Do partnership dissolutions and living alone affect systemic chronic inflammation? A cohort study of Danish adults

Karolina Davidsen ,[1] Simon Carstensen,[1] Margit Kriegbaum ,[2] Helle Bruunsgaard,[3] Rikke Lund [1,4,5]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jech-2021-217422).

[1]Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[2]Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Department of Clinical Immunology; Centre of Inflammation and Metabolism; Centre for Physical Activity Research, Copenhagen University Hospital, Copenhagen, Denmark
[4]Section of Social Medicine, Department of Public Helath, University of Copenhagen, Copenhagen, Denmark
[5]Center for Healthy Aging, University of Copenhagen, Kobenhavn, Denmark

Correspondence to
Professor Rikke Lund, Department of Public Health, University of Copenhagen Social Medicine Section, Kobenhavn, Denmark; rilu@sund.ku.dk

Received 7 June 2021
Accepted 13 November 2021
Published Online First 10 January 2022

To cite: Davidsen K, Carstensen S, Kriegbaum M, *et al*. *J Epidemiol Community Health* 2022;**76**:490–496.

ABSTRACT

Background Partnership breakups and living alone are associated with several adverse health outcomes. The aim of this study, carried out in Denmark, is to investigate whether accumulated numbers of divorces/partnership breakups or years lived alone across 26 years of adult life are associated with levels of inflammation, and if vulnerability with regards to gender or educational level can be identified.

Methods 4835 participants from the Copenhagen Aging and Midlife Biobank (CAMB) aged 48–62 years were included. Data on accumulated numbers of partnership breakups and years living alone were retrieved from a national standardised annual register. Inflammatory markers interleukin 6 (IL-6) and high sensitivity C-reactive protein (hsCRP) were measured in blood samples. Multivariate linear regression analyses were adjusted for age, educational level, early major life events, body mass index, chronic diseases, medicinal intake affecting inflammation, acute inflammation and personality scores.

Results For men, an association was found between an increasing number of partnership breakups or number of years living alone and higher levels of inflammatory markers. No such association was found for women, and no evidence of partnership breakups and educational level having a joint effect was found for either gender.

Conclusion The findings suggest a strong association between years lived alone or accumulated number of partnership breakups and low-grade inflammation for middle-aged men, but not for women. Among those of either sex with a lower level of education, no specific vulnerability to accumulated years lived alone or number of breakups was identified.

INTRODUCTION

People undergoing partnership breakups or divorces are at increased risk of developing poorer health than the continuously married.[1 2] These life-altering events have been associated with increased risk of many types of adverse health outcomes,[2 3] including chronic diseases,[1 4] cardiovascular disease,[2] poor mental health outcomes,[5 6] maladaptive immunological responses[7 8] and increased mortality.[9–11] Partnership breakups and divorces are often followed by the partners involved living alone—in some cases for a major part of life. Living alone is also becoming more common, and is likewise associated with a variety of health-related challenges including poorer physical functioning,[12] psychological distress[13] and increased mortality.[14 15]

Most studies looking at the end of partner cohabitation are cross-sectional. Only a few have looked at the detrimental health consequences of accumulated numbers of partnership breakups[4 16] or years living alone.[17] Furthermore, most previous studies are limited by only looking at *marital* breakups, despite it becoming increasingly common in Western societies to be involved in one or more cohabitation partnerships during a life course, and to experience several partnership breakups.[18]

The adverse health outcomes associated with breakups and living alone may be mediated through increased levels of stress experienced.[8] This mental stress combined with physical stress affects many bodily functions, including, over time, the workings of the immune system.[7]

The decline in function of the immune system is a major factor in the overall susceptibility that comes with ageing.[19] From an immunological perspective, ageing is characterised by a decreased adaptive immune function, the dysregulation of inflammatory responses[20] and a low-grade chronic inflammatory state with two- to fourfold increased serum concentrations of inflammatory cytokines.[21] Systemic chronic inflammation has been proposed to play a crucial role in driving several age-related pathologies (eg, cancer, cardiovascular disease, type 2 diabetes).[22 23] In light of this, previous studies have used markers of the immune system to study the process of ageing[24] and mortality in the elderly.[25]

Divorce, partnership breakups and living alone are more common in lower socioeconomic groups, and the association between partnership-breakups or living alone and adverse health effects may be especially strong for people in these groups,[26] as a consequence of differential vulnerability.[27] Further, people in these strata tend to experience higher levels of physical, social and behavioural adversity,[28] which can increase the risk of accumulative and interacting effects between these life-changing events.

The health-related consequences of partnership breakups or living alone potentially differ between men and women. An example of this is seen in the association between divorce and increased mortality among divorced men compared with divorced women.[9] This difference may stem from men experiencing greater health gains from marriage than

women,[29] as well as younger men's relatively greater inflammatory responses to adversity.[30]

AIM

The purpose of our study is to investigate whether an accumulated number of partnership breakups or years lived alone across 26 years of adult life are associated with higher levels of low-grade inflammation in middle-aged men and women. Based on previous literature we hypothesise that: an increased number of breakups/years lived alone will be associated with higher levels of low-grade inflammation; and that low socioeconomic position (low educational level) as well as being of male gender increases the levels of vulnerability to exposure to accumulated breakups or years lived alone.

METHODS

Data sources

Data for this study originate from the Copenhagen Aging and Midlife Biobank (CAMB), a Danish population-based late-midlife follow-up study that combines detailed life-course information with measures of physiological functioning, biomarkers and health. The CAMB cohort is based on three pre-existing Danish cohorts, two of which have been followed since the participants' births in 1953 (Metropolit cohort, male only) or 1959–61 (Copenhagen perinatal cohort), and the third cohort which has been followed for the past 20 years with participants being born in either 1949 or 1959 (Danish Longitudinal Study on Work, Unemployment and Health (DALWUH) cohort). All participants were invited to the CAMB follow-up in 2009–11 if they lived in eastern Denmark and had not formally resigned (n=17 937); 31% of those invited (n=5576) completed a questionnaire and showed up for clinical testing. The comprehensive questionnaire included questions on health behaviour, psychosocial factors, and physical conditions. All participants were linked to the Danish registers at Statistics Denmark by a unique personal identification number. CAMB is described in detail elsewhere.[31]

The population for the present study was conditioned by having full information on the included variables: n=4612 on the number of breakups (n=3170 men and n=1442 women); n=4835 on the number of years lived alone (n=3336 men and n=1499 women).

Exposures

Definition of cohabitation

Statistics Denmark provides information on presumed cohabiting couples on an annual basis. A cohabiting couple is defined as a 'couple' if they are: married (heterosexually, or homosexually since 1989); cohabiting with joint children (heterosexuals only); or if they are all of the following: of opposite sex, >16 years old, have an age difference of <15 years, and are not related or living with other adults.[32]

Measurement of broken partnerships

The accumulated number of broken partnerships was defined as the sum of broken partnerships across the study period (1986–2011), summing up both divorces and dissolutions of partnership cohabitation. It counts individuals who were cohabiting in year x−1, but during year x were living without a partner or with a new partner.

Accumulated cohabitation status was categorised into: people living continuously with one partner, or moving in with one, thus experiencing no breakups (reference group); people who underwent one breakup; and people who underwent two or more breakups. Very few (n=83) became widows or widowers during the study period. Despite the difference in nature, these cases of widowhood were included as broken partnerships. This was done because of the similarity between bereavement and relationship breakdown in regard to the social consequences perceived by the individuals who had lived through these experiences.[33] In the analyses of partnership breakups, participants living without a partner throughout the observation period were excluded, as the purpose was to estimate the effect of experiencing a breakup from living with a partner. Furthermore, they were excluded because never living with a partner (ie, always living singly) is a very different type of living arrangement from living continuously with the same partner without experiencing a breakup; thus the two modes of living should not be categorised together.

Measurement of years living alone

Based on the same register, information on the accumulated number of years living alone across the study period (1986–2011) was categorised into: 0–1 year (reference group); 2–6 years; or ≥7 years. This categorisation was chosen based on our expectation of 1 year lived alone during adult life to be comparable in risk to 'no exposure' due to its relatively high frequency in society, and it being considered 'normal' (acceptable) during adult life, and thus a linear association was not expected. Further, the categorisation was driven by the intention that the three groups should be relatively evenly sized; and also to be able to illustrate the potential higher risk in the most exposed. The years lived alone after the death of a spouse were, in these few cases, included as years lived alone. Additional multivariate linear regression analyses, including years lived alone as a continuous variable, were performed and can be found online (online supplemental table 1).

Outcomes

Markers of low-grade inflammation

High sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) were used as measures of inflammatory ageing. They were derived from blood samples collected on non-fasting participants by skilled laboratory technicians. The blood samples were fractioned in EDTA plasma, serum and DNA and stored at –80°C, until individually analysed. The analyses were carried out by the Clinical Biochemical Laboratory (high sensitivity (hs)-CRP) and Centre for Inflammation and Metabolism (IL-6) at Rigshospitalet, University Hospital of Copenhagen. hsCRP was analysed in plasma samples by Roche/Hitachi MODULAR P. IL-6 was analysed in EDTA plasma by the electrochemiluminescence multiplex system on a sector 2400 image with commercial kits from Meso Scale Discovery (Gaithersburg, USA). The same lot number was used for all cytokine analyses, the samples were run as duplicates and only intra-assay variation <20% was accepted. Two controls were included in all runs: one fasting plasma sample from a healthy young subject; and one plasma sample after endotoxin administration in vivo. To approach normality, the inflammatory markers were log-transformed before analysis, and all estimates were then back-transformed before presentation.

Covariates

Potential confounders were identified by directed acyclic graphs (DAG).

Gender (reference (ref.) female), *age* (continuous variable) and *socioeconomic position* (measured as highest attained educational level in 2009–11) were all assessed based on register

information. The latter was grouped into three categories according to the International Standard Classification of Education (ISCED) system[34]: 'Low' being up to 10 years of education (ISCED level 0–2), 'Middle' being 11–12 years of education (ISCED level 3), and 'High' being 13 or more years of education (ISCED level 4–6).

Based on the CAMB data collection, we assessed: *original cohort* (grouped as: the Metropolit cohort, DALWUH (ref. group) and Copenhagen perinatal cohort); *number of chronic diseases* by self-reporting on whether individuals had ever had any of 21 specific diseases (grouped into six groups, according to the number of diseases, ref. group=0); *recent acute inflammatory events* by self-reporting on different relevant exposures (grouped according to presence (ref. group)); *pharmaceutical intake* by self-reporting on drugs known to influence inflammatory levels (statins, steroids, non-steroidal anti-inflammatory drugs, immunosuppressive agents) (grouped into four groups, according to number of drugs taken, ref. group=0); *early major life events* (eMLE) by self-reporting whether, during childhood, they had experienced death or serious illness of a parent, conflict-ridden childhood, financial difficulties or stays in foster care (grouped into five groups according to number of events, ref. group=0).

Body mass index (BMI) was objectively measured without shoes and with light clothing (grouped as underweight (BMI ≤18) or normal weight (18<BMI≤25) (ref. group), overweight (25<BMI≤30) or obese (BMI >30)). *Personality scores* were assessed by the short Danish version of the NEO five factor inventory (grouped by scores on three traits included as continuous variables: neuroticism, agreeableness and conscientiousness).

Joint variables between partnership breakups/years lived alone and highest educational level/gender were developed. Partnership breakup status was dichotomised into 'none' and 'one or more breakups', and combined with gender 'male' or 'female' categories; or educational level dichotomised as 'high' or 'low'. Similarly, 'years living alone' was categorised into three groups of having lived alone '0–1 years', '2–6 years' or '7+ years' and combined with gender or educational level.

Statistics

For the descriptive tables, significance was tested with χ^2 test on categorical variables and F-test, t-test or Wilcoxon on continuous variables. The association between partnership breakups and inflammatory markers (IL-6 or hsCRP) was analysed with a multiple linear regression on log-transformed variables. Regression coefficients are judged to be statistically significant if they are within the 95% confidence intervals, meaning that an estimated coefficient of 1.05 is interpreted as a 5% higher level of the inflammatory marker compared with reference level.

Adjusted models included adjustments for gender, age, educational level, cohort, chronic diseases, acute inflammatory events, pharmaceutical intake, eMLE, personality, and BMI. In the joint effect analysis the main effects and the joint effect of the combined variables are presented and all are adjusted for the selected covariates. A product term between gender and education, respectively, and years lived alone/number of partnership breakups were included to test interaction on the additive scale in multivariate regression models.

RESULTS

Table 1 shows the characteristics of the study sample. Most participants were men (69%), mainly due to the male-only Metropolit cohort being part of CAMB. About half of the

Table 1 Distribution of demographic, health and personality variables by number of breakups

	Females		Males		P value
Total number	1499	30.8%	3363	69.2%	
Number of partnership breakups/divorces					<0.0001
0	731	48.8%	1810	54.3%	
1	440	29.4%	896	26.9%	
2+	271	18.1%	464	13.9%	
None and never cohabitated*	57	3.8%	166	5.0%	
Number of years lived alone					0.0072
0–1	695	46.4%	1693	50.7%	
2–6	327	21.8%	716	21.5%	
7+	477	31.8%	927	27.8%	
Age (mean and SD† in years)	52.7	4.35	55.3	3.22	<0.0001
Educational level					0.13
Low	307	20.5%	644	19.3%	
Middle	35	2.3%	54	1.6%	
High	1157	77.2%	2638	79.1%	
Original cohort‡					<0.0001
Metropolit	–	–	2187	65.6%	
DALWUH	681	45.4%	501	15.0%	
CPC	818	54.6%	648	19.4%	
Number of chronic diseases§					0.8263
0	566	37.8%	1242	40.9%	
1	553	36.9%	1198	37.0%	
2	262	17.5%	595	28.7%	
3	82	5.5%	203	22.7%	
4	28	1.9%	76	25.2%	
5+	8	0.5%	22	0.8%	
Present acute inflammation¶					0.2906
Yes	461	30.8%	1077	32.3%	
No	1038	69.2%	2259	67.7%	
Recent medicinal intake**					0.0108
0	1213	80.9%	2662	79.8%	
1	278	18.5%	617	18.5%	
2	8	0.5%	52	1.6%	
3	0	0.0%	5	0.1%	
Number of eMLE††					<0.0001
0	733	48.9%	1870	56.1%	
1	358	23.9%	725	21.7%	
2	233	15.5%	420	12.6%	
3	103	6.9%	219	6.6%	
4+	72	4.8%	102	3.1%	
BMI‡‡					<0.0001
Under weight (18.5<BMI<25)	34	2.3%	14	0.4%	
Normal weight (BMI <25)	787	52.5%	1229	36.8%	
Overweight (25<BMI<30)	471	31.4%	1582	47.6%	
Obese (BMI >30)	207	13.8%	511	15.3%	
Personality score§§					
Neuroticism (median, Q1, Q3)	18	24	16	21	<0.0001
Agreeableness (median, Q1, Q3)	35	39	33	36	<0.0001
Conscientiousness (median, Q1, Q3)	34	37	34	37	0.1213

*Excluded from analyses on numbers of partnerships breakups.
† SD, standard deviation.
‡ Cohorts: Metropolit cohort (men only); DALWUH, Danish Longitudinal Study on Work, Unemployment and Health; CPC, Copenhagen perinatal cohort
§ Chronic diseases: allergies, diabetes, hypertension, myocardial infarction, stroke, lung disease (including asthma, chronic bronchitis, emphysema), autoimmune diseases and arthritis, cancer including leukaemia, mental disorders.
¶ Acute inflammation includes information on recent inflammatory events or dentist's appointments, infections, fever, or vaccinations.
**Pharmaceutical intake of inflammatory importance: non-steroidal anti-inflammatory drugs (NSAIDs), statins, steroids and immunosuppressive agents.
††eMLE: early major life events.
‡‡Body mass index, kg/m^2
§§Q1, lower quartile; Q3, upper quartile.

Table 2 Multivariate linear regression analysis of partnership breakups/years lived alone and hsCRP or IL-6 adjusted main models

Partnership breakups: hsCRP						Partnership breakups: IL-6					
Women (1442)	**N**	**Estimate, mean**	**Coefficient, mg/L**	**95% CI**	**P value**	Women **(1442)**	**N**	**Estimate, mean**	**Coefficient, pg/mL**	**95% CI**	**P value**
0	731	1.48	–	–	0.3418	0	731	2.05	–	–	0.2907
1	440	1.52	1.03	0.92 to 1.16		1	440	2.20	1.07	0.98 to 1.17	
2+	271	1.36	0.92	0.80 to 1.06		2+	271	2.08	1.01	0.91 to 1.13	
Men (3170)					**0.0088**	**Men (3170)**					**0.0002**
0	1810	1.50	–	–		0	1810	2.88	–	–	
1	896	1.59	1.06	0.98 to 1.15		1	896	2.86	0.99	0.94 to 1.06	
2+	464	1.75	1.17	1.06 to 1.29		2+	464	3.37	1.17	1.08 to 1.26	
Years lived alone: hsCRP						**Years lived alone: IL-6**					
Women (1499)	**N**	**Estimate, mean**	**Coefficient, mg/L**	**95% CI**	**P value**	**Women (1499)**	**N**	**Estimate, mean**	**Coefficient, pg/mL**	95% CI	**P value**
0–1 year	695	1.38	–	–	0.152	0–1 year	695	2.15	–	–	0.2489
2–6 years	327	1.28	0.92	0.81 to 1.06		2–6 years	327	1.98	0.92	0.83 to 1.02	
7+ years	477	1.47	1.06	0.94 to 1.20		7+ years	477	2.12	0.99	0.90 to 1.08	
Men (3336)					**0.0256**	**Men (3336)**					**<0.0001**
0–1 year	1693	1.33	–	–		0–1 year	1693	2.76	–	–	
2–6 years	716	1.33	1.00	0.92 to 1.09		2–6 years	716	2.62	0.95	0.89 to 1.02	
7+ years	927	1.48	1.11	1.02 to 1.21		7+ years	927	3.09	1.12	1.05 to 1.19	

Models adjusted for: gender, age, educational level, cohort, chronic diseases, acute inflammatory events, pharmaceutical intake, eMLE, BMI, personality. Statistically significant estimates are presented in bold.
BMI, body mass index; eMLE, early major life events; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin 6.

included population (51% of females, 46% of males) had experienced a partnership breakup, and a similar percentage had lived more than 1 year alone (54% of females, 49% of males). Age in the population ranged from 48 years to 62 years, with mean ages of 52.7 for women and 55.3 for men. Approximately 20% had a low educational level (10 years or less), approximately 60% had one or more chronic diseases, approximately 50% had experienced early major life events, and approximately 50% of females and 65% percent of males were overweight or obese.

Table 2 shows estimates of biomarker concentrations for men and women in adjusted models for the association with number of breakups or years lived alone. Among men, the highest levels of inflammatory markers are found in the groups with most partnership breakups, with 17% higher inflammatory levels than the reference group, and in the group of most years lived alone with 11–12% higher inflammatory levels. For women, the biomarker levels showed no significant association with regard to either partnership breakups or number of years living alone.

An example of how all covariates are associated with inflammatory marker levels are shown in a key regression analysis (number of years lived alone and hsCRP; see the online material online supplemental table 2).

To explore whether the nearest partner status made a difference to the associations, a sensitivity analysis stratified by partner status in the year of blood testing was carried out, but this did not show any differences between those who had or did not have a partner with whom they shared a household (data not shown).

Table 3 shows the main and joint effects of educational level and partnership breakups or years living alone, for men. The main effects of partnership breakups or years lived alone and educational level were significantly associated with CRP and IL-6 (except for the one case of partnership breakups' main effect on IL-6), but we did not find any indication of increased vulnerability to accumulated number of partnership breakups or years lived alone among those of low educational level. The highest levels of biomarkers were found in the group of men with high educational level and one or more breakups. The highest levels of both biomarkers for years lived alone were found in the group of men with high educational level and 2–6 years lived alone for CRP, and ≥7 years alone for IL-6. In women (results not shown) we found no main or joint effects between partnership breakups or years lived alone and educational level (see online supplemental table 3).

A model was created of the joint effects of gender and partnership breakups or years living alone, with females with zero breakups or 0–1 years lived alone as the reference group. A joint effect was found on partnership breakups in hsCRP (highest levels among females with zero breakups and males with one or more breakups, and lowest levels among males with zero breakups). No effect was found on years lived alone in hsCRP or IL-6 levels.

DISCUSSION

In a large cohort study of middle-aged adults, our findings suggest that among men, the experience of two or more partnership breakups as well as 7 or more years lived alone across 26 years of adult life is associated with increased CRP and IL-6 levels. We found a 17% CRP-level and IL-6-level increase for men with two or more partnership breakups; and an 11% CRP-level increase and a 12% IL-6-level increase for men with 7 or more years lived alone compared with the reference group of

Table 3 Men: multivariate linear regression analysis of men's main and joint effects of breakups/years lived alone and highest attained educational level on IL-6 or CRP

Partnership breakups: hsCRP						Partnership breakups: IL-6					
	N	Estimate, mean	Coefficient, mg/L	95% CI	P value		N	Estimate, mean	Coefficient, pg/mL	95% CI	P value
Breakups					**0.0102**	*Breakups*					**0.0822**
None (0)	1810	1.49	–	–		None (0)	1810	2.87	–	–	
One or more (1+)	1360	1.63	1.10	1.02 to 1.18		One or more (1+)	1360	3.01	1.05	0.99 to 1.11	
*Educational level**					**0.0364**	*Educational level**					**0.0120**
High	2580	1.49	–	–		High	2580	2.81	–	–	
Low	590	1.63	1.10	1.01 to 1.20		Low	590	3.07	1.09	1.02 to 1.17	
Interaction†					0.7453	*Interaction†*					0.5554
High/ 0	1516	1.42	–	–		High/ 0	1516	2.74	–	–	
High/ 1+	363	1.72	1.21	1.08 to 1.36		High/ 1+	363	3.32	1.21	1.11 to 1.32	
Low/ 0	294	1.58	1.11	0.99 to 1.26		Low/ 0	294	3.01	1.10	1.00 to 1.21	
Low/ 1+	997	1.54	1.09	1.01 to 1.18		Low/ 1+	997	2.80	1.02	0.96 to 1.09	
Years lived alone: hsCRP						**Years lived alone: IL-6**					
	N	Estimate, mean	Coefficient, mg/L	95% CI	P value		N	Estimate, mean	Coefficient, pg/mL	95% CI	P value
Years lived alone					0.0256	*Years lived alone*					<0.0001
0–1 year	1693	1.30	–	–		0–1 year	1693	2.69	–	–	
2–6 years	716	1.30	1.00	0.92 to 1.09		2–6 years	716	2.56	0.95	0.89 to 1.02	
7+ years	927	1.44	1.11	1.03 to 1.21		7+ years	927	3.01	1.12	1.05 to 1.19	
*Educational level**					**0.0359**	*Educational level**					**0.02**
High	2692	1.28	–	–		High	2692	2.64	–	–	
Low	644	1.41	1.10	1.01 to 1.20		Low	644	2.85	1.08	1.01 to 1.15	
Interaction†					0.3679	*Interaction†*					0.3512
High/ 0–1 year	1411	1.24	–	–		High/ 0–1 year	1411	2.57	–	–	
High/ 2–6 years	581	1.21	0.97	0.88 to 1.06		High/ 2–6 years	581	2.48	0.96	0.90 to 1.04	
High/ 7+ years	700	1.39	1.12	1.02 to 1.22		High/ 7+ years	700	2.94	1.14	1.07 to 1.23	
Low/ 1–0 year	282	1.32	1.06	0.93 to 1.20		Low/ 1–0 years	282	2.92	1.14	1.03 to 1.25	
Low/ 2–6 years	135	1.51	1.21	1.01 to 1.44		Low/ 2–6 years	135	2.61	1.01	0.89 to 1.16	
Low/ 7+ years	227	1.48	1.18	1.03 to 1.36		Low/ 7+ years	227	3.01	1.18	1.06 to 1.31	

Models adjusted for: gender, age, cohort, chronic diseases, acute inflammatory events, pharmaceutical intake, eMLE, BMI, personality. P values for the product term. Statistically significant estimates are presented in bold.
*Education: highest attained educational level.
†Test for interaction by the inclusion of a product term: partnership breakups + education + partnership breakups x education + covariates,
BMI, body mass index; eMLE, early major life events; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin 6.

men with no partnership breakups or who had lived 0–1 years alone. No significant differences were found for women in our models.

In our study, we were uniquely able to adjust the models for a broad range of confounders including: educational level, early major life events and personality scores. Joint effect analyses lent no support for low educational level to constitute a specific vulnerable group. Only regarding the number of partnership break-ups did men seem more vulnerable to increased levels of CRP. No other interactions with gender were suggested.

Djundeva's lifecourse study of 10 662 Germans and Britons found men in trajectories with multiple marital disruptions to have higher CRP than their male counterparts with fewer or no marital disruptions.[4] In Sbarra's cross-sectional study of 1715 currently or previously married men and women, marriage was found to remain a unique protective factor against elevated CRP levels for men only.[11] In Kiecolt-Glaser's cross-sectional study of 32 separated or divorced men, these men were found to have poorer immune function than their socio-demographically matched married counterparts, measured as antibody titres to two herpes viruses.[35]

These studies all find effects of marriage or divorce status on CRP levels and immune function, supporting our findings that men are, in contrast to women, significantly disadvantaged by divorce in terms of chronic higher CRP levels. In our study we found evidence that there is a particularly vulnerable group that has lived through many partnership breakups and/or has lived many years alone. Small numbers of breakups or years lived alone

is not in itself a risk of poor health, but the combination of (many) years lived alone and several breakups is in our study shown to affect both CRP and IL-6 levels significantly. Since the number of one-person households has been increasing throughout the past 50–60 years in most high-income countries,[36] this group of people going through relationship breakups, or who are living on their own for different reasons, are part of at-risk groups.

There are several potential explanations for the lack of association for women in the present study. Leopold *et al* theorised that the difference stems from men experiencing greater health gains from marriage than women, which means that a divorce will put them at higher risk of declining health.[29] Another explanation may lie in younger men's greater inflammatory responses to adverse exposures, and the persistence of these into old age.[30] Furthermore, men have been found to display more externalising behaviour following a partnership breakup, for example, in the form of increased alcohol intake, whereas women have been found to internalise their problems in the form of more depressive symptoms,[37] which may influence inflammatory levels differently. It is, however, important to keep in mind that not all studies find this gender difference in health-related consequences of partnership breakups.[1 38] As our study is limited by a relatively smaller group of women (n=1499) this might explain the non-significant results. We thus cannot reject the possibility of the existence of a true association for women. Larger studies including more women are needed in order to explore this.

The study has several strengths, including a large study population with linkage of survey and inflammation data to standardised register-based information across 26 years. There are also limitations to our study, the most severe being the possible selection bias that lies in the participant dropout and influences the internal validity of the cohort data (questionnaire and blood samples rate: 31%). Foverskov *et al* analysed the association between income levels and aging outcomes in the same population, finding that the associations were most likely too conservative, due to a selective dropout of the least resourceful CAMB participants with more frequent histories of divorce or partnership breakups. We find it likely that a similar conclusion can be drawn regarding our results.[39]

We found no clear joint effect between partnership breakups and educational level. This lack of a differential vulnerability may be caused by the heterogeneity of the group of people classified as having a 'high' level of education. This group included all educational levels above 10 years of education in the joint effect analyses, where low power forced the decision to dichotomise the education variable.

A bias arising from the possible selection out of marriage by health might be present in our study, even though we tried to adjust for this through comorbidities. People who do not end up getting married or cohabiting might be rejected, by potential long-term partners, or might opt out of marriage or cohabitation, based on their poorer health.[40]

A limitation pertaining to the inflammatory markers of our study lies in their connection to age. As our participants have a mean age of 54.5 years, it is possible that the full consequences of the exposures have not yet reached the peak. And as men generate stronger inflammatory responses than women of the same age,[30] the levels for women might need to be interpreted differently.

Furthermore, systemic inflammation also reflects levels of cardiovascular disease, BMI and senescent cells secretion/cytokine profile, which in our study affects the interpretation of findings as the participating males had higher BMIs than the females.

The levels of inflammation in our study are low, but they are also significant, clinically relevant and most likely a risk factor for increased mortality. The means found in our groups suggest that there are notable numbers of individuals with chronic low-grade inflammation in clinically relevant areas. In a review of the predictive value of minor elevation of CRP for atherosclerotic events, Kushner and colleagues[41] found minor elevations of 3–10 mg/L (defined as high cardiovascular risk by the American Heart Association), to carry negative prognostic implications for age-related diseases and to predict mortality. An interesting addition to our findings would be to investigate whether the effect was diluted over time. This does, however, require multiple blood samples from each individual, which our data do not contain. In our population, the average time since last breakup was 12 years, and therefore we interpret the effects of the exposure to be lasting.

CONCLUSION

In conclusion, this large study in a Danish midlife population finds a significant association between partnership breakups or years lived alone and inflammation for men only, after adjustment for selected confounders. In women, we find no such effect. We find no joint effect of partnership breakups and educational level for either gender.

What is already known on this subject

- For men, getting divorced often leads to a decline in health and has ultimately been found to be associated with increased mortality. It is a topic of interest to general medicine, since it enables a targeted effort for at-risk groups of a very common exposure, with easily measurable biomarkers of interest.

What this study adds

- This study adds knowledge as to the consequences of living alone for a shorter or longer period of time. It also investigates whether similar effects are found after living through zero, one or several divorces or breakups from committed cohabitation. The exposure measures are the immune system biomarkers CRP and IL-6, which are found in significantly increased levels in men with several breakups or years lived alone.

Acknowledgements We are grateful to Kirsten Avlund, Erik Lykke Mortensen, Helle Bruunsgaard, Åse Marie Hansen, Rikke Lund, Erik Lykke Mortensen, Nils-Erik Fiehn and Poul Holm-Pedersen who established the Copenhagen Ageing and Midlife Biobank. The authors thank the staff at Department of Public Health and National Research Centre for the Working Environment, who undertook the data collection, as well as the initiators of The Copenhagen Perinatal Cohort, the Metropolit Cohort and The Danish Longitudinal Study on Work, Unemployment and Health. The authors also want to thank Drude Molbo, Section of Social Medicine for valuable advice regarding statistical analyses.

Contributors KD and RL generated the idea for the paper, and KD, RL and MK prepared an analytical plan and conducted all data analyses. KD and RL drafted the introduction, methods, results and discussion sections. HB and SC contributed to critical revision of the design and statistical analyses. KD designed figures. All the authors contributed to the interpretation of the results and critical revision of the paper and approved the final version. RL is guarantor of overall content.

Funding This work was funded by the Centre for Healthy Ageing at the University of Copenhagen established by a grant from the Nordea Foundation. The research leading to these results was carried out as part of the Social Inequalities in Ageing (SIA) project, funded by NordForsk, Project No. 74 637. The Copenhagen Ageing

and Midlife Biobank has been supported by a generous grant from the VELUX FOUNDATIONS (VELUX26145 and 31539).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Danish Data Protection Agency (No: 2008-41-2938) and by the local ethics committee (No: H-A-2008–126).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data cannot be made publicly available due to regulations. A SAS code for the project is available upon request from MK.

ORCID iDs
Karolina Davidsen http://orcid.org/0000-0002-0822-3378
Margit Kriegbaum http://orcid.org/0000-0001-9078-1194
Rikke Lund http://orcid.org/0000-0002-0381-4291

REFERENCES

1 Hughes ME, Waite LJ. Marital biography and health at mid-life. *J Health Soc Behav* 2009;50:344–58.
2 Robles TF, Kiecolt-Glaser JK. The physiology of marriage: pathways to health. *Physiol Behav* 2003;79:409–16.
3 McFarland MJ, Hayward MD, Brown D. I've got you under my skin: marital biography and biological risk. *J Marriage Fam* 2013;75:363–80.
4 Djundeva M. Partnership trajectories and cardiovascular health in late life of older adults in England and Germany. *SSM Popul Health* 2018;6:26–35.
5 Björkenstam E, Hallqvist J, Dalman C, *et al*. Risk of new psychiatric episodes in the year following divorce in midlife: cause or selection? A nationwide register-based study of 703,960 individuals. *Int J Soc Psychiatry* 2013;59:801–4.
6 Yip PSF, Yousuf S, Chan CH, *et al*. The roles of culture and gender in the relationship between divorce and suicide risk: a meta-analysis. *Soc Sci Med* 2015;128:87–94.
7 Jaremka LM, Lindgren ME, Kiecolt-Glaser JK. Synergistic relationships among stress, depression, and troubled relationships: insights from psychoneuroimmunology. *Depress Anxiety* 2013;30:288–96.
8 Kiecolt-Glaser JK. Marriage, divorce, and the immune system. *Am Psychol* 2018;73:1098–108.
9 Shor E, Roelfs DJ, Bugyi P, *et al*. Meta-analysis of marital dissolution and mortality: reevaluating the intersection of gender and age. *Soc Sci Med* 2012;75:46–59.
10 Sbarra DA, Law RW, Portley RM. Divorce and death: a meta-analysis and research agenda for clinical, social, and health psychology. *Perspect Psychol Sci* 2011;6:454–74.
11 Sbarra DA. Marriage protects men from clinically meaningful elevations in C-reactive protein: results from the National Social life, Health, and Aging Project (NSHAP). *Psychosom Med* 2009;71:828–35.
12 Ramel A. Living alone is associated with poorer physical function and bone mineral density in Icelandic old adults. *Innov Aging* 2019;3:S482–S82.
13 Shaw RJ, Cullen B, Graham N, *et al*. Living alone, loneliness and lack of emotional support as predictors of suicide and self-harm: a nine-year follow up of the UK Biobank cohort. *J Affect Disord* 2021;279:316–23.
14 Abell J, Steptoe A. Living alone transitions and mortality in older men and women. *Innov Aging* 2020;4:642–42.
15 Redfors P, Isaksén D, Lappas G, *et al*. Living alone predicts mortality in patients with ischemic stroke before 70 years of age: a long-term prospective follow-up study. *BMC Neurol* 2016;16:80–84.
16 Dupre ME, Beck AN, Meadows SO. Marital trajectories and mortality among US adults. *Am J Epidemiol* 2009;170:546–55.
17 Nilsson CJ, Nørgaard S, Foverskov E, *et al*. Positive and negative aspects of social relations and low-grade inflammation in Copenhagen aging and midlife Biobank. *Eur J Ageing* 2020;17:531–46.
18 Kennedy S, Ruggles S. Breaking up is hard to count: the rise of divorce in the United States, 1980-2010. *Demography* 2014;51:587–98.
19 Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol* 2004;39:687–99.
20 Milan-Mattos JC, Anibal FF, Perseguini NM, *et al*. Effects of natural aging and gender on pro-inflammatory markers. *Braz J Med Biol Res* 2019;52:e8392–e92.
21 Furman D, Campisi J, Verdin E, *et al*. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019;25:1822–32.
22 Macaulay R, Akbar AN, Henson SM. The role of the T cell in age-related inflammation. *Age* 2013;35:563–72.
23 Cevenini E, Monti D, Franceschi C. Inflamm-ageing. *Curr Opin Clin Nutr Metab Care* 2013;16:14–20.
24 Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, *et al*. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 2003;100:9090–5.
25 Harris TB, Ferrucci L, Tracy RP, *et al*. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999;106:506–12.
26 Hogendoorn B, Leopold T, Bol T. Divorce and diverging poverty rates: a Risk-and-Vulnerability approach. *J Marriage Fam* 2020;82:1089–109.
27 Diderichsen F, Hallqvist J, Whitehead M. Differential vulnerability and susceptibility: how to make use of recent development in our understanding of mediation and interaction to tackle health inequalities. *Int J Epidemiol* 2019;48:268–74.
28 Nordahl H, Lange T, Osler M, *et al*. Education and cause-specific mortality: the mediating role of differential exposure and vulnerability to behavioral risk factors. *Epidemiology* 2014;25:389–96.
29 Leopold T. Gender differences in the consequences of divorce: a study of multiple outcomes. *Demography* 2018;55:769–97.
30 Bruunsgaard H, Pedersen AN, Schroll M, *et al*. Impaired production of proinflammatory cytokines in response to lipopolysaccharide (LPS) stimulation in elderly humans. *Clin Exp Immunol* 1999;118:235–41.
31 Lund R, Mortensen EL, Christensen U. Cohort profile: the Copenhagen Aging and Midlife Biobank (CAMB). *Int J Epidemiol* 2016;45:dyv149.
32 Statistics Denmark. Satistics Denmark: households and families, 2020Statistics Denmark. Available: https://www.dst.dk/en/Statistik/emner/borgere/husstande-familier-og-boern/husstande-og-familier [Accessed 25 May 2020].
33 Luhmann M, Hofmann W, Eid M, *et al*. Subjective well-being and adaptation to life events: a meta-analysis. *J Pers Soc Psychol* 2012;102:592–615.
34 Jensen VM, Rasmussen AW, Registers DE. Danish education registers.. *Scand J Public Health* 2011;39:91–4.
35 Kiecolt-Glaser JK, Kennedy S, Malkoff S, *et al*. Marital discord and immunity in males. *Psychosom Med* 1988;50:213–29.
36 Hall R, Ogden PE, Hill C. The pattern and structure of one-person households in England and Wales and France. *Int J Popul Geogr* 1997;3:161–81.
37 Simon RW, Simon Robin W. Revisiting the relationships among gender, marital status, and mental health. *AJS* 2002;107:1065–96.
38 Robles TF, Slatcher RB, Trombello JM, *et al*. Marital quality and health: a meta-analytic review. *Psychol Bull* 2014;140:140–87.
39 Foverskov E, Petersen GL, Pedersen JLM, *et al*. Economic hardship over twenty-two consecutive years of adult life and markers of early ageing: physical capability, cognitive function and inflammation. *Eur J Ageing* 2020;17:55–67.
40 Franke S, Kulu H. Mortality differences by partnership status in England and Wales: the effect of living arrangements or health selection? *Eur J Popul* 2018;34:87–118.
41 Kushner I, Rzewnicki D, Samols D. What does minor elevation of C-reactive protein signify? *Am J Med* 2006;119:166.e17–166.e28.