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 greater for women in the present study.

Multimorbidity according to birth phases

The prevalence of MM and every single chronic disease was higher in phase three. Various factors could explain this: Since the age distribution was different in the five phases, we used the standardized age variable in our analyses, and age could affect MM rise. It is also well known that MM and chronic diseases increase with increasing age [2]. We found that the OR of MM was significantly increased in phase three compared with phase five, even after adjusting for

age and further covariates. This rise could be explained by the fact that the most unfavorable living conditions were observed in the late war phase in the South of Germany. Large parts of the city of Augsburg were devastated during the most extensive bombing raid at the end of February 1944 [20]. Participants born during the last years of war were thus exposed to the food crisis and the famine situation in Germany in 1945 in their early life [10]. In this context, it has previously been shown that maternal and early-life malnutrition can negatively affect adults mental and physical health [21]. 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 [22].

Clusters of chronic diseases

We identified three major clusters with the clustering approach to recognize individuals with similar MM diseases. The internal organ cluster included illnesses related to the main body organs like the stomach and intestines, kidneys, liver, and lung, which indicated the same co-occurrence in both men and women and individuals born in different phases.

We verified the association between joint diseases and psychosomatic disorders in the second cluster, and it was more prevalent in women. Previous studies have widely established the link between rheumatoid arthritis and mood disturbances, and neurological diseases [23,24]. Lee et al. [23] confirmed the coexistence of parkinsonian and rheumatics. Lwin et al. [24] 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 [5,25]. Sowers et al. [25] confirmed 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 percent 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 [26] with individuals born around World War II, which 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 diseases pattern. This huge database also contained information about demographic, sociodemographic, physical, and mental health factors, which helped us adjust our results for 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 and enabled us to evaluate the data without any bias introduced by the study design [27].

The clustering method helped us 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.

There are some limitations to our study as well. 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 since people mostly tend to report less weight. The real value for BMI goes far from the reported one, and the estimate might be biased [28]. 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, and we did not have any information about childhood diet, mothers health or exposure to adversity, birth weight, separation of the child from the parent, and amongst others, which may determine MM later in life. Since we examined the longitudinal association of birth phases with MM, we were able to identify the temporal sequence between exposure and outcome, which supports a potential causal link. However, all other covariables used for model adjustment were assessed simultaneously, which precludes any cause and effect interpretation.

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 increased 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. internal organ diseases (lung, gastrointestinal, kidney, liver). Although the adverse situation of WW II and famine increased the MM risk at retirement age, more detailed childhood and life course circumstances are required to explain long-term health consequences. Future research on the diseases clustering focusing on three significant clusters and their association with genetic effects, environmental factors, and polypharmacy is suggested, which may decrease treatment efficacy, other disease development, and unexpected adverse events.

Declarations

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Conflict of interest

There was no conflicts of interest declared by the authors.

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.

Informed consent

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

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Tables

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

Characteristic		Total (3,377)	Sex		P- value	Birth phases					P- value
			Male(1,616)	Female(1,761)		Phase 1 (684)	Phase 2 (1,236)	Phase 3 (283)	Phase 4 (574)	Phase 5 (600)	
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 (birth year in KORA-Age 1/ KORA- Age 3)	65	14.4	15.2	13.6	0.371	0.0	20.7	0.0	0.0	38.3	...
	66	14.7	15.5	13.8		0.0	20.2	0.0	0.0	41.0	
	67	15.0	14.4	15.6		0.0	24.1	0.0	14.9	20.0	
	68	15.5	14.6	16.4		0.0	25.3	0.0	37.1	0.0	
	69	14.8	14.9	14.6		28.2	9.7	0.0	32.4	0.0	
	70	11.8	12	11.6		35.8	0.0	22.9	15.5	0.0	
	71	13.7	13.2	14.2		35.9	0.0	77.1	0.0	0.0	
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	

P-value from Chi-square test for categorical variables

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	Phase 1 (684)	Phase 2 (1,236)	Phase 3 (283)	Phase 4 (574)	Phase 5 (600)	P- va
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
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%)	0.001
multimorbidity	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

P-value from Chi-square test for categorical variables

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 4
age	1.12 (1.08-1.16)		1.12 (0.99-1.29)	1.11 (0.96-1.27)
Birth phases (ref: Phase 5)	Phase 1	1.64 (1.32-2.05)	1.26 (0.88-1.82)	1.35 (0.92-1.98)
	Phase 2	1.16 (0.95-1.41)	1.09 (0.88-1.34)	1.08 (0.87-1.34)
	Phase 3	2.3 (1.72-3.07)	1.69 (1.08-2.64)	1.83 (1.15-2.91)
	Phase 4	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 (0.8-1.2)
	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 grade I			1.92 (1.55-2.38)
	Obesity grade II or III			3.09 (2.21-4.33)
Smoking behavior(ref: never)	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

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

Cluster	Total (1,667)	Sex		Birth phases						
		Male(788)	Female(879)	P- value	Phase 1 (370)	Phase 2 (561)	Phase 3 (176)	Phase 4 (310)	Phase 5 (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

Figures

Figure 1

Participants of the KORA-Age 1 and KORA-Age 3. combined study population (N = 3,377) and birth phases.

Figure 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 squared lines shows three main clusters on the matrix (right).

Supplementary Files

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