Received: 5 December 2023 | Accepted: 29 May 2024

DOI: 10.1002/gps.6113

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Gender-specific factors associated with case complexity in middle-aged and older adults—Evidence from a large population-based study

Cinara Paul[1] | Ben Schöttker[2] | Mechthild Hartmann[1] | Hans-Christoph Friederich[1,3] | Hermann Brenner[2,4] | Beate Wild[1]

[1]Department of General Internal Medicine and Psychosomatics, Medical University Hospital, Heidelberg, Germany

[2]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany

[3]DZPG German Centre for Mental Health—Partner Site Heidelberg/Mannheim/Ulm, Heidelberg, Germany

[4]Network Aging Research, University of Heidelberg, Heidelberg, Germany

Correspondence

Cinara Paul, Department of General Internal Medicine and Psychosomatics, Medical University Hospital, Im Neuenheimer Feld 410, Heidelberg 69120, Germany.
Email: cinara.paul@med.uni-heidelberg.de

Funding information

Saarland state Ministry for Social Affairs, Health, Women and Family Affairs; Baden-Wuerttemberg state Ministry of Science, Research and Arts; Federal Ministry of Education and Research; Federal Ministry of Family Affairs, Senior Citizens, Women and Youth

Abstract

Objectives: To investigate gender-specific factors associated with case complexity in a population-based sample of middle-aged and older adults using a holistic approach to complexity.

Methods: Data were derived from the 8-year follow-up home visits of the ESTHER study—a German population-based study in middle-aged and older adults. Cross-sectional analyses were conducted for 2932 persons (aged 57–84). Complexity was assessed by the well-established INTERMED for the elderly interview, which uses a holistic approach to the definition of case complexity. The association between various bio-psycho-social variables and case complexity was analyzed using gender-specific logistic regression models, adjusted for sociodemographic factors (age, marital status, education).

Results: Prevalence of complexity was 8.3% with significantly higher prevalence in female (10.6%) compared to male (5.8%) participants ($p < 0.001$). Variables associated with increased odds for complexity in both, women and men were: being divorced (odds ratio [OR] women: 1.86, 95% CI 1.05–3.30; OR men: 3.19, 1.25–8.12), higher total somatic morbidity (women: 1.08, 1.04–1.12; men: 1.06, 1.02–1.11), higher depression severity (women: 1.34, 1.28–1.40; men: 1.35, 1.27–1.44), and higher loneliness scores (women: 1.19, 1.05–1.36; men: 1.23, 1.03–1.47). Women (but not men) with obesity (Body mass index [BMI] ≥30) had higher odds (1.79, 1.11–2.89) for being complex compared to those with a BMI <25. High oxidative stress measured by derivatives of reactive oxygen metabolites in serum was associated with 2.02 (1.09–3.74) higher odds for complexity only in men.

Conclusions: This study provides epidemiological evidence on gender differences in prevalence and factors associated with case complexity in middle-aged and older adults. Moreover, this study adds to the holistic understanding of complexity by identifying novel variables linked to complexity among middle-aged and older

individuals. These factors include loneliness for both genders, and high oxidative stress for men. These findings should be confirmed in future longitudinal studies.

KEYWORDS
bio-psycho-social, complexity, loneliness, older adults, oxidative stress

Key points

- Prevalence of complexity was found to be 8.3% with significantly higher prevalence in women (10.6%) compared to men (5.8%) ($p < 0.001$).
- Being divorced, higher total somatic morbidity, higher depression severity, and higher loneliness scores were associated with higher odds for complexity in both genders.
- Obesity was linked to higher odds for complexity only in women, while high oxidative stress was linked to complexity only in men.
- This study expands the holistic understanding of complexity by identifying novel variables associated with complexity in middle-aged and older adults, including loneliness for both genders and high oxidative stress for men.

1 | INTRODUCTION

Demographic changes have led to an increase in prevalence of multimorbidity and patient complexity.[1] Although there is no consensus definition on complexity most authors concur that case complexity is not understood only by a specific number of diagnoses. Rather, complexity constitutes a complicated interplay between biomedical and other factors, such as sociodemographic characteristics, psychosocial vulnerability, and individual patient behaviors.[2,3]

Complexity is associated with adverse health outcomes in chronic conditions, as well as higher health care resource utilization and costs.[4] Older adults are a particularly vulnerable group for complexity due to accumulation of multiple chronic conditions in older age, frequent co-occurrence of mental disorders, and various social challenges confronting older individuals.[5]

Factors contributing to complexity have been elaborated in expert interviews and several conceptional models have been proposed as a result.[2,6] Moreover, research on factors associated with complexity has been conducted in clinical samples.[7] Population-based studies have the advantage to be less prone to selection bias and may provide information about individuals belonging to groups that are underrepresented among patients. To date, to the best of our knowledge, population-based studies on factors potentially contributing to complexity in older adults only used validated tools that do not incorporate other dimensions of complexity besides the biomedical.[8,9]

Among screening tools for patient complexity, the INTERMED interview[10] is one of the best studied, valid, and reliable instruments for this purpose.[11,12] It applies a holistic, bio-psycho-social approach to identify complex patients. The INTERMED for the elderly (IM-E) is an adapted version specifically for use in elderly populations[5] and has proven to be well suited in an epidemiological context.[4,13]

From clinical practice and research it is well known that women and men in older age differ in prevalence of somatic and mental health morbidities,[14,15] attitudes and behavior toward health,[16] as well as social resources.[17] It is therefore crucial to investigate complexity in older age separately for women and men.

The aim of this paper was to investigate gender-specific factors associated with case complexity from bio-psycho-social dimensions in a cross-sectional population-based sample of middle-aged and older adults. Complex patients were identified by the INTERMED for the elderly interview.

2 | METHODS

2.1 | Study design

This cross-sectional analysis is based on data derived from the 8-year follow-up (FU) (July 2008—December 2010) of the ESTHER study—an ongoing population-based cohort study in middle-aged and older adults conducted in the federal state of Saarland, Germany. Detailed information is reported elsewhere.[18] In short, at baseline (July 2000—December 2002), 9940 participants aged 50–75 years were recruited during a routine health checkup by their general practitioner (GP). Participants and GPs completed standardized questionnaires regarding sociodemographic, lifestyle, psychosocial and biomedical variables at baseline and during follow-ups. 6071 persons participated actively in the 8-year FU by providing a participants' questionnaire and/or participating in home visits. At the 8-year FU, all ESTHER participants were offered to participate in home visits, which were conducted by trained medical doctors and comprised a comprehensive geriatric assessment, which included the IM-E. Moreover, blood samples were collected during home visits. Out of

the 6071 active 8-year FU participants, $n = 3124$ persons agreed to be visited at home.

The study was approved by the Ethics Committees of the Medical Faculty of the University of Heidelberg and of the Medical Board of the Medical Association of the Federal State of Saarland. Written informed consent was obtained from each participant.

2.2 | Study sample

All 3124 persons who agreed to participate in home visits during the 8-year FU were eligible for analysis. Of these, 192 (6.2%) were excluded due to one or more missing values on the INTERMED interview, resulting in a final sample size of n = 2939 for analysis. A flow chart for the sample selection process is provided in Figure S1.

2.3 | Assessment of complexity

During the geriatric assessment, complexity was determined by trained medical doctors using the INTERMED for the elderly interview (IM-E). The IM-E is an adapted version of the INTERMED interview specifically for use in elderly populations.[5] The INTERMED assesses case complexity using a holistic approach. It has been developed by an international working group with the aim to identify patients who require integrated care.[19] Trained healthcare professionals can conduct and rate the INTERMED within 15–20 min. According to recent reviews,[11,12] the INTERMED is one of the best studied tools for observer-rated assessment of complexity. It has proven to be a powerful diagnostic tool and has successfully been applied to identify complex individuals in clinical[19] and epidemiological settings.[4,13] The INTERMED integrates information from four domains: (1) biological; (2) psychological; (3) social; and (4) healthcare related. The questions and ratings in each domain are related to a time axis (history, current state, and prognosis). Five items per each domain are scored from 0 *"no vulnerability or need"* to 3 *"high vulnerability or need"* resulting in domain scores ranging from 0 to 15. The respective scores of the four domains are summed up to a total score ranging from 0 to 60. A cutoff point of ≥21 has been established, which detects complex patients.[5] The IM-E and a scoring instruction are provided in Table S1.

2.4 | General practitioner reported data

Total somatic morbidity was measured by calculating the Somatic Morbidity Index (SMI) with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). GPs were asked to score 14 organ systems with 1–4 points for the presence of mild to very severe disease.[20] The 13 scores (excluding the score for psychiatric illness) were summed up to the SMI with a range from 0 to 52 points.[18]

2.5 | Serum biomarkers for oxidative stress

Blood samples were taken during the home visits. Oxidative stress arises when the production of reactive oxidative species (ROS) overwhelms the biological system's anti-oxidative capacity. ROS cannot be directly measured in blood samples due to short half-life. An established proxy for ROS production, which is stable in blood samples, are the derivatives of reactive oxygen metabolites (d-ROM).[21] The D-ROM levels were measured in serum samples shipped to the Laboratory for Health Protection Research, Bilthoven, the Netherlands, in which the assay used to measure d-ROM (Diacron, Grosseto, Italy) was adapted to an autoanalyzer (LX20-Pro, Beckman-Coulter, Woerden, the Netherlands). D-ROM levels were modeled as a categorical variable, with manufacturer-recommended cut-offs for moderate (341–400 Carr units (U)) and high (≥401 Carr U) oxidative stress with reference to subjects exhibiting no increased or low oxidative stress (≤340 Carr U).[22]

2.6 | Patient-reported data

Sociodemographic data (age, gender, marital status, education) and smoking status were assessed by self-report questionnaires. Body mass index (BMI) was calculated from weight and height, which were measured during home visits. Age, marital status, education, smoking status, and BMI were modeled as categorical variables with the definitions shown in Table 1.

Depression severity was assessed during home visits using the well-established eight-item depression module of the Patient Health Questionnaire. The PHQ-8 consists of eight of the nine DSM-IV criteria for a major depressive disorder.[23] The ninth criterion asks for suicidality and was omitted, as it is common in epidemiological settings. The total sore of the PHQ-8 ranges from 0 to 24, with higher scores indicating more severe depressive symptoms.[24]

The degree of loneliness was measured by using three items derived from the Groningen Frailty Index[25]: *"Does the patient sometimes experience an emptiness around him/her?," "Does the patient sometimes miss people around him/her?," "Does the patient sometimes feel abandoned?."* The response categories are coded 1 (hardly ever), 2 (some of the time), and three (often). The total score is summed up ranging from 0 to 9, with a higher sum score indicating a higher degree of loneliness.

2.7 | Statistical analysis

Standard descriptive methods were used to describe the study sample according to complexity status. Differences between complex and non-complex individuals were assessed by chi^2-tests for categorical variables or *t*-test for continuous variables. Differences in INTERMED total and domain scores between complex women and men were calculated using *t*-tests. Logistic regression analyses were

TABLE 1 Descriptive statistics for the total population by complexity status (n = 2932)[a].

	Total population (n = 2932)	Complex[b] (n = 244)	Non-complex (n = 2688)	p-value[c]
Age, mean (SD)	69.6 (6.3)	69.4 (6.7)	69.6 (6.3)	0.561
Age, median (IQR)	70.0 (64.0–74.0)	70.0 (63.3–74.0)	70.0 (65.0–74.0)	
Age, *N* (%)				
<65	736 (25.1)	67 (27.5)	669 (24.9)	0.795
65–69	651 (22.2)	50 (20.5)	601 (22.4)	
70–79	1364 (46.5)	113 (46.3)	1251 (46.5)	
≥80	181 (6.2)	14 (5.7)	167 (6.2)	
Gender				
Male, *N* (%)	1386 (47.3)	80 (32.8)	1306 (48.6)	**<0.001**
Female, *N* (%)	1546 (52.7)	164 (67.2)	1382 (51.4)	
Marital status, *N* (%)				
Married	2079 (71.7)	134 (56.1)	1945 (73.1)	**<0.001**
Single	99 (3.4)	12 (5.0)	87 (3.3)	
Divorced	216 (7.5)	34 (14.2)	182 (6.8)	
Widowed	505 (17.4)	59 (24.7)	446 (16.8)	
Education, *N* (%)				
≤9years	1919 (66.4)	162 (67.8)	1757 (66.3)	0.134
10–11years	512 (17.7)	49 (20.5)	463 (17.5)	
≥12years	458 (15.9)	28 (11.7)	430 (16.2)	
BMI (kg/m^2), *N* (%)				
<25	844 (29.4)	65 (27.5)	779 (29.6)	**<0.001**
25–<30	1321 (46.0)	80 (33.9)	1241 (47.1)	
≥30	702 (24.5)	91 (38.6)	611 (23.2)	
Smoking, *N* (%)				
Never	1559 (53.8)	128 (53.6)	1431 (53.8)	0.657
Former	1115 (38.5)	89 (37.2)	1026 (38.6)	
Current	224 (7.7)	22 (9.2)	202 (7.6)	
Total somatic morbidity CIRS-G SMI score, mean (SD)	6.4 (5.0)	9.1 (6.1)	6.2 (4.9)	**<0.001**
Oxidative stress biomarker d-ROM (Carr U), *N* (%)				
≤340	1110 (44.5)	64 (32.3)	1046 (45.6)	**<0.001**
341–400	827 (33.2)	74 (37.4)	753 (32.8)	
≥401	556 (22.3)	60 (30.3)	495 (21.6)	
Depression PHQ-8 score, mean (SD)	2.7 (3.3)	7.4 (4.5)	2.3 (2.8)	**<0.001**
Loneliness score, mean (SD)	1.1 (1.4)	1.9 (1.5)	1.0 (1.3)	**<0.001**

Note: Bold values are $p < 0.05$.

Abbreviations: BMI, Body mass index; Carr U, Carratelli Units; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; d-ROM, Derivatives of reactive oxygen metabolites; PHQ-8, 8-item depression module of the patient health questionnaire; SMI, somatic morbidity index.

[a]Data were derived from the 8-year follow-up (2008–2010) of the ESTHER study.

[b]INTERMED for the elderly Score ≥21.

[c]χ2-test/*t*-Test for the difference between complex and non-complex.

performed with complexity as a dichotomous dependent variable. According to the definition provided in the introduction[2,3] and based on literature review[6,18,26–28] we selected independent variables of interest from bio-psychosocial dimensions from the pool of ESTHER data that are potentially associated with patient complexity: total somatic morbidity according to CIRS-G SMI score, BMI, smoking

status, oxidative stress biomarker d-ROM, PHQ-8 depression scale, loneliness scale. Crude odds ratios (ORs) were calculated for univariate associations. Independent variables found significant at $p < 0.10$ in univariate analyses for the total sample were included in the multivariable model for the total sample, as well as gender-specific multivariable models. Analyses were adjusted for socio-demographic variables (age, gender, marital status, education) as potential confounders,[26] even when these variables were non-significant in univariate associations. Associations between predictors and complexity were assessed for women and men combined, as well as separately for women and men. For each predictor, potential differences of associations with complexity between women and men were tested for statistical significance by inclusion of a pertinent interaction term in the model for both genders combined. Multicollinearity was tested and not detected (all variance inflation factors < 5).

The proportion of missing values for all variables was <2% except for the CIRS-G 13 somatic organ items (range: 10.1%–11.0%) and d-ROM measurements (15.0%). To the best of our knowledge, items were missing at random. To deal with missing items, multiple imputation was used. 20 complete datasets were imputed using the Markov chain Monte Carlo method. Statistical analyses were performed using SPSS software ver. 27.0 (IBM, Armonk, NY, USA) and R software (version 4.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Characteristics of the total study population are shown in Table 1. Median age was 70 years (range: 57–84 years). Descriptive statistics for men and women separately are shown in Tables S2 and S3, respectively. Overall, 244 participants (8.3%) were complex. Complex and non-complex individuals did not differ significantly in age. Prevalence of complexity was higher in female (10.6%) compared to male (5.8%) participants ($p < 0.001$). Complex participants were more likely to be divorced and to be obese. Moreover, complex participants had a higher SMI score, as well as higher scores on the PHQ-8 depression scale and the loneliness scale.

Except for age, education, and smoking status, all independent variables of interest were significant in univariate logistic regression analyses for the total sample. Adjusted ORs from multivariable logistic regression are shown in Table 2 for the total population, and in Table 3 for women and men. Results from logistic regression with interaction terms are included in Table 3. Crude ORs are provided in Table S4. Variables associated with increased odds for complexity in both genders were: being divorced; higher total somatic morbidity on the CIRS-G SMI score; higher scores on the PHQ-8 depression scale; and higher scores on the loneliness scale. Obesity (BMI ≥30) versus BMI <25 was linked to 1.79 (95% CI 1.11–2.89) higher odds for complexity only in women. High oxidative stress (vs. no or low oxidative stress) was associated with 2.02 (95% CI 1.09–3.74) higher odds for complexity only in men. Of the interaction terms only the interaction between gender and oxidative stress was significant.

Gender differences in the INTERMED total and the four domain scores for complex individuals are shown in Table 4, and for non-complex in Table S5. Female participants had significantly higher scores on the psychological domain, while no gender differences were found for the other domains.

4 | DISCUSSION

In this population-based study of 2932 middle-aged and older adults we examined cross-sectional associations between independent variables from bio-psycho-social dimensions and case complexity as assessed by the INTERMED for the elderly interview.

Prevalence of case complexity was found to be 8.3%. This prevalence rate of complexity appears to be low compared to results from other studies.[29,30] However, the ESTHER cohort is a population-based sample and cannot be compared with studies in hospital settings. There are two population-based cross-sectional studies from the Netherlands that also applied the INTERMED for the elderly for identification of complex individuals. Peters et al.[31] found a 20% proportion of complex participants. However, sample composition compared to our study differed significantly, with over one third of the sample living in homes for the elderly/nursing homes, while the ESTHER sample consists only of community-dwelling participants. Bleijenberg et al.[32] reported a complexity prevalence of about 8% in community-dwelling older adults, which aligns with the prevalence we found in the ESTHER sample.

In our study, prevalence of case complexity was significantly higher in women. Additionally, women were found to have significantly higher scores on the psychological domain of the INTERMED, while no gender differences were found for the other domains. Criteria for complexity are often limited to somatic morbidity.[6] However, while somatic disease burden can be regarded as a significant aspect of complexity, we advocate the hypothesis that patient complexity extends beyond, warranting a holistic approach which incorporates non-medical dimensions as well. In our approach, case complexity refers to the characteristics which describe how patients with similar types and stages of disease vary in their health care needs and utilization.[19] Case complexity is thus not only determined by diagnoses, but also by a variety of other parameters such as patient behavior, psychosocial challenges, and difficulties in coping with the burden of disease.

In previous research the INTERMED has demonstrated to identify patients at risk for poor health outcomes. For example, patients admitted to a general internal medical ward identified as being complex according to the INTERMED had an extended length of hospital stay.[30] In dialysis patients INTERMED scores correlated with poor quality of life outcomes,[29] and in diabetes patients INTERMED scores were associated with higher HBA1c values up to 9 months after assessment.[33] While these studies are based on selected patient groups, further longitudinal population-based research is needed to confirm whether the INTERMED can identify individuals at risk for deteriorating health in non-selected samples.

TABLE 2 Adjusted odds ratios from multivariable logistic regression for the cross-sectional association between various variables and complexity in the total population (n = 2932).

	Cases (%)[a]	OR (95% CI)	p-value
Age			
<65	67 (27.5)	Ref	
65–69	50 (20.5)	1.15 (0.74–1.78)	0.541
70–79	113 (46.3)	0.85 (0.58–1.26)	0.427
≥80	14 (5.7)	0.76 (0.37–1.58)	0.466
Gender			
Male	80 (32.8)	Ref	
Female	164 (67.2)	1.10 (0.76–1.56)	0.632
Marital status			
Married	136 (55.7)	Ref	
Single	13 (5.3)	1.34 (0.64–2.79)	0.434
Divorced	34 (13.9)	2.06 (1.27–3.35)	**0.004**
Widowed	61 (25.0)	1.19 (0.78–1.81)	0.419
Education			
≤9years	164 (67.2)	Ref	
10–11years	51 (20.9)	1.37 (0.87–2.17)	0.176
≥12years	29 (11.9)	1.09 (0.64–1.88)	0.745
BMI (kg/m^2)			
<25	67 (27.5)	Ref	
25 – <30	84 (34.4)	0.94 (0.64–1.38)	0.739
≥30	93 (38.1)	1.57 (1.06–2.33)	**0.024**
Total somatic morbidity CIRS-G SMI score (per unit)	244 (100)	1.07 (1.04–1.11)	**<0.001**
Oxidative stress biomarker d-ROM (Carr U)			
≤340	77 (31.6)	Ref	
341–400	88 (36.1)	1.41 (0.90–2.21)	0.138
≥401	74 (30.3)	1.45 (0.97–2.18)	0.072
Depression PHQ-8 score (per unit)	244 (100)	1.34 (1.29–1.39)	**<0.001**
Loneliness score (per unit)	244 (100)	1.19 (1.08–1.33)	**<0.001**

Note: Bold values are $p < 0.05$.

Abbreviations: BMI, Body mass index; Carr U, Carratelli Units; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; d-ROM, Derivatives of reactive oxygen metabolites; PHQ-8, 8-item depression module of the patient health questionnaire; ORs, odds ratios; SMI, somatic morbidity index.

[a]Case numbers exemplarily taken from imputed data set no. 1.

Depression severity and degree of loneliness were associated with higher odds for complexity in both genders. Psychosocial vulnerability is regarded as a major factor contributing to patient complexity and typically includes mental illness and/or social isolation.[26] Mental illness may lead to poor compliance and is known to worsen prognosis in several somatic conditions, such as type 2 diabetes.[34] Research regarding social risk factors for complexity has been focused on poor social support or social isolation,[3,26] but, to the best of our knowledge, to date, there is a lack of evidence for the association between loneliness and complexity. Social isolation and loneliness are related concepts but do differ and do not necessarily co-exist. While social isolation is defined as an objective lack of social contacts,[35] loneliness refers to the subjective negative feelings as an emotional reaction to social isolation.[36] Loneliness in older age is a growing public health concern,[37] and may aggravate complexity in older adults due to increased risk for functional[38] and cognitive decline.[39] A recent study has also shown that loneliness in older women is associated with increased use of outpatient health care services.[40] Furthermore, aggravated complexity may arise from an increased risk for polypharmacy and pain medication use in lonely older adults.[41,42] While psychosocial variables are considered to significantly

TABLE 3 Adjusted odds ratios from multivariable logistic regression for the cross-sectional association between various variables and complexity in women and men.

	Women (n = 1546)			Men (n = 1386)			Interaction predictor x gender
	Cases (%)[a]	OR (95% CI)	p-value	Cases (%)[a]	Or (95% CI)	p-value	p-value
Age							
<65	50 (30.5)	Ref		17 (21.3)	Ref		
65–69	35 (21.3)	1.14 (0.65–1.90)	0.690	15 (18.8)	1.26 (0.57–2.80)	0.568	0.898
70–79	70 (42.7)	0.72 (0.45–1.16)	0.179	43 (53.8)	1.20 (0.60–2.39)	0.610	0.308
≥80	9 (5.5)	0.70 (0.28–1.72)	0.436	5 (6.3)	0.82 (0.23–2.96)	0.765	0.732
Marital status							
Married	78 (47.6)	Ref		58 (72.5)	Ref		
Single	8 (4.9)	1.53 (0.58–4.08)	0.392	5 (6.3)	1.19 (0.37–3.80)	0.770	0.779
Divorced	27 (16.5)	1.86 (1.05–3.30)	**0.033**	7 (8.8)	3.19 (1.25–8.12)	**0.015**	0.369
Widowed	51 (31.1)	1.06 (0.66–1.72)	0.800	10 (12.5)	1.80 (0.74–4.42)	0.197	0.276
Education							
≤9years	118 (72.0)	Ref		46 (57.5)	Ref		
10–11years	35 (21.3)	1.18 (0.73–1.90)	0.510	16 (20.0)	0.89 (0.50–1.60)	0.686	0.834
≥12years	11 (6.7)	0.68 (0.31–1.48)	0.327	18 (22.5)	0.80 (0.34–1.82)	0.579	0.636
BMI (kg/m^2)							
<25	48 (29.3)	Ref		19 (23.8)	Ref		
25–<30	52 (31.7)	1.02 (0.63–1.65)	0.938	32 (40.0)	0.70 (0.36–1.36)	0.288	0.366
≥30	64 (39.0)	1.79 (1.11–2.89)	**0.018**	29 (36.3)	1.09 (0.54–2.21)	0.809	0.170
Total somatic morbidity CIRS-G SMI score (per unit)	164 (100)	1.08 (1.04–1.12)	**<0.001**	80 (100)	1.06 (1.02–1.11)	**0.007**	0.415
Oxidative stress biomarker d-ROM (Carr U), *N* (%)							
≤340	37 (22.6)	Ref		40 (50.0)	Ref		
341–400	63 (38.4)	1.14 (0.67–1.92)	0.634	25 (31.3)	1.74 (0.76–3.96)	0.190	0.280
≥401	60 (36.6)	1.22 (0.70–2.12)	0.479	14 (17.5)	2.02 (1.09–3.74)	**0.025**	**0.030**
Depression PHQ-8 score (per unit)	164 (100)	1.34 (1.28–1.40)	**<0.001**	80 (100)	1.35 (1.27–1.44)	**<0.001**	0.752
Loneliness score (per unit)	164 (100)	1.19 (1.05–1.35)	**0.008**	80 (100)	1.24 (1.03–1.48)	**0.021**	0.772

Note: Bold values are $p < 0.05$.

Abbreviations: BMI, Body mass index; Carr U, Carratelli Units; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; d-ROM, Derivatives of reactive oxygen metabolites; PHQ-8, 8-item depression module of the patient health questionnaire; ORs, odds ratios; SMI, somatic morbidity index.

[a]Case numbers exemplarily taken from imputed data set no. 1.

TABLE 4 Gender differences for complex individuals regarding the INTERMED total score and the four domain scores.

	Female complex (n = 164)	Male complex (n = 80)	p-value
INTERMED_total, mean (SD)	24.14 (3.59)	23.60 (2.70)	0.235
INTERMED_biological, mean (SD)	9.51 (1.71)	9.55 (1.79)	0.853
INTERMED_psychological, mean (SD)	6.74 (2.27)	5.74 (2.72)	**0.003**
INTERMED_social, mean (SD)	2.21 (2.38)	2.59 (2.52)	0.260
INTERMED_healthcare related, mean (SD)	5.68 (1.74)	5.73 (1.75)	0.860

Note: Bold values are $p < 0.05$.

contribute to complexity, it is important to note that they may also occur as consequences of complex somatic morbidity.

Prior to our study, to the best of our knowledge, no associations between biomarkers and case complexity have been investigated. Our study found that men with high oxidative stress had significantly higher odds for being complex. Oxidative stress arises from an imbalance between antioxidant defenses and ROS causing cellular damage in, for instance, endothelial and neuronal tissue, which contributes to the pathogenesis and accumulation of chronic conditions, such as cardiovascular disease, cancer, and neurodegenerative diseases.[43] These effects can contribute to an overall decline in physical health and cognitive function, thereby increasing an individual's complexity status. In line with our findings on the association of d-ROM with complexity, a strong link between d-ROM and frailty was found in a prior study.[44] Oxidative stress plays an important role in the aging process and the pathogenesis of frailty, a construct marked by the reduction of homeostasis reserves leading to higher stressor vulnerability,[45] which may likewise increase complexity. In a prior analysis of the ESTHER cohort, oxidative stress measured by d-ROM has been found to be associated with multimorbidity, and consistent with our results on complexity, stronger associations between d-ROM and multimorbidity were found in men than in women.[18] There are several prior studies investigating gender disparities in oxidative stress. Women appear to have lower oxidative stress levels compared to men due to various reasons such as differences in lifestyle behaviors, abdominal adiposity, and hormones.[46,47] Furthermore, oxidative stress seems to have different health consequences in women and men, with women being less susceptible to its damaging effects. For example, higher antioxidant enzyme activity levels are proposed as one of multiple underlying protective mechanisms explaining lower risk for cardiovascular disease incidence and lower cardiovascular mortality in women.[47] Hence, gender differences regarding the therapeutic effectiveness of antioxidants in cardiovascular conditions are being discussed.[48] Our finding that high oxidative stress is linked to increased odds for complexity in men may hint at gender-specific therapeutic considerations involving antioxidants to ameliorate harmful effects of oxidative stress on overall health. However, as our analysis is cross-sectional, we must emphasize that oxidative stress may also be a consequence of underlying complexity rather than being its cause.

Women with obesity (BMI ≥30) had significantly higher odds for being complex, while such an association was not found in men. Obesity is known to increase complexity due to higher risk for several somatic co-morbidities.[49] Furthermore, obesity may also cause psychosocial distress through negative impact on self-esteem, as well as increased risk for social isolation and psychiatric illness, which may further exaggerate complexity.[50] There appear to be gender-specific differences in the potential negative effect of obesity on psychosocial functioning. A meta-analysis of community-based studies found a more pronounced link between obesity and depression in women compared to men.[51] Similarly, a previous analysis of the ESTHER cohort showed that women, but not men, in obesity classes II and III at baseline had significantly higher odds for depression 5 years later.[52] Various reasons for these gender-specific differences in the psychosocial burden of obesity are discussed, among which are higher obesity-associated distress and higher vulnerability to weight discrimination in women compared to men.[53]

When compared to married individuals, the odds of being complex were significantly higher among divorced participants. A recent population-based study in older adults found that marital disruption through divorce was strongly associated with adverse health outcomes such as poor quality of life and high psychological distress.[54] The adverse effects of divorce on health were found to be stronger in men than women. There is supporting evidence for this finding stating that following a divorce, men are more likely and severely to lose social ties.[55] In our study, however, we cannot conclude a gender-specific negative effect of divorce on complexity, given the overlap in confidence intervals for men and women and the absence of a statistically significant interaction between gender and marital status. In general, marriage seems to ameliorate disease progression in several chronic conditions, such as coronary artery disease.[56] However, there are also findings indicating that in older adults, marriage of poor quality may have a negative impact on health and mortality, with effects being more pronounced in women than in men.[57]

Unexpectedly, age as another sociodemographic variable known to be associated with complexity showed no significant association with case complexity as assessed by the INTERMED. Advanced age is usually regarded as a risk factor for complexity, however, particularly when complexity is mainly defined through and measured with tools focusing on multimorbidity.[6,26] The INTERMED for the elderly (IM-E) assesses not only case complexity but also care complexity. Higher scores also indicate higher health care needs, and a patient is classified as complex if he/she has a total score ≥21. Thus, a complex patient also has high bio-psycho-social health care needs—which

must not necessarily be associated with age. A previous study also found no difference in age between complex and non-complex individuals as assessed by the IM-E.[29]

The odds for complexity rose with increase on the CIRS-G SMI score for both genders. A study on general practitioners' perspectives on complexity suggests that other factors besides somatic morbidity may have a bigger impact on complexity.[7] This finding is also reflected by the results of our study, indicating that somatic disease burden, as measured by the SMI score, has a lower impact on complexity in the multivariable model compared to variables from the psychosocial dimension.

Some limitations must be considered when interpreting the findings. First, this is a cross-sectional analysis which precludes conclusions about temporal relationships and causality. Future longitudinal studies are warranted to elucidate causality. Second, additional variables potentially associated with complexity in middle-aged and older adults, such as pain, cognitive decline, and difficulties in healthcare navigation have not been included in this analysis. Third, the study sample may not be representative of the general German population. During the 8-year FU of the ESTHER study, all participants were offered to participate in a home visit. It is possible that persons who agreed to participate in the home visits were healthier compared to those who did decline. Fourth, our data is quite old. Nevertheless, it should be stated that sample size and comprehensive geriatric assessment as well as thorough assessment of complexity by trained study doctors applying a holistic, validated tool are strengths of this study.

In conclusion, this study adds epidemiological evidence on gender differences in prevalence and factors associated with case complexity in middle-aged and older adults. Furthermore, this study contributes to the holistic understanding of complexity by identifying novel variables associated with complexity among middle-aged and older individuals, namely loneliness for both genders, and high oxidative stress according to serum biomarker d-ROM for male older adults. These findings should be confirmed in future longitudinal studies.

ACKNOWLEDGMENTS

The ESTHER study was funded by grants from the Saarland state Ministry for Social Affairs, Health, Women and Family Affairs (Saarbruecken, Germany), the Baden-Wuerttemberg state Ministry of Science, Research and Arts (Stuttgart, Germany), the Federal Ministry of Education and Research (Berlin, Germany) and the Federal Ministry of Family Affairs, Senior Citizens, Women and Youth (Berlin, Germany).

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

No data are available. The ESTHER data cannot be made publicly available due to legal restrictions. However, data can be shared based on research proposals that are in accordance with the study's aims.

ETHICS STATEMENT

The study was approved by the Ethics Committees of the Medical Faculty of the University of Heidelberg and of the Medical Board of the Medical Association of the Federal State of Saarland. Written informed consent was obtained from each participant.

ORCID


Cinara Paul https://orcid.org/0000-0002-5196-3283

REFERENCES

1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43. https://doi.org/10.1016/s0140-6736(12)60240-2
2. Zullig LL, Whitson HE, Hastings SN, et al. A systematic review of conceptual frameworks of medical complexity and new model development. *J Gen Intern Med*. 2016;31(3):329-337. https://doi.org/10.1007/s11606-015-3512-2
3. Loeb DF, Binswanger IA, Candrian C, Bayliss EA. Primary care physician insights into a typology of the complex patient in primary care. *Ann Fam Med*. 2015;13(5):451-455. https://doi.org/10.1370/afm.1840
4. Wild B, Heider D, Maatouk I, et al. Significance and costs of complex biopsychosocial health care needs in elderly people: results of a population-based study. *Psychosom Med*. 2014;76(7):497-502. https://doi.org/10.1097/psy.0000000000000080
5. Wild B, Lechner S, Herzog W, et al. Reliable integrative assessment of health care needs in elderly persons: the INTERMED for the Elderly (IM-E). *J Psychosom Res*. 2011;70(2):169-178. https://doi.org/10.1016/j.jpsychores.2010.09.003
6. Nicolaus S, Crelier B, Donzé JD, Aubert CE. Definition of patient complexity in adults: a narrative review. *J Multimorb Comorb*. 2022;12:26335565221081288. https://doi.org/10.1177/26335565221081288
7. Grant RW, Ashburner JM, Hong CS, Chang Y, Barry MJ, Atlas SJ. Defining patient complexity from the primary care physician's perspective: a cohort study. *Ann Intern Med*. 2011;155(12):797-804. https://doi.org/10.7326/0003-4819-155-12-201112200-00001
8. Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Association of patient-centered outcomes with patient-reported and ICD-9-based morbidity measures. *Ann Fam Med*. 2012;10(2):126-133. https://doi.org/10.1370/afm.1364
9. Legler A, Bradley EH, Carlson MD. The effect of comorbidity burden on health care utilization for patients with cancer using hospice. *J Palliat Med*. 2011;14(6):751-756. https://doi.org/10.1089/jpm.2010.0504
10. Stiefel FC, de Jonge P, Huyse FJ, et al. INTERMED--an assessment and classification system for case complexity. Results in patients with low back pain. *Spine*. 1999;24(4):378-384. discussion 385. https://doi.org/10.1097/00007632-199902150-00017
11. Kaneko H, Hanamoto A, Yamamoto-Kataoka S, et al. Evaluation of complexity measurement tools for correlations with health-related outcomes, health care costs and impacts on healthcare providers: a scoping review. *Int J Environ Res Publ Health*. 2022;19(23):16113. https://doi.org/10.3390/ijerph192316113
12. Marcoux V, Chouinard MC, Diadiou F, Dufour I, Hudon C. Screening tools to identify patients with complex health needs at risk of high use of health care services: a scoping review. *PLoS One*. 2017;12(11):e0188663. https://doi.org/10.1371/journal.pone.0188663
13. Wild B, Heider D, Schellberg D, et al. Caring for the elderly: a person-centered segmentation approach for exploring the association between health care needs, mental health care use, and costs in

Germany. *PLoS One*. 2019;14(12):e0226510. https://doi.org/10.1371/journal.pone.0226510
14. Maxwell CJ, Mondor L, Pefoyo Koné AJ, Hogan DB, Wodchis WP. Sex differences in multimorbidity and polypharmacy trends: a repeated cross-sectional study of older adults in Ontario, Canada. *PLoS One*. 2021;16(4):e0250567. https://doi.org/10.1371/journal.pone.0250567
15. Luppa M, Sikorski C, Luck T, et al. Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. *J Affect Disord*. 2012;136(3):212-221. https://doi.org/10.1016/j.jad.2010.11.033
16. Stelander LT, Høye A, Bramness JG, Wynn R, Grønli OK. Sex differences in at-risk drinking and associated factors-a cross-sectional study of 8,616 community-dwelling adults 60 years and older: the Tromsø study, 2015-16. *BMC Geriatr*. 2022;22(1):170. https://doi.org/10.1186/s12877-022-02842-w
17. Lozano-Hernández CM, López-Rodríguez JA, Rico-Blázquez M, et al. Sex differences in social support perceived by polymedicated older adults with multimorbidity. MULTIPAP study. *PLoS One*. 2022;17(7):e0268218. https://doi.org/10.1371/journal.pone.0268218
18. Schöttker B, Saum KU, Jansen EH, Holleczek B, Brenner H. Associations of metabolic, inflammatory and oxidative stress markers with total morbidity and multi-morbidity in a large cohort of older German adults. *Age Ageing*. 2016;45(1):127-135. https://doi.org/10.1093/ageing/afv159
19. Stiefel FC, Huyse FJ, Söllner W, et al. Operationalizing integrated care on a clinical level: the INTERMED project. *Med Clin*. 2006;90(4):713-758. https://doi.org/10.1016/j.mcna.2006.05.006
20. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatr Res*. 1992;41(3):237-248. https://doi.org/10.1016/0165-1781(92)90005-n
21. Kotani K, Sakane N. C-reactive protein and reactive oxygen metabolites in subjects with metabolic syndrome. *J Int Med Res*. 2012;40(3):1074-1081. https://doi.org/10.1177/147323001204000326
22. Schöttker B, Brenner H, Jansen EH, et al. Evidence for the free radical/oxidative stress theory of ageing from the CHANCES consortium: a meta-analysis of individual participant data. *BMC Med*. 2015;13(1):300. https://doi.org/10.1186/s12916-015-0537-7
23. Loewe B, Kroenke K, Herzog W, Gräfe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). *J Affect Disord*. 2004;81(1):61-66. https://doi.org/10.1016/s0165-0327(03)00198-8
24. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114(1-3):163-173. https://doi.org/10.1016/j.jad.2008.06.026
25. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci*. 2004;59(9):M962-M965. https://doi.org/10.1093/gerona/59.9.m962
26. Schaink AK, Kuluski K, Lyons RF, et al. A scoping review and thematic classification of patient complexity: offering a unifying framework. *J Comorbidity*. 2012;2:1-9. https://doi.org/10.15256/joc.2012.2.15
27. Grembowski D, Schaefer J, Johnson KE, et al. A conceptual model of the role of complexity in the care of patients with multiple chronic conditions. *Med Care*. 2014;52(suppl 3):S7-s14. https://doi.org/10.1097/mlr.0000000000000045
28. Shippee ND, Shah ND, May CR, Mair FS, Montori VM. Cumulative complexity: a functional, patient-centered model of patient complexity can improve research and practice. *J Clin Epidemiol*. 2012;65(10):1041-1051. https://doi.org/10.1016/j.jclinepi.2012.05.005
29. de Jonge P, Ruinemans GM, Huyse FJ, ter Wee PM. A simple risk score predicts poor quality of life and non-survival at 1 year follow-up in dialysis patients. *Nephrol Dial Transplant*. 2003;18(12):2622-2628. https://doi.org/10.1093/ndt/gfg453
30. de Jonge P, Bauer I, Huyse FJ, Latour CH. Medical inpatients at risk of extended hospital stay and poor discharge health status: detection with COMPRI and INTERMED. *Psychosom Med*. 2003;65(4):534-541. https://doi.org/10.1097/01.psy.0000077504.01963.1b
31. Peters LL, Boter H, Slaets JP, Buskens E. Development and measurement properties of the self assessment version of the INTERMED for the elderly to assess case complexity. *J Psychosom Res*. 2013;74(6):518-522. https://doi.org/10.1016/j.jpsychores.2013.02.003
32. Bleijenberg N, Ten Dam VH, Drubbel I, Numans ME, de Wit NJ, Schuurmans MJ. Associations between frailty, complex care needs and quality of life in multi-morbid older people. *J Frailty Aging*. 2014;3(3):166-172. https://doi.org/10.14283/jfa.2014.19
33. Fischer CJ, Stiefel FC, De Jonge P, et al. Case complexity and clinical outcome in diabetes mellitus. A prospective study using the INTERMED. *Diabetes Metab*. 2000;26(4):295-302.
34. Zou Y, You W, Wang J, et al. Depression and retinopathy in patients with type 2 diabetes mellitus: a meta-analysis. *Psychosom Med*. 2021;83(3):239-246. https://doi.org/10.1097/psy.0000000000000924
35. Gardner I, Brooke E, Ozanne E, Kendig H. *Improving Health and Social Isolation in the Australian Veteran Community*. A Summary of Research Findings from the Improving Social Networks Study Commonwealth Department of Veteran's Affairs, Australian Capital Territory (ACT); 1999.
36. Heinrich LM, Gullone E. The clinical significance of loneliness: a literature review. *Clin Psychol Rev*. 2006;26(6):695-718. https://doi.org/10.1016/j.cpr.2006.04.002
37. Cacioppo JT, Cacioppo S. The growing problem of loneliness. *Lancet*. 2018;391(10119):426. https://doi.org/10.1016/s0140-6736(18)30142-9
38. Pollak C, Verghese J, Blumen H. Loneliness and functional decline in aging: a systematic review. *Res Gerontol Nurs*. 2023;16(4):1-11. https://doi.org/10.3928/19404921-20230503-02
39. Boss L, Kang DH, Branson S. Loneliness and cognitive function in the older adult: a systematic review. *Int Psychogeriatr*. 2015;27(4):541-553. https://doi.org/10.1017/s1041610214002749
40. Boehlen FH, Heider D, Schellberg D, et al. Gender-specific association of loneliness and health care use in community-dwelling older adults. *BMC Geriatr*. 2023;23(1):502. https://doi.org/10.1186/s12877-023-04201-9
41. Boehlen F, Herzog W, Quinzler R, et al. Loneliness in the elderly is associated with the use of psychotropic drugs. *Int J Geriatr Psychiatr*. 2015;30(9):957-964. https://doi.org/10.1002/gps.4246
42. Vyas MV, Watt JA, Yu AYX, Straus SE, Kapral MK. The association between loneliness and medication use in older adults. *Age Ageing*. 2021;50(2):587-591. https://doi.org/10.1093/ageing/afaa177
43. Sharifi-Rad M, Anil Kumar NV, Zucca P, et al. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. *Front Physiol*. 2020;11:694. https://doi.org/10.3389/fphys.2020.00694
44. Saum KU, Dieffenbach AK, Jansen EH, et al. Association between oxidative stress and frailty in an elderly German population: results from the ESTHER cohort study. *Gerontology*. 2015;61(5):407-415. https://doi.org/10.1159/000380881
45. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397. https://doi.org/10.1016/j.jamda.2013.03.022
46. Fujita K, Nishizawa H, Funahashi T, Shimomura I, Shimabukuro M. Systemic oxidative stress is associated with visceral fat

accumulation and the metabolic syndrome. *Circ J*. 2006;70(11):1437-1442. https://doi.org/10.1253/circj.70.1437
47. Kander MC, Cui Y, Liu Z. Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. *J Cell Mol Med*. 2017;21(5):1024-1032. https://doi.org/10.1111/jcmm.13038
48. Komici K, Conti V, Davinelli S, et al. Cardioprotective effects of dietary phytochemicals on oxidative stress in heart failure by a sex-gender-oriented point of view. *Oxid Med Cell Longev*. 2020;2020:2176728. https://doi.org/10.1155/2020/2176728
49. Wilson PW, Kannel WB. Obesity, diabetes, and risk of cardiovascular disease in the elderly. *Am J Geriatr Cardiol*. 2002;11(2):119-123, 125. https://doi.org/10.1111/j.1076-7460.2002.00998.x
50. Sarwer DB, Polonsky HM. The psychosocial burden of obesity. *Endocrinol Metab Clin N Am*. 2016;45(3):677-688. https://doi.org/10.1016/j.ecl.2016.04.016
51. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatr Res*. 2010;178(2):230-235. https://doi.org/10.1016/j.psychres.2009.04.015
52. Wild B, Herzog W, Lechner S, et al. Gender specific temporal and cross-sectional associations between BMI-class and symptoms of depression in the elderly. *J Psychosom Res*. 2012;72(5):376-382. https://doi.org/10.1016/j.jpsychores.2012.01.019
53. Hackett RA, Jackson SE, Corker E, Steptoe A. The role of stress and health behaviour in linking weight discrimination and health: a secondary data analysis in England. *BMJ Open*. 2023;13(9):e072043. https://doi.org/10.1136/bmjopen-2023-072043
54. Ding D, Gale J, Bauman A, Phongsavan P, Nguyen B. Effects of divorce and widowhood on subsequent health behaviours and outcomes in a sample of middle-aged and older Australian adults. *Sci Rep*. 2021;11(1):15237. https://doi.org/10.1038/s41598-021-93210-y
55. Leopold T. Gender differences in the consequences of divorce: a study of multiple outcomes. *Demography*. 2018;55(3):769-797. https://doi.org/10.1007/s13524-018-0667-6
56. Schultz WM, Hayek SS, Samman TA, et al. Marital status and outcomes in patients with cardiovascular disease. *J Am Heart Assoc*. 2017;6(12). https://doi.org/10.1161/jaha.117.005890
57. Grundy EM, Tomassini C. Marital history, health and mortality among older men and women in England and Wales. *BMC Publ Health*. 2010;10(1):554. https://doi.org/10.1186/1471-2458-10-554

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Paul C, Schöttker B, Hartmann M, Friederich H-C, Brenner H, Wild B. Gender-specific factors associated with case complexity in middle-aged and older adults—Evidence from a large population-based study. *Int J Geriatr Psychiatry*. 2024;e6113. https://doi.org/10.1002/gps.6113