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**Biomarkers of Inflammation and Malnutrition Associated with Early Death in Healthy Elderly.**

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Abbreviated title: Inflammation, malnutrition and mortality in elderly.

**ABSTRACT**

**Objectives:** To determine whether malnutrition and inflammation biomarkers predict all-cause, cancer and cardiovascular mortality in healthy elderly subjects.

**Design:** Prospective cohort.

**Setting:** Population-based study, Sète, French Mediterranean coast.

**Participants:** 553 men and 888 women aged 60+ years from the POLA (Pathologies Oculaires Liées à l'Age) cohort, free of known co-morbidities.

**Measurements:** Plasma levels of cholesterol, albumin, transthyretin (TTR), C-reactive protein (CRP) and alpha 1-acid glycoprotein (AAG) were measured at baseline. To investigate the risks of 5-year (early) and 5-9 year (late) mortality hazard ratios (HR) were evaluated using Cox models.

**Results:** In men, the early death risk was increased for high CRP and AAG and for low albumin and TTR. In women, early death was associated with high AAG, low TTR and cholesterol. For late death, the only significant association was with CRP in men. A synergistic effect was observed between biomarkers of inflammation and malnutrition. The adjusted HR of early death was 4.98(95% Confidence Interval(CI)= 2.25-11.01) for both CRP in the highest quartile and albumin in the lowest in men. This risk was increased for AAG in the highest quartile and TTR in the lowest in men and women with an HR of 6.86(95%CI= 3.20-14.71) and 4.64(95%CI= 1.79-12.05) respectively. Cancer mortality was increased for high CRP and AAG and for low albumin and TTR in men but not in women.

**Conclusions:** Biomarkers of inflammation and malnutrition together predict early mortality. In healthy elderly subjects TTR and AAG could be helpful in identifying elderly subjects at higher risk of death.

**Key words: inflammation, malnutrition, mortality, frailty**

## INTRODUCTION

The geriatric syndrome of frailty is a physiological state characterized by low functional reserve, high susceptibility to stressors and unstable homeostasis, resulting from simultaneous decline in multiple physiological systems (1, 2). This extensive dysfunction inhibits recuperation of optimal homeostatic equilibrium after a destabilizing event, such as a disease or a trauma.

The phenotypical manifestation of frailty involves multiple factors, including hormone levels, immune response, balance between free radical production and antioxidant mechanisms and the dynamic balance between sympathetic and parasympathetic tone (3). The inflammatory process plays an important role in aging and seems to be a major determinant of frailty (4, 5). Some authors have hypothesized a dynamic model of frailty in which inflammation, neuroendocrine dysregulation, and sarcopenia contribute to a spiralling decline in physiological processes and function (6, 7). With aging there is also a decline in food intake due to multiple causes including an increase in the activity of the peripheral satiation system and a decline in the activity of the central feeding system. This anorexia of aging accelerates a decline in muscle mass, considered as a central criterion of frailty (8). With the development of malnutrition, a vicious cycle is established in which the older person develops recurrent infections leading to further cytokine release and cachexia, or wasting syndrome (9). Proposed frailty syndrome definitions have been based on physical and cognitive performance limitations and nutritional clinical measurements (8, 10-13). Biomarkers of inflammation and malnutrition are thus hypothesized to constitute early indicators of this frailty syndrome.

With aging the presence of comorbidity, an aggregation of clinically manifest diseases, increases markedly and may coexist with frailty (14). To distinguish the two concepts we planned to analyze biological parameters of inflammation and undernutrition as markers of frailty predicting

mortality in a selected group of elderly people without history of chronic disease. The central aim is thus to identify the characteristics of pre-clinical frailty also named primary frailty; this may be the most effective point for intervention programs promoting successful aging.

Sex differences in the effects of inflammation on mortality have been reported; the association being more pronounced in men (15, 16). We sought to explore these differences considering also that the trajectories from frailty to disability or death may be different between men and women (12, 17).

In the present longitudinal study we examined the relationship between inflammatory and nutritional biomarkers and early and late mortality (≤ 5 years and > 5 years respectively) in a high functioning elderly cohort, free of known co-morbidities, stratified by gender. We examined both all-cause mortality risk and several specific causes including cancer and cardiovascular death.

## METHODS

### Study population

The POLA (Pathologies Oculaires Liées à l'Age) study is a population-based study, aiming at the identification of risk factors for cataract and age-related maculopathy (18). Briefly, from 1995 to 1997, 2584 subjects aged 60 years or more were recruited from the population of Sète, a harbour on the French Mediterranean.

At baseline, diabetes was defined as self-reported history of diabetes confirmed by current antidiabetic therapy and/or fasting blood glucose ≥ 7 mmol/l. Coronary heart disease (CHD) was defined as the presence of at least one of the following criteria: (a) self-reported history of myocardial infarction and/or angina pectoris and/or coronary artery bypass, confirmed by use of medications (beta-blockers, nitrates, calcium channel blockers, potassium channel openers,

molsidomine, bépridil), (b) use of specific angina pectoris medications (nitrates, potassium channel openers, molsidomine, bépridil), (c) self-reported history of myocardial infarction and use of aspirin medication.

For the present study subjects with a history of the following diseases were excluded: diabetes, coronary heart disease and self-reported history of stroke, lower limb arterial disease, cancer, asthma and respiratory disease. Subjects treated with non-steroidal anti-inflammatory drugs or with oral corticosteroid treatment were also excluded.

Among the 2584 subjects originally included in the POLA study, 1031 (39.9 %) subjects were excluded from the analysis because they presented at least one of the preceding exclusion criteria. Of the 1553 remaining subjects, 112 (7.2%) had some missing data in adjustment covariables or in biochemical variables leaving 1441 subjects for the statistical analyses: 553 men and 888 women. For the analysis involving cholesterol as a risk factor, we only considered subjects without any lipid lowering treatment at inclusion (n=451 and 671 for men and women respectively).

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent prior to participation in the study. The design of this study has been approved by the Ethical Committee of the Montpellier University Hospital.

**Measures**

Biological measures were made from fasting blood samples performed at home on the morning of the first examination. They included plasma measures (cholesterol, triglycerides, glucose, vitamin A, E and C). In 2001, we performed a new series of biochemical measurements. The plasma samples were kept frozen at -80°C, for approximately 5 years before these measurements were performed. Plasma albumin, transthyretin (TTR) and alpha 1-acid glycoprotein (AAG)

were determined by immunonephelometric methods on Immage system (Beckman Coulter, Villepinte, France) while highly sensitive C-reactive protein (CRP) was determined by latex-enhanced immunoturbidimetric method using reagents from Olympus (Rungis, France) on a Olympus AU2700 biochemistry analyzer. The prognostic inflammatory and nutritional index (PINI) was defined as the quotient of (CRP x AAG) by (Albumin x TTR) (19).

Vital status and cause of death were provided by the French National Death Registry and the Center for Epidemiology of Medical causes of Death (CepiDc-Inserm). The registry provided 96.4% ascertainment of mortality status. The 3.7% subjects not found by this procedure were considered to be alive up to the last examination or phone contact and subsequently considered as censored. Of the 1441 subjects considered in this paper, 111 men (20.1%) and 110 women (12.4%) were found to be dead 9 years after inclusion. The causes of death were known for 96 men (86.5%) and 98 women (89.1%). We only considered the main cause of death as mentioned on the medical certificate of death.

At inclusion, a standardized interview was performed to assess: socio-demographic variables, medical history, all medications currently used and lifestyle factors (smoking, physical exercise). The interviewer then measured height, weight, waist and hip circumferences, systolic and diastolic blood pressure.

Participants were considered as having high education if they had reached at least the end of high school. Body mass index was defined as weight(kg) / [height(m)]$^2$. Subjects were asked whether they felt in better, similar or worse health than other people of the same age. When the answer was “worse”, they were considered as having “bad perceived health”.

**Statistical analyses**

To investigate the association between biochemical parameters with mortality, the Cox model was used taking age as the basic time scale and birth as the time origin (20). This method adjusts hazard ratio (HR) for age and thus avoids the problem of non proportionality of the risk of death with age. To analyze possible non-linear associations, continuous covariates were categorized by quartiles. We created three groups (low quartile, middle quartiles, high quartile) and the HR of mortality for each biochemical variable was expressed relative to the middle category. We performed univariate and multivariate models adjusted for potential confounders: educational level, perceived health and current smoking. Analyses were stratified by gender to investigate potential sex-specific interactions and the quartiles are sex specific. Analyses were carried out using SAS software (version 9.1).

## RESULTS

### Baseline risk factors and death during follow-up

The sample consists of 553 men and 888 women with a mean age at inclusion (SD) of 70.0 years (6.6). Baseline characteristics are shown in table 1. Men had a higher educational level, were more frequently current or past smokers and had a BMI slightly higher, while women had worse perceived health. Albumin and TTR were very significantly lower in women while, in the absence of treatment by statins or fibrates, cholesterol was higher. These differences justified the use of different quartiles for each sex.

Of the 111 men and 110 women who died during the 9 years of follow-up, 50 (45.0%) and 45 (40.9%) deaths occurred in the first 5 years (early deaths) and 61 (55.0%) and 65 (59.1%) deaths occurred between 5 and 9 years of follow-up (late deaths) for men and women, respectively. Thirty nine (35.1%) and 31 (28.2%) deaths had cardiovascular causes and 29 (26.1%) and 33 (30.0%) deaths were due to cancer for men and women, respectively.

**Associations of biomarkers with early death**

In men, the risk of early death was significantly increased in the upper quartile of CRP and AAG in unadjusted and adjusted models (table 2). The HR (95% confidence interval (CI)) were 2.15 (1.14-4.02) and 2.26 (1.19-4.31) for CRP and AAG, respectively, in the model adjusted for age, educational level, perceived health and smoking. In women, only the upper quartile of AAG was associated with early death. The HR (95%CI) was 2.61 (1.27-5.35) in the adjusted model.

With regard to biomarkers of malnutrition, the lower quartiles of albumin and TTR were highly significantly associated with an increased risk of early death in men, in both unadjusted and adjusted models. The HR (95%CI) were 2.72 (1.44-5.14) and 2.23 (1.21-4.13) for albumin and TTR in the adjusted model, respectively. There was also a tendency for a protective effect for the upper quartile of TTR and to an increased risk for the lower quartile of cholesterol. Among women, the lower quartile of TTR and cholesterol showed a significant higher risk of death compared to the middle category with an HR (95%CI) equal to 2.39 (1.24-4.58) and 2.21 (1.06-4.62) respectively.

The PINI index confirmed these results in men but no significant relationship was found in women.

None of the biochemical parameters showed interaction with current smoking. In women, use of hormonal replacement therapy was not significant ($P$>0.90) in all multivariate models. Further adjustments on cholesterol, BMI and hypertension did not change the results for CRP, AAG, albumin and TTR in men and women.

**Associations of biomarkers with late death**

When the same analyses were performed for late death, no significant associations were found, except for the upper quartile of CRP and PINI in men (table 3). The CRP association remained

strongly significant with an HR (95%CI) equal to 2.37 (1.36-4.15). A protective effect was also found for the lowest quartile of AAG in men (HR (95%CI)= 0.38 (0.16-0.92)).

**Combined association of inflammation and malnutrition biomarkers with early death**

Considering that CRP and albumin are the most common biochemical parameters of inflammation and malnutrition in medical practice, we calculated their combined risk of early death. This risk increased markedly in men when both CRP is in the highest quartile and albumin in the lowest (HR(95%CI)= 4.98(2.25-11.01)) compared to low or middle quartiles for CRP and to high or middle quartiles for albumin after adjustment for other risk factors (figure 1). This combination of CRP and albumin was not significant in women.

However, when we considered the combination of AAG and TTR the risk is increased in both genders for AAG in the highest quartile and TTR in the lowest with HR(95%CI)= 6.86(3.20-14.71) and HR(95%CI)= 4.64(1.79-12.05) in men and women respectively compared to low or median quartiles for AAG and to high or median quartiles for TTR after adjustment for other risk factors (figure 1).

**Associations of biomarkers with cancer and cardiovascular death**

Due to small numbers of deaths, only 9-year mortality was examined. In men, the risk of mortality by cancer was significantly increased in the highest quartile of CRP (HR(95%CI)= 3.05(1.50-6.18)) and AAG (HR(95%CI)= 2.04(1.01-4.12)) and in the lowest quartile of albumin (HR(95%CI)= 2.04(1.04-4.02)) and TTR (HR(95%CI)= 3.39(1.64-7.00)). By contrast the risk of mortality by cardiovascular disease was only increased for high CRP levels with a HR (95%CI) equal to 2.77 (1.22-6.30), but no significant difference was found for malnutrition parameters. In women neither cancer nor cardiovascular mortality were found to be significantly associated

with biochemical parameters or BMI, but high PINI levels were associated with cardiovascular death (HR(95%CI)= 2.47(1.10-5.57)).

## DISCUSSION

The findings from this sample of apparently healthy community-dwelling older persons showed that high AAG levels and low TTR levels were strongly associated with an increased risk of early death in both men and women. We observed a very significant synergistic effect between AAG and TTR in predicting higher early mortality. For CRP and albumin this increase in risk was found only in men. Prediction of early death was again enhanced by the joint effect of these two markers. In contrast these associations were not found for the risk of late death except for CRP in men. Similarly hypocholesterolemia was slightly associated with early death in women and nearly significantly associated in men. But as already found by Okamura et al (21) this association disappeared after excluding deaths in the first 5 years of follow-up. As the number of deaths observed between 5 and 9 years (and thus the power of the statistical analysis) was higher than the number of early deaths, we believe that if an association between AAG or biomarkers of malnutrition with late mortality exists, it is far weaker than that with early death.

These attenuated associations with late death could be explained by a survivor effect. Inflammation may be influenced by subclinical disease such as cardiovascular disease, diabetes and cancer. Our selection of healthy subjects mainly based on current drug prescriptions and self reported history of diseases, possibly kept in the analysis subjects with undiagnosed inflammatory diseases. The subjects with the highest levels of inflammation biomarkers at baseline are thus most susceptible to mortality during the first 5 years while the healthier subjects continue to be followed.

Alternatively, there may be changes in inflammation or malnutrition status of the subjects over time and a single measurement at inclusion cannot capture the time-dependent nature of the process. The last deaths (5-9 years from the inclusion) are then less likely to be related to baseline determinations.

Another limitation of our study is the stability of the frozen samples over time. Since plasma samples were kept frozen at -80°C for about 5 years, it is possible that the observed biochemical levels were underestimated in the present study, due to long-term instability. Since all samples were treated and stored in a similar manner, this is however unlikely to have affected the associations between mortality and plasma measurements.

In the elderly population, several studies have demonstrated that inflammation biomarkers remain predictive of mortality after adjustment for malnutrition parameters (22-24) or inversely, that malnutrition parameters remain significant after adjustment for inflammation biomarkers (25). However, the concomitant effect of a high level in an inflammation marker and a low level in a malnutrition marker has seldom been explored. Reuben et al observed that in high-functioning subjects with low levels of IL6, low albumin predicted an increased risk of 4-year mortality. In the presence of high levels of IL6, higher or lower serum albumin levels had a similar risk (26). In our study, stratifying by sex and CRP, we observed that the adjusted effect of low albumin on early death was only significant for low levels of CRP in men (HR=2.75 (1.25-6.05), data not shown), although the small number of death events by strata make it difficult to draw a definitive conclusion. However we found that taking into account both inflammation and malnutrition parameters clearly enhances prediction. The PINI index is often used to jointly evaluate inflammatory and nutritional status in clinical practice but is very sensitive to significant and rapid variations of the CRP parameter. The CRP level is then the most important

determinant of the PINI variations. The results seem more informative if the biomarkers are kept separate but interpreted together.

From our results we tend to consider that the combination of AAG and TTR is the best predictor for elderly persons free of known chronic disease. In our study we encountered moderate elevations of inflammatory biomarkers corresponding more to a chronic inflammation phase than to an acute phase. The CRP concentration with a half-life of 6-18 hours is better for detection of acute inflammatory phase (27) while the AAG with a half-life between 2 and 3 days, is more stable and indicates a longer chronic inflammatory process. Associated with albumin or TTR, the AAG determination allows distinguishing exogenous undernutrition (low energy intakes with normal AAG) from endogenous undernutrion (inflammatory disease with increased AAG)(28). Concerning biomarkers of visceral protein, hypoalbuminemia has been associated with long-term deterioration in nutritional status while TTR is a marker of recent protein-calorie malnutrition (29). Previous studies have underlined that TTR, a negative acute phase protein known as a complex transporter of thyroxine, retinol binding protein and vitamin A showed higher correlation coefficients with nutritional indices than albumin and appeared to be better at quickly reflecting nutritional status changes (30, 31).

Other biochemical parameters have also been investigated as potential indicators of malnutrition in the elderly. The retinol-binding protein (RBP) (not available in our study) has been associated with nutritional status while the transferrin seems to have a weaker association (32).

In our study low BMI was not found to be associated with mortality but our cut-off defined by the lowest quartile was relatively high (24.1 and 22.9 for men and women). More specific clinical markers of malnutrition such as triceps skinfold thickness or arm muscle circumference, were not measured at inclusion. The predictive value of these indicators could not be compared

with that of the biochemical parameters.

In our study four biochemical parameters predicted early death in men: CRP, AAG, albumin and TTR, whereas only AAG, TTR and low cholesterol were significant predictors in women. The numbers of death events were very close in both genders suggesting that this gender difference could not be explained by a difference in statistical power. This result was also found by Jenny et al (16) where the association of high CRP with 3-year death was weaker in women and the association with 4-8 year mortality became non significant in women while persisting in men.

Interestingly we found a relationship of both inflammation and malnutrition biomarkers with 9-year mortality for cancer mortality in men. This association was particularly strong for CRP and TTR. In contrast, the cardiovascular mortality was only significantly predicted by inflammation biomarkers but not by malnutrition parameters in men. The role of inflammation has often been described in the field of cardiovascular disease (33-35) and is also implicated in cancer. The inflammatory response includes the release of proinflammatory cytokines, some of which may promote tumor growth and hence influence survival (36). Cytokines affect the production and activity of many hormones that can promote cancer (7). Malnutrition may play a separate role by inducing nutritional deficiencies involved in cancerogenesis.

From a methodological point of view and in comparison with other studies, our analysis has the advantage of 1) using models suited for survival data in the elderly taking into account the non proportionality of the risk of death with age, 2) stratifying by sex to investigate potential sex-specific associations and 3) selecting subjects without known inflammatory pathologies to better characterize the biological features of the frailty syndrome. Although some elderly subjects with undiagnosed diseases may possibly have remained in our sample this selection effect would also

occur if screening for frailty elderly subjects at a population level. Future studies should confirm the value of TTR and AAG measures as predictors of mortality.

## ACKNOWLEDGMENT

### Conflict of Interest Disclosures:

| Elements of Financial/Personal Conflicts | IC | | AMD | | AL | | JPC | | CD | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No |
| Employment or Affiliation | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| Grants/Funds | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| Honoraria | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| Speaker Forum | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| Consultant | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| Stocks | | X | | X | | X | | X | | X |
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|---|---|---|---|---|---|---|---|---|---|---|
| **Royalties** | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| **Expert Testimony** | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| **Board Member** | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| **Patents** | | X | | X | | X | | X | | X |
| | | | | | | | | | | |
| **Personal Relationship** | | X | | X | | X | | X | | X |
| | | | | | | | | | | |

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**Author Contribution:** IC: study concept, statistical analyses and drafting of manuscript, AMD, JPC: biological determinations, interpretation of the results, AL: data acquisition and management, CD: study concept and design, management of the cohort. All authors contributed to and approved the final version of the manuscript.

**Sponsor's Role:** None

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Table 1: Description of the POLA Study Sub-group*, Free of Known Co-morbidities at Inclusion, According to 9-Years Mortality.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Alive n=442 | Died n=111 | $P^{\dagger}$ | Alive n=778 | Died n=110 | $P^{\dagger}$ |
| Age, n (%) | | | < 0.0001 | | | < 0.0001 |
| 60-69 | 280 (63.4) | 33 (29.7) | | 463 (59.5) | 21 (19.1) | |
| 70-79 | 141 (31.9) | 42 (37.8) | | 282 (36.3) | 45 (40.9) | |
| 80+ | 21 (4.7) | 36 (32.4) | | 33 (4.2) | 44 (40.0) | |
| Educational level, n (%) | | | 0.11 | | | 0.17 |
| Primary school | 225 (50.9) | 65 (58.6) | | 442 (56.8) | 70 (63.6) | |
| Smoking, n (%) | | | 0.39 | | | 0.75 |
| Current | 70 (15.8) | 22 (19.8) | | 44 (5.7) | 8 (7.3) | |
| Former | 249 (56.3) | 63 (56.8) | | 68 (8.7) | 10 (9.1) | |
| Never | 123 (27.8) | 26 (23.4) | | 666 (85.6) | 92 (83.6) | |
| Bad perceived health, n (%) | 28 (6.3) | 13 (11.7) | 0.04 | 94 (12.1) | 19 (17.3) | 0.09 |
| BMI in $kg/m^2$ | | | 0.01 | | | 0.60 |
| < 25 | 156 (35.3) | 37 (33.3) | | 372 (47.8) | 58 (52.7) | |
| 25-30 | 245 (55.4) | 53 (47.8) | | 299 (38.4) | 37 (33.6) | |
| 30+ | 41 (9.3) | 21 (18.9) | | 107 (13.8) | 15 (13.6) | |
| Cholesterol in mmol/L (mean ± SD) | 5.62 (0.94) | 5.39 (1.15) | 0.01 | 5.98 (1.09) | 5.82 (1.19) | 0.13 |
| Albumin in g/L (mean ± SD) | 42.33 (4.43) | 40.43 (4.71) | <0.0001 | 41.08 (4.77) | 39.83 (5.59) | 0.01 |
| TTR in g/L (mean ± SD) | 0.28 (0.05) | 0.25 (0.05) | < 0.0001 | 0.24 (0.05) | 0.22 (0.05) | < 0.0001 |
| CRP in $\log_{10}$ mg/L (mean ± SD) | 0.20 (0.48) | 0.47 (0.49) | < 0.0001 | 0.21 (0.46) | 0.26 (0.48) | 0.27 |
| AAG in g/L (mean ± SD) | 0.77 (0.22) | 0.85 (0.25) | 0.0002 | 0.77 (0.20) | 0.79 (0.27) | 0.39 |

*Subjects without history of diabetes, coronary heart disease and self-reported history of stroke, lower limb arterial disease, cancer, asthma and respiratory disease and not treated with non-steroidal anti-inflammatory drugs or with oral corticosteroid treatment.
†Unadjusted Cox model
POLA: Pathologies Oculaires Liées à l'Age
TTR: transthyretin, CRP: C-reactive protein, AAG: alpha 1-acid glycoprotein.

Table 2: Hazard Ratios of Early Death (≤ 5 years after baseline measurements)

| | Men (n=553) | | | | | | Women (n=888) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 50 deaths | | | | | | 45 deaths | | | | | |
| | Univariate† | | | Multivariate‡ | | | Univariate† | | | Multivariate‡ | | |
| | HR | 95%CI | *P* | HR | 95%CI | *P* | HR | 95%CI | *P* | HR | 95%CI | *P* |
| CRP (mg/L) | | | | | | | CRP (mg/L) | | | | | |
| < 0.86 | 0.79 | 0.35-1.80 | 0.57 | 0.70 | 0.31-1.63 | 0.41 | < 0.79 | 1.61 | 0.78-3.32 | 0.20 | 1.45 | 0.70-3.04 | 0.32 |
| 0.86-3.31 | 1 | | | 1 | | | 0.79-3.27 | 1 | | | 1 | | |
| ≥3.31 | 2.57 | 1.39-4.74 | 0.002 | 2.15 | 1.14-4.02 | 0.02 | ≥3.27 | 1.37 | 0.67-2.77 | 0.39 | 1.32 | 0.65-2.69 | 0.45 |
| AAG (g/L) | | | | | | | AAG (g/L) | | | | | |
| < 0.64 | 1.11 | 0.51-2.40 | 0.80 | 1.03 | 0.47-2.28 | 0.94 | < 0.64 | 1.82 | 0.87-3.81 | 0.11 | 1.99 | 0.95-4.16 | 0.07 |
| 0.64-0.90 | 1 | | | 1 | | | 0.64-0.90 | | | | 1 | | |
| ≥ 0.90 | 2.33 | 1.24-4.39 | 0.009 | 2.26 | 1.19-4.31 | 0.01 | ≥ 0.90 | 2.44 | 1.20-4.96 | 0.01 | 2.61 | 1.27-5.35 | 0.009 |
| Cholesterol (mmol/L)* | | | | | | | Cholesterol (mmol/L)* | | | | | |
| < 4.95 | 2.01 | 1.03-3.91 | 0.04 | 1.72 | 0.88-3.39 | 0.12 | < 5.23 | 2.17 | 1.04-4.52 | 0.04 | 2.21 | 1.06-4.62 | 0.03 |
| 4.95-6.18 | 1 | | | 1 | | | 5.23-6.61 | 1 | | | 1 | | |
| ≥ 6.18 | 1.15 | 0.52-2.54 | 0.72 | 1.19 | 0.54-2.62 | 0.68 | ≥ 6.61 | 1.42 | 0.64-3.15 | 0.39 | 1.38 | 0.62-3.07 | 0.43 |
| Albumin (g/L) | | | | | | | Albumin (g/L) | | | | | |
| < 39.44 | 3.10 | 1.66-5.80 | 0.0004 | 2.72 | 1.44-5.14 | 0.002 | < 38.93 | 1.33 | 0.69-2.62 | 0.40 | 1.37 | 0.70-2.70 | 0.36 |
| 39.44-44.78 | 1 | | | 1 | | | 38.93-43.94 | | | | 1 | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 44.78 | 1.35 | 0.57-3.20 | 0.49 | 1.34 | 0.56-3.19 | 0.51 | ≥ 43.94 | 1.46 | 0.67-3.20 | 0.34 | 1.32 | 0.60-2.90 | 0.48 |
| TTR (g/L) | | | | | | | TTR (g/L) | | | | | | |
| < 0.24 | 2.42 | 1.32-4.42 | 0.004 | 2.23 | 1.21-4.13 | 0.01 | < 0.21 | 2.25 | 1.18-4.29 | 0.01 | 2.39 | 1.24-4.58 | 0.009 |
| 0.24-0.30 | 1 | | | 1 | | | 0.21-0.27 | 1 | | | 1 | | |
| ≥0.30 | 0.40 | 0.13-1.18 | 0.10 | 0.39 | 0.13-1.16 | 0.09 | ≥0.27 | 0.99 | 0.41-2.36 | 0.98 | 0.97 | 0.41-2.33 | 0.95 |
| BMI (kg/m$^2$) | | | | | | | BMI (kg/m$^2$) | | | | | | |
| < 24.13 | 0.88 | 0.44-1.76 | 0.71 | 0.71 | 0.35-1.44 | 0.34 | < 22.89 | 1.74 | 0.89-3.38 | 0.10 | 1.71 | 0.88-3.33 | 0.12 |
| 24.13-28.04 | 1 | | | 1 | | | 22.89-28.10 | 1 | | | 1 | | |
| ≥ 28.04 | 1.28 | 0.65-2.51 | 0.47 | 1.13 | 0.57-2.24 | 0.72 | ≥ 28.10 | 1.04 | 0.47-2.32 | 0.92 | 1.05 | 0.47-2.35 | 0.91 |
| PINI | | | | | | | PINI | | | | | | |
| < 0.052 | 0.73 | 0.31-1.74 | 0.47 | 0.66 | 0.27-1.58 | 0.35 | < 0.055 | 1.38 | 0.67-2.87 | 0.38 | 1.28 | 0.61-2.68 | 0.51 |
| 0.052-0.266 | 1 | | | 1 | | | 0.055-0.295 | 1 | | | 1 | | |
| ≥0.266 | 2.44 | 1.33-4.48 | 0.004 | 2.13 | 1.15-3.95 | 0.02 | ≥0.295 | 1.38 | 0.69-2.77 | 0.37 | 1.33 | 0.66-2.68 | 0.43 |

*on subjects not treated with statins or fibrates (1122/1441)

†Adjusted for age

‡Adjusted for age, educational level, perceived health and smoking

HR: hazard ratio, CI: confidence interval, AAG: alpha 1-acid glycoprotein, CRP: C-reactive protein, TTR: transthyretin, PINI: prognostic inflammatory and nutritional index.

Table 3: Hazard Ratios of Late Death (between 5 and 9 years after baseline measurements)

| | Men (n=553) 61 deaths | | | | | | | Women (n=888) 65 deaths | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate | | | Multivariate† | | | | Univariate | | | Multivariate† | | | |
| | HR | 95%CI | *P* | HR | 95%CI | *P* | | HR | 95%CI | *P* | HR | 95%CI | *P* |
| CRP (mg/L) | | | | | | | CRP (mg/L) | | | | | | | |
| < 0.86 | 0.61 | 0.28-1.35 | 0.22 | 0.60 | 0.27-1.33 | 0.21 | < 0.79 | 0.82 | 0.42-1.59 | 0.56 | 0.82 | 0.42-1.59 | 0.55 |
| 0.86-3.31 | 1 | | | 1 | | | 0.79-3.27 | 1 | | | | | |
| ≥3.31 | 2.50 | 1.45-4.33 | 0.001 | 2.37 | 1.36-4.15 | 0.002 | ≥3.27 | 1.08 | 0.62-1.91 | 0.78 | 1.05 | 0.60-1.85 | 0.86 |
| AAG (g/L) | | | | | | | AAG (g/L) | | | | | | | |
| < 0.64 | 0.40 | 0.17-0.96 | 0.04 | 0.38 | 0.16-0.92 | 0.03 | < 0.64 | 0.66 | 0.35-1.25 | 0.20 | 0.68 | 0.36-1.29 | 0.23 |
| 0.64-0.90 | 1 | | | 1 | | | 0.64-0.90 | 1 | | | 1 | | |
| ≥ 0.90 | 1.58 | 0.92-2.72 | 0.10 | 1.44 | 0.82-2.53 | 0.20 | ≥ 0.90 | 1.07 | 0.58-1.97 | 0.83 | 1.10 | 0.60-2.02 | 0.77 |
| Cholesterol (mmol/L)* | | | | | | | Cholesterol (mmol/L)* | | | | | | | |
| < 4.95 | 1.12 | 0.58-2.17 | 0.73 | 1.07 | 0.54-2.09 | 0.85 | < 5.23 | 1.17 | 0.57-2.40 | 0.68 | 1.24 | 0.60-2.56 | 0.56 |
| 4.95-6.18 | 1 | | | 1 | | | 5.23-6.61 | 1 | | | 1 | | |
| ≥ 6.18 | 1.22 | 0.60-2.45 | 0.58 | 1.21 | 0.60-2.44 | 0.60 | ≥ 6.61 | 1.06 | 0.54-2.10 | 0.86 | 1.05 | 0.53-2.08 | 0.88 |
| Albumin (g/L) | | | | | | | Albumin (g/L) | | | | | | | |
| < 39.44 | 1.13 | 0.62-2.09 | 0.68 | 1.13 | 0.61-2.11 | 0.69 | < 38.93 | 0.86 | 0.49-1.51 | 0.60 | 0.84 | 0.48-1.48 | 0.54 |
| 39.44-44.78 | 1 | | | 1 | | | 38.93-43.94 | 1 | | | 1 | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 44.78 | 0.98 | 0.50-1.91 | 0.95 | 1.04 | 0.53-2.05 | 0.91 | ≥ 43.94 | 0.81 | 0.39-1.70 | 0.58 | 0.81 | 0.39-1.69 | 0.57 |
| TTR (g/L) | | | | | | | TTR (g/L) | | | | | | |
| < 0.24 | 1.10 | 0.60-2.02 | 0.75 | 1.17 | 0.64-2.17 | 0.61 | < 0.21 | 1.38 | 0.79-2.41 | 0.25 | 1.36 | 0.77-2.38 | 0.29 |
| 0.24-0.30 | 1 | | | 1 | | | 0.21-0.27 | 1 | | | 1 | | |
| ≥0.30 | 0.84 | 0.45-1.57 | 0.59 | 0.89 | 0.47-1.68 | 0.72 | ≥0.27 | 1.01 | 0.50-2.02 | 0.98 | 1.04 | 0.52-2.10 | 0.90 |
| BMI (kg/m$^2$) | | | | | | | BMI (kg/m$^2$) | | | | | | |
| < 24.13 | 0.73 | 0.38-1.41 | 0.35 | 0.67 | 0.34-1.32 | 0.25 | < 22.89 | 0.99 | 0.54-1.82 | 0.97 | 1.01 | 0.55-1.87 | 0.98 |
| 24.13-28.04 | 1 | | | 1 | | | 22.89-28.10 | 1 | | | 1 | | |
| ≥ 28.04 | 1.32 | 0.73-2.39 | 0.36 | 1.25 | 0.69-2.29 | 0.46 | ≥ 28.10 | 1.35 | 0.74-2.46 | 0.32 | 1.39 | 0.75-2.55 | 0.29 |
| PINI | | | | | | | PINI | | | | | | |
| < 0.052 | 0.54 | 0.23-1.25 | 0.15 | 0.53 | 0.23-1.23 | 0.14 | < 0.055 | 0.78 | 0.39-1.55 | 0.48 | 0.78 | 0.39-1.56 | 0.49 |
| 0.052-0.266 | 1 | | | | | | 0.055-0.295 | 1 | | | 1 | | |
| ≥0.266 | 2.64 | 1.54-4.54 | 0.0004 | 2.50 | 1.44-4.36 | 0.001 | ≥0.295 | 1.28 | 0.73-2.23 | 0.38 | 1.25 | 0.72-2.18 | 0.43 |

*on subjects not treated with statins or fibrates (1122/1441)

†Adjusted for age

‡Adjusted for age, educational level, perceived health and smoking

HR: hazard ratio, CI: confidence interval, AAG: alpha 1-acid glycoprotein, CRP: C-reactive protein, TTR: transthyretin, PINI: prognostic inflammatory and nutritional index.

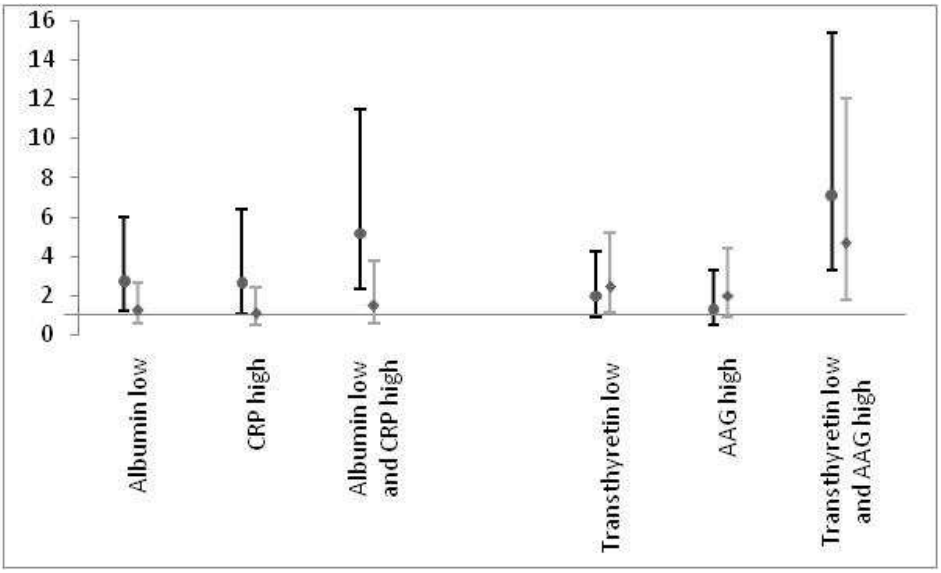


Figure 1: Adjusted Hazard Ratios of early death (≤ 5 years) in men (●, black bar) and women (♦, grey bar) according to combined criteria. Vertical bars show 95% confidence intervals (CI). The association is significant when the CI does not contain the value one (horizontal axis).