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ORIGINAL ARTICLE

Interleukin-8 is associated with increased total mortality in women but not in men—findings from a community-based cohort of elderly

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Abstract

Objective. **To elucidate the association among circulating IL-8 and total mortality in a cohort of elderly, and to explore potential sex differences in the observed association.**

Methods. **The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) is a cohort of 70-year-old men and women living in Uppsala, Sweden; baseline period: 2001–2004. IL-8 serum measurements were performed in 1003 participants.**

Results. **In total, 61 men and 40 women died during follow-up (median 7.9 years). Baseline IL-8 concentrations were higher in women than in men ($P = 0.03$). In a multivariable model adjusting for age, established cardiovascular risk factors, and C-reactive protein, log-transformed standard deviation increments in IL-8 levels were weakly associated with an increased risk for total mortality (hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.02–1.23, $P < 0.05$) in the whole cohort. Stratified analysis revealed an association in women (HR 1.18, 95% CI 1.06–1.30, $P < 0.01$) but not in men (HR 0.98, 95% CI 0.76–1.26).**

Conclusions. **A weak association between IL-8 serum levels and an increased risk for mortality was observed. The prospective data support the role of IL-8 as a biomarker of interest; yet, further studies are warranted to elucidate validity of our finding and the possibility of a sex difference.**

Key words: All-cause mortality, community-based cohort, cytokines, inflammation, interleukin-8

Key messages

- An elevated serum level of IL-8 was associated with an increased risk of all-cause mortality in elderly women.
- This relationship was independent of traditional cardiovascular risk factors and inflammation (CRP).
- No association between IL-8 and mortality was found in elderly men.

Introduction

Interleukin 8 (IL-8) was the first member of the chemokine superfamily (C-X-C) to be discovered, and it has both chemotactic and immunoactivating effects. Macrophages have been shown to represent a major source of IL-8 production (1), but it is also released from virtually all nucleated cells (2).

Pleiotropic properties of IL-8 have been well characterized in cardiometabolic diseases. In the setting of cardiovascular disease (CVD), IL-8 participates in the process of atherogenesis (3,4), plaque destabilization (5), neovascularization (6), and angiogenesis (7). In cancer, IL-8 recruits leukocyte infiltration and neovascularization, crucial factors that precede the invasiveness and metastatic potential of malignant cells (8,9).

A few previous population-based studies have reported controversial associations of circulating IL-8 levels with the risk for coronary artery disease (10–12), and some previous studies have reported an association between higher IL-8 and adverse outcomes in patients with cancer (13). To the best of our knowledge, prospective studies on the association of IL-8 and total mortality are scarce. Results from the MEMO study indicated that IL-8 levels are associated with total mortality (14). However, this study has a relatively small sample size.

Based on the previous experimental and observational studies suggesting a potential role of IL-8 in both CVD and cancer, we wanted to explore the hypothesis of circulating IL-8 as a biomarker for an increased mortality risk in a larger cohort.

Thus, the primary aim of this study was to investigate the association between increments in IL-8 serum levels and the risk of total mortality in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, a community-based sample of elderly men and women. Due to reported sex differences in IL-8 levels and cardiovascular outcomes (12), we also aimed to

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explore potential sex differences regarding the strength of these associations.

Materials and methods

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)

All 70-year-old men and women living in Uppsala, Sweden, 2001–2004 were eligible for the PIVUS study (15) (described in detail on http://www.medsci.uu.se/pivus/pivus.htm). Of 2025 invited individuals, 1016 agreed to participate. Of these, participants were excluded due to missing data on IL-8, leaving 1003 participants as the present study sample. All participants gave written informed consent, and the Ethics Committee of Uppsala University approved the study protocol.

Baseline investigations

The baseline investigations in PIVUS included anthropometrical measurements, blood pressure measurements, blood sampling, and questionnaires regarding socio-economic status, medical history, smoking habits, medication, and physical activity level (15,16). Venous blood samples were drawn in the morning after an overnight fast and stored at −70°C until analysis.

Serum levels of IL-8 were analyzed on the Evidence® array biochip analyzer (Randox Laboratories Ltd, Crumlin, UK) (17). The functional sensitivity for IL-8 was 1.5 pg/mL. High-sensitivity CRP measurements were performed with the use of an Architect ci8200 in PIVUS (18). Diabetes mellitus was diagnosed as fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL), or use of anti-diabetic medication (19). Adiponectin serum levels were assessed with a double-antibody RIA (Linco Research, St. Louis, MO, USA).

Prevalent cardiovascular disease at baseline was defined as a history of ischemic heart disease or cerebrovascular disease, or Q-, QS-complexes, or left bundle-branch block in baseline ECG.

End-point definitions

The Swedish cause-of-death register was used to identify those who died during follow-up. The completeness of this register has been shown to be very high (20).

Statistical analysis

Primary analyses

We initially investigated distributions of all variables. We thereafter investigated cohort-specific associations of serum IL-8 (primarily modeled as a log-transformed continuous variable, per standard deviation (SD); and secondarily by stratification at the median with low levels as referent) with total mortality using Cox proportional hazards regression in the following multivariable models (using the participants' age as the timeline): A) age; B) age and established cardiovascular risk factors (sex, systolic blood pressure, diabetes, smoking, BMI, total cholesterol, HDL-cholesterol, antihypertensive treatment, lipid-lowering treatment, and prevalent cardiovascular disease) were explored to determine to what extent associations with these factors can explain our findings; and C) factors in Models A and B, and inflammation (CRP).

Proportional hazards assumptions were confirmed by Schoenfeld's tests.

Secondary analyses

We performed secondary analyses in the PIVUS cohort in which serum adiponectin levels were added to Models B and C to explore if an association between IL-8 and adiponectin can explain our findings. We investigated effect modification by gender and CRP by including multiplicative interaction terms in Model C in PIVUS.

Additionally, we calculated the risks associated with combinations of high/low IL-8 levels with normal–high C-reactive protein (CRP) levels (< 3 mg/L versus > 3 mg/L) (21).

Several tests were performed to determine model discrimination in the prediction of mortality for IL-8 and CRP. Model discrimination was quantified by the C-statistic for Cox regression, which can be interpreted as the area under the receiver-operating characteristic curve for a corresponding logistic regression model (22). Likelihood ratio tests have been suggested to be optimal to test the null hypothesis, whether the Cox regression models improve significantly when a biomarker is added (23). We tested if IL-8 and CRP added significantly to models with established CVD risk factors.

A two-sided P value < 0.05 was regarded as significant in all analyses. Stata11.2 (Stata Corp College Station, TX, USA) was used for all analyses.

Results

Mean values ± standard deviations for continuous variables and prevalence rates for categorical variables are presented for men and women in Table I. The median IL-8 and confidence intervals (CI) were significantly different among sexes (pg/mL): 6.3 (6.0–6.5) in men and 6.8 (6.4–7.2) in women, respectively (P = 0.03).

During follow-up (median 7.9 years; range 0.9–9.7 years), 61 men and 40 women died. The mortality rate (MR) per 100 person years follow-up and 95% CI according to IL-8 categorized as below and above the median are shown in Table II.

Results from Cox regression using IL-8 as a continuous and as a categorized exposure are given in Table III for the entire cohort, and in men and women, separately.

In the whole cohort, 1 SD higher ln (IL-8 circulating levels) was associated to 11%–12% higher risk in all multivariable models. The association between IL-8 and mortality remained unaltered when we explored the influence of adiponectin added to model C, hazard ratio per SD increase (HR), 95% CI 1.10 (1.00–1.21). No statistically significant effect modification by sex was present (P = 0.29). There was also no significant interaction between CRP and sex (P = 0.85) or between CRP and IL-8 (P = 0.78).

In women, 1 SD higher ln (IL-8 circulating levels) was associated to 18% higher total mortality rate in the crude model, and it

Table I. Baseline characteristics in the PIVUS cohort.

Variable	Men	Women
Number of subjects	504	499
Serum interleukin 8 (IL-8) (pg/mL)	8.5 ± 13.4	9.1 ± 17.7
Serum interleukin 6 (IL-6) (pg/mL)	32.7 ± 91.4	27.2 ± 76.9
C-reactive protein (CRP) (mg/L)	2.6 ± 6.4	2.4 ± 3.7
Body mass index (kg/m^2)	27.0 ± 3.7	27.1 ± 4.9
Serum total cholesterol (mg/dL)	5.1 ± 1.0	5.7 ± 1.0
Serum HDL cholesterol (mg/dL)	1.4 ± 0.4	1.7 ± 0.4
Systolic blood pressure (mmHg)	146 ± 22	153 ± 23
Diastolic blood pressure (mmHg)	79.4 ± 10.3	78.1 ± 10.1
Fasting glucose (mmol/L)	5.5 ± 1.7	5.2 ± 1.4
Smoking, *n* (%)	50 (9.9)	58 (11.6)
Diabetes, *n* (%)	52 (10.3)	35 (7.1)
Previous cardiovascular disease, *n* (%)	108 (21.4)	57 (11.4)
Lipid-lowering treatment, *n* (%)	89 (17.8)	71 (14.2)
Antihypertensive treatment, *n* (%)	158 (31.5)	151 (30.7)

Data are mean ± standard deviation for continuous variables and *n* (%) for categorical variables.

Table II. Incidence rates of serum IL-8 for total mortality in the PIVUS cohort by gender.

	The PIVUS cohort					
Total mortality	All		Men		Women	
	NE/NR	IR (95% CI)	NE/NR	IR (95% CI)	NE/NR	IR (95% CI)
IL-8 below median	43/471	1.1 (0.8–1.5)	31/245	1.5 (1.0–2.1)	12/226	0.6 (0.4–1.1)
IL-8 above median	58/431	1.5 (1.2–2.0)	30/198	1.7 (1.2–2.4)	28/233	1.4 (0.9–2.0)

Estimated rates (per 100) and lower/upper bounds of 95% confidence intervals.
IR = incidence rates per 100 person years follow-up; NE/NR = number of events/numbers at risk.

remained significant after adjustments for established cardiovascular risk factors. An increased, non-significant point estimate, however, was observed after adjustments by CRP.

The group of women with the IL-8 levels above the median was at a doubled risk of total mortality when compared with participants with the lowest IL-8 levels. The association between circulating IL-8 levels above the median and total mortality was still significant after further adjustments for traditional cardiovascular risk factors and inflammatory biomarkers (Models B and C). The cumulative incidences of mortality in female participants above versus below median of IL-8 are shown in Figure 1A.

No association between IL-8 and mortality was found in men in any model (Table III, Figure 1B)

The C-statistics to predict mortality for a model with CRP, sex, and established cardiovascular risk factors was 0.667. The C-statistics increased to 0.675 when SD increments of IL-8 were added to the model. Sex-adjusted likelihood ratio tests of the whole cohort revealed that neither IL-8 ($P = 0.06$) nor CRP ($P = 0.43$) added significantly to the prediction of mortality in Cox regression models adjusted for established cardiovascular risk factors.

Discussion

Principal findings

The major finding of the present study is that elevated serum levels of IL-8 are weakly associated with an increased risk of all-cause mortality, an association that was present in elderly women but not men in a stratified analysis. This relationship was independent of established cardiovascular risk factors and inflammation (CRP).

Comparison with literature

There are a few previous studies that have reported the longitudinal association between circulating levels of IL-8 and adverse events. In the MEMO study, IL-8 levels were significantly higher in participants who died during the follow-up as compared to survivors, yet higher levels of IL-8 were not a predictor of total mortality in the analysis by tertiles (14). Of note, and in agreement with our findings, the authors reported a higher point estimate in women than in men, although non-significant. We have analyzed our exposure using IL-8 as a continuous variable (log-transformed) and using the median as a cut-off value. In this context, no consensus so far has been established when using cut-off for biomarkers in population-based studies. As compared to the previous study, we did not adjust for interleukin 6 (IL-6) in the final model, since we consider IL-6 to be in the intermediate pathway and not a confounder for the association of IL-8 and total mortality (24). As well, differences in baseline characteristics from both populations could also partially explain the discrepancy in the results of both cohorts of elderly. Likewise, higher IL-8 levels have been shown to predict cardiovascular mortality and all-cause mortality in a small cohort of patients with end-stage renal disease (25).

Current studies into the association of IL-8 levels as an independent predictor of CVD are scarce and have not reached consensus. The MONICA/KORA, a prospective case-cohort study, included as a composite outcome of fatal, incident, and non-fatal myocardial infarction (MI) and sudden cardiac death before the age of 75, reported that IL-8 levels precede but do not represent independent risk factors (11), whereas the EPIC-Norfolk, a nested case-control study that comprised fatal and non-fatal MI, observed an association of IL-8 levels and increased risk of incident CVD (10). Recently, in a large population-based MI case-control study, elevated levels of serum IL-8 were associated with a reduced MI occurrence among women aged 45–70 years, possibly explained by different effects of IL-8 over different stages of CVD (12).

In the context of cancer diseases, IL-8 levels have been demonstrated to be an independent prognostic factor of survival for hepatocellular carcinoma (26) and is associated with 10 different types of cancer: colorectal cancer, hepatocellular cancer, bone sarcomas, gastric cancer, metastastic breast cancer, esophageal cancer, soft tissue sarcoma, prostate cancer, diffuse large B cell lymphoma, and non-small cell lung cancer (13). In fact, IL-8 has been shown to have a prognostic impact on breast cancer recurrence according to breast cancer subtype (27), suggesting a profound effect of IL-8 on the tumor microenvironment (28).

Table III. Cox proportional hazard regression models.

	All	Men	Women
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Continuous models: per SD higher lnIL-8			
Model A	1.14* (1.05–1.25)	1.01 (0.78–1.33)	1.18*** (1.08–1.29)
Model B	1.11* (1.01–1.23)	0.97 (0.75–1.27)	1.18** (1.06–1.30)
Model C	1.12* (1.02–1.23)	0.98 (0.76–1.26)	1.18** (1.06–1.30)
Above versus below median (referent)			
Model A	1.46 (0.98–2.17)	1.16 (0.70–1.91)	2.16* (1.09–4.24)
Model B	1.50* (1.00–2.24)	1.07 (0.65–1.79)	2.53* (1.22–5.24)
Model C	1.52* (1.01–2.23)	1.09 (0.65–1.83)	2.53* (1.22–5.23)

Model A: adjusted by sex; Model B: factors in Model A, and established cardiovascular risk factors (BMI, smoking, lipid-lowering treatment, diabetes, systolic blood pressure, previous cardiovascular disease, HDL-cholesterol, total cholesterol, antihypertensive treatment); and Model C: factors in Model B, and inflammation (CRP).
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

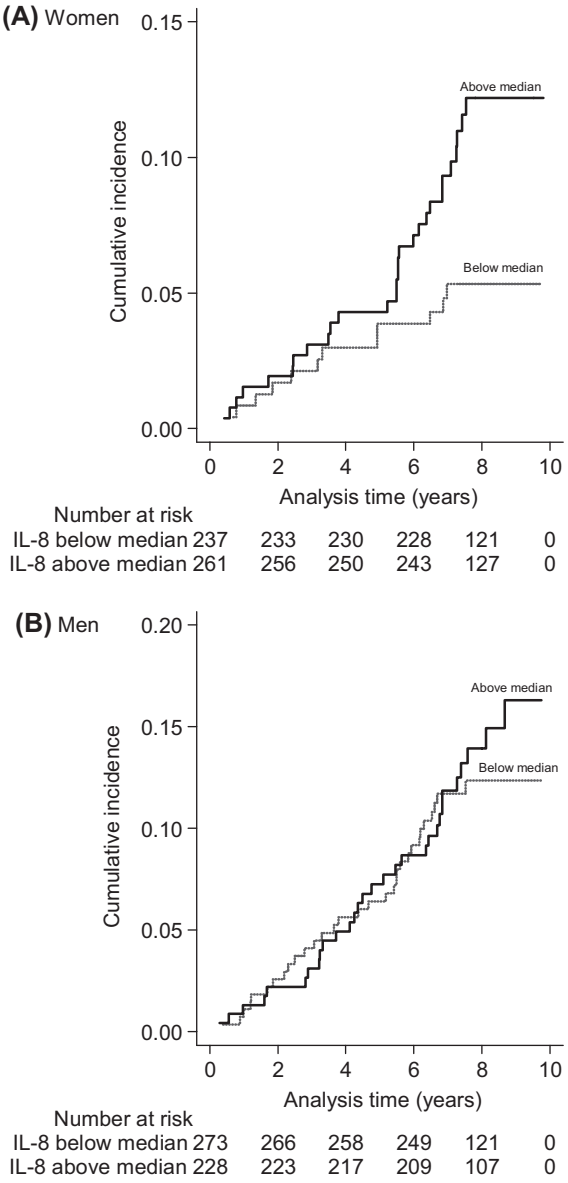

Figure 1. Nelson–Aalen survival curve. (A) Women. (B) Men.

Potential mechanisms for the observed associations

Although it is not possible to establish causality in this observational study, there are several important properties of IL-8 that may explain the association between higher IL-8 and increased risk for mortality. Evidence shows that IL-8 exerts pro-inflammatory, pro-atherogenic, pro-angiogenic, and tumorigenic activities (29–31). IL-8 is involved from the initiation and progression of atherosclerosis to cardiovascular remodeling (3,5,32,33). Circulating levels of IL-8 have been shown to be higher in individuals with established coronary heart disease (CHD) than in individuals without CVD (34,35). In cancer, IL-8 has been associated to tumor size, depth of infiltration, or associated with increasing stage of disease stage (13).

The reason to why the association between IL-8 and mortality was predominantly seen in women in the present study is not clear. However, speculatively, there are some potential mechanisms that may explain these findings.

First, we observed a significantly higher circulating IL-8 levels in women than in men at baseline. Concomitantly, smoking was more prevalent in women. It has been shown that nicotine stimulates IL-8 release from neutrophils (36) and that smoking decreases the adiponectin concentrations more in women than in men (37), which may be of relevance since adiponectin has been shown to down-regulate IL-8 production (38) . Additionally, elevated adiponectin levels have been associated with total mortality and cardiovascular mortality in subjects with established atherosclerosis (39). Yet our results remained significant after adjustments for current smoking and circulating adiponectin levels, indicating that this is not a major pathway explaining our findings.

Second, more men were prescribed statin treatment than women in our study. Drug therapy with statins has been shown to down-regulate IL-8 production by the endothelium and leukocytes (40). These observations could partly explain the sex differences on circulating IL-8 at baseline and the lack of association between IL-8 levels and mortality in men. Yet, this cannot be the sole explanation as adjustments for statin treatment did not change our results.

Third, adiposity is strongly associated with low-grade systemic inflammation, and women tend to have a higher percentage of body fat, especially subcutaneous fat, than do men, despite comparable amounts of liver and intra-abdominal fat (41). Nevertheless, aging, in particular, increases the visceral fat component of weight gain in women (42). In fact, postmenopausal women have increased inflammatory responses in the subcutaneous fat and higher serum IL-8 than those of premenopausal women (43). Even though our observed association is independent of BMI, women at age 70 might have a higher visceral adiposity that is not reflected by the body mass index (44). We have further adjusted for waist circumference, and the results did not change: HR 95% (CI) 2.6 (1.23–5.47). Of note, studies in animal models have shown that estradiol, per se, lowers the basal and hypercholesterolemia-induced increases in IL-8 receptor mRNA and protein (45,46); however, it has also been reported that IL-8 serum levels are not regulated by the IL-8 receptor gene (12).

Fourth, IL-8 has been associated with mobilized progenitor cells in acute MI and may in this case have a potential beneficial effect (6). Several studies have demonstrated that circulating endothelial progenitor cells (EPCs) are reduced in the presence of classic cardiovascular risk factors, including non-modifiable risk factors such as age. In particular, males have lower EPCs than females do; however, whether EPCs levels in postmenopausal women are higher than in men of the same age is debated (47–49). Hence, taken together, it can be speculated that IL-8 homing capacity of EPCs is affected in women after menopause, a process that may interfere with neovascularization after MI and increased CV mortality. We have not been able to find any data on the effects of IL-8 in cancer mortality.

Clinical implications

Aging has been positively correlated with chemokine concentrations, including IL-8 (11,14), and a chronic low-grade inflammatory activity has been associated with age-related diseases and increased mortality risk in cohorts of elderly (50). Although rates of death attributable to CVD have declined in many developed countries (51), CVD was the main cause of death followed by cancer during the follow-up period in the present study (52). Thus, it is likely that the association between IL-8 and mortality to a large degree is driven by an association with mortality due to CVD or cancer.

Our findings suggest that IL-8 may be particularly promising in elderly women. Since IL-8 serum levels add additional prognostic information identified by normal C-reactive protein (CRP) levels, IL-8 measurements could be of value to identify women

with a higher CVD-risk associated with an increased inflammatory level beyond what CRP does. However, likelihood ratio tests for IL-8 as well as CRP were non-significant when the whole cohort was analyzed in the present study, indicating that the clinical use of IL-8 and CRP is limited when it comes to the prediction of mortality in the elderly in general.

Many cytokines are associated to one another, which is why adjustments for many of them in the same model are of little interest clinically. Yet, IL-8 was associated with mortality in models adjusted for CRP and established cardiovascular risk factors in the present study, indicating its independence.

Strengths and limitations

The strength of the study includes the homogeneous, community-based study samples with longitudinal data and the detailed characterization of the study participants pertaining to lifestyle and cardiovascular risk factors.

The present population-based sample had a moderate participation; however, a sensitivity analysis showed the present sample to be representative of the total population regarding MI, cardiovascular treatment, and coronary revascularization, whereas diabetes, heart failure, and prior stroke were more common in non-participants (15). Our interaction analysis did not support the notion of an effect modification by gender on the strength of the association between IL-8 and mortality. Additional, much larger studies are needed to investigate this issue properly. However, men and women have different mortality risks in general (53,54), as well as differences with regard to IL-8 and other inflammatory cytokines (12,14,55). Thus, we believe that a stratified analysis is justified.

The main limitation of the present study is that PIVUS is limited to elderly individuals of Caucasian origin, and therefore our results might not necessarily be extrapolated to other ethnic and age-groups. Our study participants were recruited at the age of 70 and may have been subject to healthy cohort effects. Moreover, Sweden has a high average mortality age (80.1 years for men and 83.7 years for women in 2013 according to Statistics Sweden). The relatively few events during follow-up resulted in fairly wide confidence intervals and consequently a greater uncertainty regarding the true risk estimates. The lack of data on cause-specific mortality is also a limitation; however, that would also require a larger cohort study. Since IL-8 circulating levels might be a reflection of different stages of CVD (12), we cannot exclude residual confounding as a result of unmeasured (prevalent CV/inflammatory diseases) or unknown risk factors. Yet, with the present length of follow-up, and limited number of fatalities, we believe that a multi-marker approach with many biomarkers would hamper the power of the study. Therefore, our findings require validation in other populations preferably using repetitive measurements for IL-8.

Conclusions

A weak association between IL-8 serum levels and an increased risk for mortality was observed. Given the hallmark of IL-8 contribution to atherogenesis and tumorigenesis, further studies assessing the role of IL-8 as a marker of mortality in CVD and cancer with emphasis on sex differences are advocated to evaluate the potential utility of this biomarker for prognosis in clinical settings.

Declaration of interest: The authors report no conflicts of interest.

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