AGE (2011) 33:209–217
DOI 10.1007/s11357-010-9165-5

Systemic inflammation (Interleukin 6) predicts all-cause mortality in men: results from a 9-year follow-up of the MEMO Study

Bernhard T. Baune · Matthias Rothermundt · Karl H. Ladwig · Christine Meisinger · Klaus Berger

Received: 9 December 2009 / Accepted: 23 June 2010 / Published online: 9 July 2010

Abstract This study aimed to investigate the association of biomarkers among circulating pro-inflammatory cytokines with all-cause mortality in elderly community dwellings of the MEMO study, Germany. All-cause mortality (cancer, cardiovascular diseases (CVD), and other causes of death) was assessed in a general population sample (N=385) of the elderly (age 65–83 years) 9 years after baseline assessment in 1998. As markers of inflammation, a variety of cytokines (IL-1beta, IL-4sR, IL-6, IL-8, IL-10, IL-12, TNF-alpha) were assessed in serum. Cox proportional Hazard model was used to estimate the association of cytokines with all-cause mortality over 9 years. In total, 110 deaths had occurred during follow-up (cancer N=36; CVD N=56; other=18). Deaths were more frequent in male (N=76, 37.4%) as compared to females (N=40, 21.9%; p=0.001). Among individual cytokines, IL-1 beta, IL-6, IL-8, IL-10, and TNF-alpha were associated with all-cause mortality, of which IL-6, IL-8, and IL-10 remained significant after adjusting for confounders. When the upper tertiles of these cytokines were compared to the lower tertiles, only IL-6 was consistently related to all-cause mortality independently of the level of adjustment and showing a dose–response relationship between IL-6 tertiles and risk of death. This effect originated in the male population. The study shows that IL-6 is a powerful predictor of all-cause mortality in male elderly community dwellings. Higher levels of IL-6 may reflect a chronic low-level systemic inflammation prospectively increasing the risk of death in the elderly.

Keywords Aging · Inflammation · Mortality · Gender

B. T. Baune (✉)
Department of Psychiatry and Psychiatric Neuroscience, School of Medicine and Dentistry, James Cook University, Townsville, QLD 4811, Australia
e-mail: Bernhard.Baune@jcu.edu.au

M. Rothermundt
Department of Psychiatry, University of Muenster, Muenster, Germany

K. H. Ladwig · C. Meisinger
Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany

K. Berger
Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany

Introduction

In recent years, the identification of biomarkers as predictors of chronic diseases has gained increased interest since biomarkers might be useful to improve existing risk prediction scores, e.g., for cardiovascular diseases such as myocardial infarction. Biomarkers might also improve knowledge of factors that determine disease prognosis, e.g., in patients with diabetes or with specific cancer types. Inflammatory biomarkers such as

C-reactive protein (CrP), cytokines, or fibrinogen have been studied in both instances, since chronic inflammatory processes are involved in the onset of many chronic diseases. In most of the prognosis studies, inflammatory biomarkers were investigated in disease-specific clinical populations or in samples underrepresented for elderly individuals (Stork et al. 2006). Mortality is one of several outcomes of interest in prognosis studies; however, it is always the ultimate outcome. It, thus, does not only apply as a parameter of interest in studies of patients with specific illnesses or treatments but also in those of the general, elderly population. In this context, it has been suggested that aging is characterized by changes in immune functions and stress response, which in the elderly leads to increased mortality following inflammatory stress (Nikolova-Karakashian et al. 2008). Some first evidence on the prospective association between inflammatory markers and all cause mortality in elderly populations has been brought forward in recent years (Stork et al. 2006; Bruunsgaard 2002; Bruunsgaard and Pedersen 2003; Bruunsgaard et al. 2001). This research is of particular importance since inflammatory processes including chronic low-level inflammation appear to be related to the onset of various age-associated diseases (Bruunsgaard et al. 2001), among them leading causes of death in Western societies (Murray and Lopez 1997), e.g., cardiovascular diseases (Csiszar et al. 2003; Cesari et al. 2003) and cancer (Shurin et al. 2007; Sansoni et al. 2008). Inflammatory markers such as CrP and the cytokines IL-6 (Stork et al. 2006; Heikkila et al. 2007) and TNF-alpha (Bruunsgaard et al. 2003) have both been associated with all cause as well as CVD mortality in populations of high age. Some of these studies used gender-specific recruitment strategies and reported associations between IL-6 and CVD-related mortality either in older men (Stork et al. 2006) or in women (Volpato et al. 2001). However, gender-specific analyses of these associations in the same study are rare in the literature.

The range of examined cytokines in most prior studies was, however, very limited and follow-up periods in these elderly populations were relatively short, ranging from 2 to 4 years. This left the question open if inflammatory markers such as cytokines are useful in the long-term prediction of all-cause mortality in the elderly.

Aim of our study was to analyze the association of seven different cytokines as inflammatory biomarkers with all-cause mortality in the general elderly population over a 9-year follow-up period.

Methods

Population

The MEMO Study (Baune et al. 2008) is a follow-up project of the 1989/90 WHO Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Survey Augsburg (S2), Germany (Keil et al. 1998; Schmidt et al. 2004). For the S2 study, a random sample of the population of Augsburg, a city in southern Germany, and the two adjacent counties was drawn from the office of registration. The sample was stratified by 5-year age groups and gender. The initial response rate for the MONICA Survey was 76.8%. For the MEMO Study, all participants of S2 aged 65 years and older were contacted again in 1997/98. The overall response proportion for the MEMO Study was 60.6% yielding a total of 385 participants. The ethics committee of the University of Muenster, Germany, approved the study. After complete description of the study to the subjects, written informed consent was obtained. All MEMO participants had a face-to-face interview, on sociodemographic variables, risk factors and medical histories. Weight, height, and blood pressure measurements and a standardized neurologic examination including a neuropsychological test battery were also performed. All examinations were done in the study center in the city of Augsburg.

The assessment of smoking status was categorized in current smoker, ex-smoker, or never smoker. Body mass index (BMI) was based on weight and height measurements in 1997/98 and was calculated as kilograms per square meter. Comorbidities were assessed according to self-reports. We summarized comorbidities in two large groups and applied two ways of categorization to each group. Vascular comorbidity was defined as having a physician diagnosis of heart failure or myocardial infarction, diabetes, or stroke or operation of an arterial vessel in either abdomen, legs, or carotid arteries or open-heart surgery. As an alternative we built a summary variable “vascular morbidity” summing these diseases and interventions up. The second large group was built by joint or bone-related morbidities and was defined as joint replacement or traumata of the

backbone or amputations of extremities. For this disease group, we also built a summary score. We considered joint and bone-related morbidity as relevant in this population of the elderly since there is growing evidence for a relationship between bone-related disorders and illnesses involving the vascular system, and vice versa (Zenovich and Taylor 2008; Yetkin and Waltenberger 2009).

Cytokine assessment

Non-fasting venous blood was collected from 370 participants. Serum was stored at −80°C for later batch analysis. Cytokine concentrations were measured using cytometric bead array (CBA, BD Biosciences, San Diego, USA) for the cytokines IL-1b, IL-6, IL-8, IL-10, IL-12p70, and TNF-α, and enzyme-linked immunosorbent assay (ELISA, R&D Systems, Minneapolis, MN, USA) for sIL-4R following manufacturer's instructions.

For the cytometric bead array, six bead populations with distinct fluorescence intensities were coated with capture antibodies specific for IL-1b, IL-6, IL-8, IL-10, IL-12p70, and TNF-a proteins. The six bead populations were mixed together to form the BD CBA, which resolved in the FL3 channel of a flow cytometer (BD FACSCalibur). The capture beads, PE-conjugated detection antibodies, and recombinant standards or test samples were incubated together to form sandwich complexes. Following acquisition of sample data using the flow cytometer, the sample results were generated in graphical and tabular format using the BD CBA Analysis Software. The intra-assay coefficients of variation were 4–7% for IL-1b, 5–8% for IL-6, 2–5% for IL-8, 5–6% for IL-10, 3–6% for IL-12p70, and 6–10% for TNF-a. The inter-assay coefficients of variation were 8–13% for IL-1b, 8–10% for IL-6, 4–7% for IL-8, 8–11% for IL-10, 6–9% for IL-12p70, and 8–15% for TNF-a.

The sIL-4R ELISA uses the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for sIL-4R has been pre-coated onto a microplate. Standards and samples were pipetted into wells, and any sIL-4R present was bound by the immobilized antibodies. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for sIL-4R was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added and color develops in proportion to the amount of sIL-4R bound in the initial step. The color development was stopped and the intensity of the color measured. The intra- and inter-assay coefficients of variation were between 2.6–4.4%and 4.6–5.5%, respectively.

Follow-up of all-cause mortality

Vital status of all MEMO study participants and causes of death of those who had died until 12/31/2007 were documented. Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person. Causes of death were coded according to ICD 9 Rev. (ICD 9. Rev.: 001–999).

Statistical analyses

Differences in sociodemographic and clinical characteristics between the deceased and surviving group were compared using two sample *t* test for continuous and Pearson χ^2 test for categorical variables. All-cause death rates were analyzed for 100 person-years of observation. Cytokine values for each of the seven cytokines were log-transformed and the resulting geometric means compared according to vital status, first using *t* tests and subsequently linear regression models additionally adjusted for age, gender, and smoking. We categorized levels of those three cytokines with significant differences subsequently into tertiles based on the log-transformed distribution. This was done to better address the low-grade inflammation hypothesis, which suggests that long-term low-grade inflammation might impact on the onset of diseases via mediation of vascular dysfunction (Singhal 2005). We then examined the association between cytokines as categorical measures (tertiles) and subsequent mortality events using serially adjusted Cox proportional hazard models and different models of adjustment stratified for gender. The models of adjustment included age, gender, and smoking status (model 1), plus additional variables of vascular and bone morbidity (model 2), and in the final model by additionally including each other cytokine (model 3). In order to rigorously evaluate whether individual cytokines were associated with mortality while simultaneously adjusting the factors listed above, we carried out sensitivity analyses. We considered dichotomized single medical

disorders instead of summary variables for bone-related and vascular disorders and, alternatively, the total number of medical disorders in the Cox models in the overall samples and in gender-specific subsamples. The proportional hazard assumption was met for all related analyses. All statistical procedures were carried out using STATA version 11.0.

Results

A total of 370 (96.1%) participants had complete data on cytokines and all covariates. The follow-up period for vital status for the MEMO Study participants was 9 years. Mean follow-up time during this period, was 6.49 years (including dead and surviving participants during follow-up). Among these participants, 110 deaths (cancer, N=36; CVD (including CHD), N=56; other, N=18) were documented with a mean survival time of 3.13 years after recruitment into the MEMO Study in 1997. Those who died during follow-up were significantly older at baseline as compared to the survivors (74.8 vs. 71.8 years of age; $p<0.0001$). Male subjects, current smokers, and participants with vascular or joint and bone-related comorbidity at baseline were more likely to die than those without these diseases (Table 1). No differences in survival were found for family status (p=0.973).

Two of the seven examined cytokines were related to age in linear regression analyses (IL-6: t value 2.51, p=0.012; IL-8: t value 4.35, p=0.002). Mean levels of each cytokine were not different between men and women. Levels of five of the seven examined cytokines (IL-1beta, IL-6, IL-8, IL-10, TNF-alpha) at baseline were significantly higher in participants who had died during follow-up compared to survivors. When these analyses were adjusted for important confounders such as age, gender, and smoking, the three cytokines IL-6, IL-8, and IL-10 were still significantly higher in those who died during follow-up compared to survivors (Table 2).

In multivariate regression analyses, the associations between tertiles of these three cytokines (IL6, IL-8, and IL-10, upper tertile as compared to lower tertile) and mortality were examined. The upper tertile of IL-6 was related to an increased risk for all-cause mortality across the three models of adjustment. The effect estimate in the fully adjusted model 3 was only slightly reduced compared to the least adjusted model 1 (HR 1.67 versus 1.88). In contrast, risk increases for the upper tertiles of IL-8 and IL-10 were smaller and insignificant (Table 3).

Subsequently, we examined effect modification of the IL-6 mortality association by gender and age. This analysis revealed that the effect of IL-6 was present in male participants only showing a moderately high effect size of 0.27. For IL-8 and IL-10 no gender effects were observed (Table 4). With regard to effect modification by age (applying median split), we found a stronger effect of IL-6 on all-cause mortality (HR 2.133, 95% CI 1.2–3.9; p=0.015) in the older group (mean age in upper half=76.9 years) as compared to the younger group (mean age in lower half=69.4 years; HR 1.45; 95% CI 0.73; p=0.32).

In order to rigorously evaluate whether IL-6 is associated with mortality while simultaneously adjusting for demographic factors, individual medical conditions, and BMI, we carried out sensitivity analyses. In these sensitivity analyses, single medical disorders (instead of summary variables of bone and vascular disorders) and BMI as dummy variables (four quantiles) and alternatively the total number of medical diseases were included to demonstrate the independent effect of IL-6 on mortality in Cox proportional hazard models in the overall and the gender-specific subsamples. As a result, we found that the effect of IL-6 on mortality in men remained significant in the overall and in the gender-specific analyses, independently of additionally adjustments. More specifically, we found that the hazard ratios varied slightly in the sensitivity analyses for the overall sample (range of HRs 1.643–1.882) and the gender-specific analyses (range of HRs for males: 2.27–2.36; range of HRs for females 1.14–1.11) depending on the model of covariates. While in the sensitivity analyses the effects of IL-6 tertiles remained significant overall (range of p values, 0.043–0.008) and for males (range of p values, 0.011–0.015) for the above reported HRs, no significant results for female participants were found.

Discussion

In this population-based cohort of the elderly, we investigated prospectively the association between seven cytokines and all-cause mortality over a period of 9 years. The main finding of the study is that IL-6 at baseline was associated with all-cause mortality in

Table 1 Sample characteristics of N=370 community dwellings of the MEMO study according to all cause mortality

Characteristics (year 1998)	All-cause mortality (12/31/2007)		
	Yes (N=110)	No (N=260)	p Value
Age (mean, SE)	74.8, 0.41	71.8, 0.25	<0.0001[a]
Gender (%)			0.0001
Female	34.5	52.8	
Male	65.5	47.2	
Education (mean, SE)	10.6, 0.2	10.7, 0.14	0.61[a]
Smoking status (%)			<0.0001[b]
Smoker	18.2	6.3	
Ex-smoker	46.1	38.8	
Never smoker	35.7	54.9	
BMI (mean, SE)	27.5, 0.38	27.5, 0.22	0.85[a]
Any vascular morbidity (%)			<0.0001[b]
Yes	46.6	24.2	
No	53.4	75.8	
Any bone morbidity (%)			0.048[b]
Yes	17.2	10.0	
No	82.8	90.0	
Aggregation inhibitor use (%)			0.52[b]
Yes	31.9	28.6	
No	68.1	71.4	

Among N=385 participants including 15 participants without cytokine data (no blood collection)

[a] Two sample t test

[b] Pearson χ^2 test

male subjects, whereas in women, no associations with mortality for any of the investigated cytokines were found. Sensitivity analyses confirmed the gender-specific effect of IL-6 on mortality in male subjects in this cohort.

The interpretations of these results should take into account that the aging process is related to chronic low-level inflammation as suggested in previous research. These prior studies showed increased levels of circulating inflammatory serum markers including elevated concentrations of IL-6 during aging (Bruunsgaard et al. 1999; Wei et al. 1992) and age-related impairments and burden of disease (Zhu et al. 2009). In support of the relationship between aging and the inflammatory state

Table 2 Geometric means of cytokines stratified for survival status among N=370 subjects of the MEMO study

All-cause mortality				
Cytokines	Yes N=110	No N=260	Crude p value[b]	Adjusted p value[c]
IL-1-beta (pg/ml)	54.4	48.4	0.015	0.116
IL-4-sR (pg/ml)	69.6	65.7	0.180	0.261
IL-6 (pg/ml)	3.0	2.4	0.003	0.047
IL-8 (pg/ml)	9.5	8.1	0.001	0.041
IL-10 (pg/ml)	2.1	1.8	0.018	0.018
IL-12 (pg/ml)	3.2	3.3	0.249	0.704
TNF-alpha (ng/ml)	2.6	2.3	0.024	0.124

Fifteen individuals of N=385 were excluded from the analyses due to missing cytokine data (no blood obtained)

[a] Crude p value of two sample t test

[b] Separate linear regression analyses of single cytokine plus covariates age, gender, smoking

Table 3 Cox proportional hazard models for prediction of all cause mortality by tertile of IL-6, IL-8, and IL-10 among *N*=370 subjects of the MEMO study

Level of Adjustment				Model 1	Model 2	Model 3
Cytokine (pg/ml) tertile		Death/N	Death/per 100 person years	HR, 95% CI; *p* value	HR, 95% CI; *p* value	HR, 95% CI; *p* value
IL-6	Lower (<0.68)	29/133	3.36	Ref.	Ref.	Ref.
	Middle (0.68–2.19)	25/114	3.38	1.05, 0.6–1.8; 0.85	1.03, 0.6–1.8; 0.93	0.97, 0.30; 0.93
	Upper (>2.19)	56/123	7.02	1.88, 1.2–3.0; 0.007	1.75, 1.1–2.8; 0.02	1.67, 1.04–2.8; 0.04
IL-8	Lower (<5.58)	30/121	3.82	Ref.	Ref.	Ref.
	Middle (5.58–8.39)	32/128	3.85	0.92, 0.6–1.5; 0.76	0.94, 0.6–1.6; 0.81	0.91, 0.5–1.5; 0.71
	Upper (>8.39)	47/121	6.0	1.49, 0.9–2.4; 0.09	1.40, 0.9–2.2; 0.16	1.29, 0.8–2.1; 0.30
IL-10	Lower (<1.41)	37/147	3.88	Ref.	Ref.	Ref.
	Middle (1.41–2.97)	30/100	4.62	1.13, 0.7–1.9; 0.62	1.13, 0.7–1.8; 0.63	1.15, 0.7–1.9; 0.57
	Upper (>2.97)	43/123	0.46	1.34, 0.9–2.1; 0.20	1.29, 0.8–2.0; 0.26	1.21, 0.8–1.9; 0.41

Fifteen individuals of *N*=385 were excluded from the analyses due to missing data

HR hazard ratio; *95% CI* 95% confidence interval; *Model 1* separate analyses of cytokine plus covariates age, gender, smoking; *Model 2* (separate analyses) model 1 plus vascular and bone morbidity; *Model 3* model 2 plus each other cytokine

in older adults, our study results showed an age effect on inflammation as shown for the cytokines IL-6 and IL-8.

While the increase in circulating inflammatory parameters appears to be small in healthy elderly humans (Bruunsgaard et al. 2001), diseases involving inflammatory processes possibly exacerbate levels of circulating inflammatory markers as shown for age-related illnesses such as atherosclerosis (Ross 1999), osteoporosis (Pacifici 1999), Alzheimer disease (Balin et al. 1998), Parkinson disease (Dobbs et al. 1999), and type 2 diabetes (Paolisso et al. 1998). Although our study was performed in the general elderly population, it should be pointed out that cardiovascular diseases, diabetes, and hypertension are common conditions in community-dwelling older adults. Moreover, a wide range of subclinical vascular disease in older adults living in the community is

Table 4 Cox proportional Hazard model for prediction of all-cause mortality by tertile of IL-6 stratified for gender among *N*=370 subjects of the MEMO study

N=370		Female (*N*=173)			Male (*N*=197)		
Cytokine (pg/ml) tertile		Death/*N*	Death/per 100 person years	HR, 95% CI; *p* value	Death/*N*	Death/per 100 person years	HR, 95% CI; *p* value
IL-6	Lower (<0.68)	16/66	3.73	Ref.	13/67	2.99	Ref.
	Middle (0.68–2.19)	7/62	1.74	0.47, 0.2–1.2; 0.10	18/52	5.33	1.74, 0.8–3.6, 0.13
	Upper (>2.19)	14/45	4.79	1.13, 0.5–2.4; 0.74	42/78	8.30	2.47, 1.3–4.7; 0.006
IL-8	Lower (<5.58)	13/68	2.95	Ref.	17/56	4.68	Ref.
	Middle (5.58–8.39)	9/57	2.43	0.67, 0.3–1.6; 0.38	23/69	5.13	1.05, 0.6–1.9; 0.89
	Upper (>8.39)	15/48	4.82	1.63, 0.7–3.6; 0.23	32/72	6.85	1.35, 0.7–2.5; 0.34
IL-10	Lower (<1.41)	14/78	2.77	Ref.	23/69	5.13	Ref.
	Middle (1.41–2.97)	10/42	3.67	1.283, 0.6–3.0; 0.562	20/58	5.31	1.14; 0.6–2.1; 0.68
	Upper (>2.97)	13/53	3.78	1.43, 0.7–3.1; 0.37	30/70	6.60	1.24, 0.7–2.1; 0.45

Fifteen individuals of *N*=385 were excluded from the analyses due to missing data; HR model=IL-6/IL-8/IL-10 tertile plus covariates age, smoking, vascular, and bone morbidity

HR hazard ratio; *95% CI* 95% confidence interval

strongly associated with inflammation and mortality (Kuller et al. 2006; McDermott et al. 1994, 2002).

The gender-specific effect for IL-6 in men in our study is supported by research carried out by Stork et al., who found that the upper tertile of IL-6 was related to all-cause and CVD mortality (Stork et al. 2006). However, the comparison between the two studies is limited since Stork et al. carried out their analyses in male participants only. On the contrary, Harris et al. found in the Iowa 65+ Rural Health Study that IL-6 was prospectively associated with all-cause mortality over 4.6 years of observation on average independent of gender (Harris et al. 1999). In general, previous research in the area only partly investigated gender-specific associations between inflammatory markers and mortality and, therefore, remains inconclusive at this stage. While some studies on the prospective association between inflammatory markers including cytokines and specific diseases, such as CVD, report gender-specific findings for men (Stork et al. 2006) or women (Volpato et al. 2001), studies in the general population investigating all-cause mortality stratifying or adjusting the analyses for gender are rare (Harris et al. 1999).

The gender-specific finding in our study suggests that men have a larger increase in some of the age-related inflammatory markers. An enhanced gender-specific inflammatory response during aging contributes to the consistent finding in Western societies of earlier death in men as compared to women (Peto et al. 1992). However, the discussion of gender-specific aspects of longevity and mortality including inflammatory markers is still inconclusive (Candore et al. 2006). Further research into gender-specific aspects of mortality needs to consider inflammatory hypotheses in general population samples, which might yield results that contribute to a pathophysiological inflammatory model of shorter life expectancy often observed in men as compared to women.

The present study has strengths and limitations. A larger array of cytokines allowed for the simultaneous investigation of pro- and anti-inflammatory cytokines. Furthermore, the long follow-up period of 9 years indicates that cytokines and IL-6 in particular have a long-term relevance in predicting all-cause mortality in the elderly. However, although the study has a prospective design, the finding should be interpreted with caution in that the cytokine IL-6 is not to be regarded as a causative factor of death, but possibly as a long-term biomarker of mortality in elderly men. This gender-specific findings needs to be seen in the context that the pro-inflammatory state in older persons is possibly related to the high prevalence of cardiovascular risk factors and other morbidities in the elderly impacting on mortality rates (Ferrucci et al. 2005). However, in our study, adjustment for vascular and bone-related morbidity did not alter the main results for men. While in this study cytokine measures were employed at baseline only due to the lack of follow-up measures, other studies suggest that prospective changes in inflammatory markers were better predictors of mortality than baseline measures (Alley et al. 2007). Therefore, our findings require replication in studies with multiple time points of inflammatory measures. Future studies might also be analyzing combined biomarkers suitable in large-scale epidemiological studies (Jenny et al. 2007). Our study sample would not allow for such an approach. Another potential limitation is insufficient power for the detection of effects of IL-6 on death in female. However, power calculations for the effects of IL-6 tertiles on deaths in male and female estimate a power of 89% (at alpha=0.5, two-sided) for IL-6 dependent differences of 1.4 in HR between male and female (Table 4). Moreover, this HR differences correspond with the number of deaths per 100-person years showing a 2.8-fold increase in deaths in male as compared to 1.3-fold increase in female between the highest IL-6 tertile vs the lowest IL-6 tertile. While we considered diseases associated with inflammation (e.g., cardiovascular diseases), other factors associated with inflammation such as diet could not be considered in this study. However, the Mediterranean diet may have an important impact on lower inflammatory markers in older subjects (Dedoussis et al. 2008).

In conclusion, aging is characterized by chronic low-level inflammatory processes, which might be enhanced for certain cytokines such as IL-6. This study suggests that IL-6 is a long-term predictor of all-cause mortality in elderly community dwelling men but not in women.

Acknowledgements The MEMO Study is supported by the German Research Society (Deutsche Forschungsgemeinschaft, grant: BE1996/1-1). Data assessment was done within the framework of the Cooperative Health Research in the Augsburg Region (KORA). The funding body had no impact on the study design or results of the study. We gratefully acknowledge the skillful technical support of Gerald Ponath. Bernhard Baune had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interests All authors declare no conflict of interest.

References

Alley DE, Crimmins E, Bandeen-Roche K, Guralnik J, Ferrucci L (2007) Three-year change in inflammatory markers in elderly people and mortality: the Invecchiare in Chianti study. J Am Geriatr Soc 55:1801–1807

Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol 187:23–42

Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, Berger K (2008) Association between IL-8 cytokine and cognitive performance in an elderly general population–the MEMO-Study. Neurobiol Aging 29:937–944

Bruunsgaard H (2002) Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations. Eur Cytokine Netw 13:389–391

Bruunsgaard H, Pedersen BK (2003) Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am 23:15–39

Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen AN, Skinhoj P, Pedersen BK (1999) A high plasma concentration of TNF-alpha is associated with dementia in centenarians. J Gerontol A Biol Sci Med Sci 54:M357–M364

Bruunsgaard H, Pedersen M, Pedersen BK (2001) Aging and proinflammatory cytokines. Curr Opin Hematol 8:131–136

Bruunsgaard H, Andersen-Ranberg K, Hjelmborg JB, Pedersen BK, Jeune B (2003) Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am J Med 115:278–283

Candore G, Balistreri CR, Listi F, Grimaldi MP, Vasto S, Colonna-Romano G, Franceschi C, Lio D, Caselli G, Caruso C (2006) Immunogenetics, gender, and longevity. Ann NY Acad Sci 1089:516–537

Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Tracy RP, Rubin SM, Harris TB, Pahor M (2003) Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). Am J Cardiol 92:522–528

Csiszar A, Ungvari Z, Koller A, Edwards JG, Kaley G (2003) Aging-induced proinflammatory shift in cytokine expression profile in coronary arteries. FASEB J 17:1183–1185

Dedoussis GV, Kanoni S, Mariani E, Cattini L, Herbein G, Fulop T, Varin A, Rink L, Jajte J, Monti D, Marcellini F, Malavolta M, Mocchegiani E (2008) Mediterranean diet and plasma concentration of inflammatory markers in old and very old subjects in the ZINCAGE population study. Clin Chem Lab Med 46:990–996

Dobbs RJ, Charlett A, Purkiss AG, Dobbs SM, Weller C, Peterson DW (1999) Association of circulating TNF-alpha and IL-6 with ageing and parkinsonism. Acta Neurol Scand 100:34–41

Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, Guralnik JM, Longo DL (2005) The origins of age-related proinflammatory state. Blood 105:2294–2299

Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH Jr, Heimovitz H, Cohen HJ, Wallace R (1999) Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 106:506–512

Heikkila K, Ebrahim S, Rumley A, Lowe G, Lawlor DA (2007) Associations of circulating C-reactive protein and interleukin-6 with survival in women with and without cancer: findings from the British Women's Heart and Health Study. Cancer Epidemiol Biomark Prev 16:1155–1159

Jenny NS, Yanez ND, Psaty BM, Kuller LH, Hirsch CH, Tracy RP (2007) Inflammation biomarkers and near-term death in older men. Am J Epidemiol 165:684–695

Keil U, Liese AD, Hense HW (1998) Classical risk factors and their impact on incident non-fatal myocardial infarction and all-cause mortality in southern Germany. Results from the MONICA Augsburg cohort study 1984-1992. Eur Heart J 19:1197–1207

Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, Burke GL, Manolio TA, Chaves PH (2006) 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. Arch Intern Med 166:71–78

McDermott MM, Feinglass J, Slavensky R, Pearce WH (1994) The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. J Gen Intern Med 9:445–449

McDermott MM, Ferrucci L, Simonsick EM, Balfour J, Fried L, Ling S, Gibson D, Guralnik JM (2002) The ankle brachial index and change in lower extremity functioning over time: the Women's Health and Aging Study. J Am Geriatr Soc 50:238–246

Murray CJ, Lopez AD (1997) Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 349:1269–1276

Nikolova-Karakashian M, Karakashian A, Rutkute K (2008) Role of neutral sphingomyelinases in aging and inflammation. Subcell Biochem 49:469–486

Pacifici R (1999) Aging and cytokine production. Calcif Tissue Int 65:345–351

Paolisso G, Rizzo MR, Mazziotti G, Tagliamonte MR, Gambardella A, Rotondi M, Carella C, Giugliano D, Varricchio M, D'Onofrio F (1998) Advancing age and insulin resistance: role of plasma tumor necrosis factor-alpha. Am J Physiol 275:E294–E299

Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr (1992) Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 339:1268–1278

Ross R (1999) Atherosclerosis–an inflammatory disease. N Engl J Med 340:115–126

Sansoni P, Vescovini R, Fagnoni F, Biasini C, Zanni F, Zanlari L, Telera A, Lucchini G, Passeri G, Monti D, Franceschi C, Passeri M (2008) The immune system in extreme longevity. Exp Gerontol 43:61–65

Schmidt WP, Roesler A, Kretzschmar K, Ladwig KH, Junker R, Berger K (2004) Functional and cognitive consequences of silent stroke discovered using brain magnetic resonance imaging in an elderly population. J Am Geriatr Soc 52:1045–1050

Shurin MR, Shurin GV, Chatta GS (2007) Aging and the dendritic cell system: implications for cancer. Crit Rev Oncol Hematol 64:90–105

Singhal A (2005) Endothelial dysfunction: role in obesity-related disorders and the early origins of CVD. Proc Nutr Soc 64:15–22

Stork S, Feelders RA, van den Beld AW, Steyerberg EW, Savelkoul HF, Lamberts SW, Grobbee DE, Bots ML (2006) Prediction of mortality risk in the elderly. Am J Med 119:519–525

Volpato S, Guralnik JM, Ferrucci L, Balfour J, Chaves P, Fried LP, Harris TB (2001) Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. Circulation 103:947–953

Wei J, Xu H, Davies JL, Hemmings GP (1992) Increase of plasma IL-6 concentration with age in healthy subjects. Life Sci 51:1953–1956

Yetkin E, Waltenberger J (2009) Molecular and cellular mechanisms of aortic stenosis. Int J Cardiol 135:4–13

Zenovich AG, Taylor DA (2008) Atherosclerosis as a disease of failed endogenous repair. Front Biosci 13:3621–3636

Zhu S, Patel KV, Bandinelli S, Ferrucci L, Guralnik JM (2009) Predictors of interleukin-6 elevation in older adults. J Am Geriatr Soc 57:1672–1677