**Prostaglandin F\(_{2\alpha}\) formation is associated with mortality in a Swedish community-based cohort of older males**

Johanna Helmersson-Karlqvist\(^1\), Johan Ärnlov\(^2,3\), Anders Larsson\(^1\), and Samar Basu\(^4,5,6\)

\(^1\)Department of Medical Sciences/Clinical Chemistry, Uppsala University, Uppsala SE-751 85, Sweden; \(^2\)Department of Public Health and Caring Sciences/Geriatrics, Uppsala University, Uppsala, Sweden; \(^3\)School of Health and Social Studies, Dalarna University, Falun, Sweden; \(^4\)Department of Public Health and Caring Sciences/Oxidative Stress and Inflammation, Uppsala University, Uppsala, Sweden; \(^5\)Centre of Excellence-Inflammation, Uppsala University Hospital, Uppsala, Sweden; and \(^6\)Laboratory of Biochemistry, Molecular Biology, and Nutrition, University d’Auvergne, Clermont-Ferrand, France

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**Introduction**

Cytokines and cytokine-induced acute phase proteins are signalling molecules related to inflammation and inflammation-related pathology. Several epidemiological studies have shown that increased concentrations of these cytokines or cytokine-induced proteins in the circulation may predict cardiovascular disease (CVD), cancer, and mortality.\(^1\)\(^-\)\(^7\) On the other hand, mediators that exert the critical bioactive effects in the initiation of inflammatory processes have been far less determined and evaluated in clinical epidemiological studies.

The cyclooxygenase-mediated prostaglandins (PGs), thromboxanes, and prostacyclins are classical examples of bioactive mediators with potent vasoconstrictive/vasodilatory and inflammatory properties exerting direct well-known effects on the endothelium and homeostasis.\(^8\)\(^-\)\(^9\) Until recently, PGs have rarely been studied in large community settings, possibly due to their short half-life and subsequent difficulties in the methodology of large-scale measurements of relatively minute amounts in biological samples (basal concentrations \(\sim 2\) pg/mL in plasma). Prostaglandin \(F_{2\alpha}\) (PGF\(_{2\alpha}\)) is one of the major stable PGs formed during both acute and chronic inflammation.

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**Aims**

An increasing number of clinical studies highlight the importance of the inflammatory mediator prostaglandin \(F_{2\alpha}\) (PGF\(_{2\alpha}\)). Prostaglandin \(F_{2\alpha}\) activity has been suggested to play pivotal roles in the development of cardiovascular diseases and cancer. However, whether systemic PGF\(_{2\alpha}\) concentrations may signal mortality is unknown. The aim was to evaluate in vivo PGF\(_{2\alpha}\) formation, by measuring urinary 15-keto-dihydro-PGF\(_{2\alpha}\), and mortality risk in a community setting.

**Methods and results**

Urinary 15-keto-dihydro-PGF\(_{2\alpha}\) was measured in a Swedish population of 670 men (aged 77–78 years) and the participants were followed up for a median of 9.7 years (383 died, among them 156 of cardiovascular causes and 102 of cancer). In Cox regression models, urinary 15-keto-dihydro-PGF\(_{2\alpha}\) was significantly associated with cardiovascular mortality [multivariate hazard ratio (HR) for 1 SD increase of urinary 15-keto-dihydro-PGF\(_{2\alpha}\): 1.18; 95% CI: 1.04–1.34; \(P = 0.01\)] independent of established cardiovascular risk factors including C-reactive protein. Urinary 15-keto-dihydro-PGF\(_{2\alpha}\) was also independently associated with total mortality (multivariate HR for 1 SD increase of urinary 15-keto-dihydro-PGF\(_{2\alpha}\): 1.11; 95% CI: 1.01–1.21; \(P = 0.03\)). The combination of 15-keto-dihydro-PGF\(_{2\alpha}\) concentrations above the median and high serum high-sensitive C-reactive protein (\(> 3\) mg/L) was independently associated with a two-fold increased risk of cancer and total mortality (\(P = 0.02\) and \(P < 0.001\), respectively).

**Conclusion**

This is the first study to show that the inflammatory mediator PGF\(_{2\alpha}\) was independently associated with mortality and specifically cardiovascular mortality 10 years later. The results are in line with the emerging evidence of the importance of the inflammatory mediator PGF\(_{2\alpha}\) in fatal cardiovascular disease.

**Keywords**

Epidemiology • Inflammation • Mortality • Prostaglandins • Risk factors
and is found locally and systemically.\textsuperscript{10–12} Owing to the risk of artefactual formation during sample collection and the short half-life of PGF\textsubscript{2a} (~1 min) in the peripheral circulation, PGF\textsubscript{2a} formation in vivo is most accurately assessed by 15-keto-dihydro-PGF\textsubscript{2a}, a major metabolite of PGF\textsubscript{2a}, in frequently collected plasma samples.\textsuperscript{12–15} 15-Keto-dihydro-PGF\textsubscript{2a} is efficiently excreted into urine together with other β- and ω-oxidized metabolites, thus explaining why endogenous primary PGF\textsubscript{2a} formation in large cohort studies preferably is assessed by measurement of urinary 15-keto-dihydro-PGF\textsubscript{2a}.\textsuperscript{14,16} Urinary 15-keto-dihydro- PGF\textsubscript{2a} can be successfully measured with a specific radioimmunoassay.\textsuperscript{17} Prostaglandin F\textsubscript{2α} has potent vasoconstrictive effects at sites of inflammation and several clinical and experimental studies have shown that 15-keto-dihydro-PGF\textsubscript{2α} concentrations are elevated in different inflammatory conditions.\textsuperscript{12,18} For long PGs and thromboxanes have established causal roles in atherosclerosis\textsuperscript{19} and studies are now emerging suggesting that PGF\textsubscript{2a}, in particular, may be of importance for CVD development.\textsuperscript{20} Moreover, several lines of evidence suggest a causal role for PGs, and possibly PGF\textsubscript{2a}, in the complex pathophysiology leading to cancer.\textsuperscript{21–26}

Based on previous studies supporting a link between PGs and the development of CVD and cancer, we hypothesized that enhanced formation of the inflammatory mediator PGF\textsubscript{2a} may potentially indicate increased mortality risk. The aim of this study was therefore to explore the associations between urinary concentrations of 15-keto-dihydro-PGF\textsubscript{2a} and the risk of cardiovascular, cancer and total death in a community-based cohort of elderly men with up to 12 years of follow-up.

**Methods**

**Study population**

The Swedish cohort Uppsala Longitudinal Study of Adult Men was initiated in 1970 when all 50-year-old men living in Uppsala county (n = 2841) were invited to participate in a health survey (participation rate 82%).\textsuperscript{27} Participants from the third re-investigation of the cohort, performed during 1997–2001 at 77–78 years of age, were included in this study. Of the 839 participants, 133 were excluded because of absent urinary collection and 36 because of missing data on covariates; thus 670 men constituted the study population. The study complies with the Declaration of Helsinki and the Ethics Committee at Uppsala University approved the study; all participants gave their informed consent.

**Baseline investigations**

Twenty-four hour urine specimens were collected, aliquoted, and stored at −70°C until analysis. Urinary 15-keto-dihydro-PGF\textsubscript{2a} concentrations were determined using a radioimmunoassay developed as previously described by Basu.\textsuperscript{17} The intra-assay coefficient of variation was 12–14%. Concentrations of 15-keto-dihydro-PGF\textsubscript{2a} were adjusted for urinary creatinine concentrations (IL Test creatinine 181672-00, Monarch 2000 analyser, Instrumental Laboratories, Lexington, MA, USA) and given in nmol/mmol creatinine (Cr). High-sensitive C-reactive protein measurements were performed by latex-enhanced reagent (Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec® analyzer (Dade Behring). Blood sampling, anthropometrical and blood pressure measurement, questionnaires regarding medication and smoking habits and diabetes definition were performed using the same standardized methods as described previously.\textsuperscript{27,28} Serum cystatin C and cholesterol and fasting plasma glucose were measured as previously described,\textsuperscript{29} and the glomerular filtration rate (GFR) in mL/min/1.73 m\textsuperscript{2} was calculated from serum cystatin C results in mg/L by using the formula $\gamma = 77.24x - 1.2623$ (eGFR\textsubscript{cysC}).\textsuperscript{30} Information of previous ischaemic heart disease or cerebrovascular disease was obtained from the Swedish Hospital Discharge Registry using the International Statistical Classification of Diseases, Ninth Revision (ICD-9) codes 410–413, 428, 433–436 and ICD-10 codes I20-I25, I50, I63-I66.

**Endpoint definitions**

The Swedish Cause of Death register was used to define the endpoints cardiovascular mortality (ICD-10 I00-99), cancer mortality (ICD-10 C00-D48), and total mortality.

**Statistics**

The associations of urinary 15-keto-dihydro-PGF\textsubscript{2a} concentrations and cardiovascular, cancer, and total mortality, respectively, were analysed with Cox proportional hazard regression in a univariable and in three multivariable models (A, B, and C). In primary models urinary 15-keto-dihydro-PGF\textsubscript{2a} was entered as a standardized continuous variable (1 SD increase) and in secondary models as a binary variable (above/below median). To construct thrify statistical multivariate models, we used the directed acyclic graph (DAG) tool software available on http://dagitty.net.\textsuperscript{31} DAGitty is a graphical and mathematical tool for analysing causal diagrams to optimize the choice of covariates in the multivariate models and thus minimize the bias of the effect estimates and maintain as many degrees of freedom as possible. Possible confounding factors (low-dose aspirin, lipid-lowering and anti-hypertensive treatment, age, systolic blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking status, diabetes, eGFR\textsubscript{cysC}, education level, physical activity, and prevalent CVD) were entered into the DAG tool. Covariates for the large models B and C were chosen according to the results of the DAG. Model A was adjusted for low-dose aspirin treatment (75–160 mg salicylic acid daily) due to the known direct therapeutic cyclooxygenase-inhibitor effect of salicylic acid on PG synthesis.\textsuperscript{32,33} Model B was adjusted for low-dose aspirin treatment and established cardiovascular risk factors including systolic blood pressure, body mass index, smoking status, diabetes, eGFR\textsubscript{cysC}, and prevalent CVD. Model C was adjusted for the same as model B and additionally for C-reactive protein. Non-linear trends of mortality risk were analysed using a restricted cubic spline Cox regression model with four degrees of freedom. The knots were set at the 10th, 50th, and 90th percentiles, corresponding to urinary 15-keto-dihydro-PGF\textsubscript{2a} at 0.168, 0.282, and 0.503 ng/mmol Cr.

To evaluate the interplay between urinary 15-keto-dihydro-PGF\textsubscript{2a} and serum C-reactive protein in risk estimation of cardiovascular, cancer, and total mortality, we divided the participants in four groups: (i) low urinary 15-keto-dihydro-PGF\textsubscript{2a} and low C-reactive protein, (ii) high urinary 15-keto-dihydro-PGF\textsubscript{2a} and low C-reactive protein, (iii) low urinary 15-keto-dihydro-PGF\textsubscript{2a} and high C-reactive protein, (iv) high urinary 15-keto-dihydro-PGF\textsubscript{2a} and high C-reactive protein. Low urinary 15-keto-dihydro-PGF\textsubscript{2a} is defined as ≤0.28 nmol/mmol Cr (below median) and high urinary 15-keto-dihydro-PGF\textsubscript{2a} as >0.28 nmol/mmol Cr. Low C-reactive protein is defined as ≤3 mg/L and high C-reactive protein as >3 mg/L according to the risk classification guidelines for CVD by American Heart Association.\textsuperscript{34} We performed tests for effect modification by prevalent CVD, diabetes, smoking, low-dose aspirin treatment, and C-reactive protein by including multiplicative interaction terms of these variables and
Results

Baseline characteristics of the study population are shown in Table 1. The participants were followed up for a median of 9.7 years (interval 0.3–12.8 years). The mortality incidence rates for urinary 15-keto-dihydro-PGF2α are shown in Table 2.

Cardiovascular mortality

One SD increase of urinary 15-keto-dihydro-PGF2α was significantly associated with an increased HR of cardiovascular mortality in the univariable model and in the models adjusting for low-dose aspirin treatment and established cardiovascular risk factors including C-reactive protein, respectively (Table 2). The regression spline suggested a linear increase in hazard for total mortality with increasing urinary 15-keto-dihydro-PGF2α (Figure 1). Participants with a urinary 15-keto-dihydro-PGF2α above the median were borderline significantly \( (P = 0.05) \) associated with an increased HR of cardiovascular mortality in the model adjusting for low-dose aspirin treatment. The cumulative incidence of cardiovascular mortality in urinary 15-keto-dihydro-PGF2α above the median vs. below the median is shown in Figure 2. Participants with a combination of high urinary 15-keto-dihydro-PGF2α and high C-reactive protein had a significant two-fold increased risk of cardiovascular mortality compared with participants with low urinary 15-keto-dihydro-PGF2α and low C-reactive protein (Table 3). However, this association was only borderline significant when cardiovascular risk factors were adjusted for.

No effect modification of prevalent CVD \( (P = 0.91) \), diabetes \( (P = 0.49) \), smoking \( (P = 0.41) \), low-dose aspirin treatment \( (P = 0.32) \), or C-reactive protein \( (P = 0.70) \) was observed for the associations between urinary 15-keto-dihydro-PGF2α and cardiovascular mortality.

Cancer mortality

We did not find any significant association between urinary 15-keto-dihydro-PGF2α and risk of cancer mortality in the continuous models or the categorical models (Table 2). However, participants with a combination of high urinary 15-keto-dihydro-PGF2α and high C-reactive protein had a significant two-fold increased risk of cancer mortality compared with participants with low urinary 15-keto-dihydro-PGF2α and low C-reactive protein concentrations (Table 3). This association did not substantially change after adjustment for cardiovascular risk factors.

Total mortality

A 1 SD increase of urinary 15-keto-dihydro-PGF2α was significantly associated with an increased hazard ratio (HR) of total mortality in the univariable model and in the models adjusting for low-dose aspirin treatment and established cardiovascular risk factors including C-reactive protein, respectively (Table 2). Participants with a urinary 15-keto-dihydro-PGF2α concentration above the median were also significantly associated with an increased HR of total mortality in the univariable model and in all multivariable models adjusting for cardiovascular risk factors including C-reactive protein (Table 2).

![Table 1](image-url)
Table 2  Associations between urinary 15-keto-dihydro-prostaglandin F$_{2\alpha}$ (nmol/mmol Cr) and cardiovascular, cancer, and total mortality, respectively, in Cox regression models

<table>
<thead>
<tr>
<th></th>
<th>Continuous models</th>
<th>Categorical models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per unit increase of PGF$_{2\alpha}$</td>
<td>P-value</td>
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<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk/number of events</td>
<td>670/156</td>
<td>335/71</td>
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<tr>
<td>Incidence rate (95% CI)*</td>
<td>2.8 (2.4–3.2)</td>
<td>2.4 (1.9–3.1)</td>
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<tr>
<td>Univariate HR (95% CI)</td>
<td>1.2 (1.08–1.38)</td>
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<tr>
<td>Model A HR (95% CI)</td>
<td>1.24 (1.10–1.40)</td>
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<tr>
<td>Model B HR (95% CI)</td>
<td>1.16 (1.02–1.31)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model C HR (95% CI)</td>
<td>1.18 (1.04–1.34)</td>
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<tr>
<td>Cancer mortality</td>
<td></td>
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<tr>
<td>Number at risk/number of events</td>
<td>670/102</td>
<td>335/45</td>
</tr>
<tr>
<td>Incidence rate (95% CI)*</td>
<td>1.8 (1.5–2.2)</td>
<td>1.6 (1.2–2.1)</td>
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<tr>
<td>Univariate HR (95% CI)</td>
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<td>0.72</td>
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<tr>
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<td>1.01 (0.83–1.24)</td>
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<td>Total mortality</td>
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<td></td>
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<tr>
<td>Number at risk/number of events</td>
<td>670/383</td>
<td>335/172</td>
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<tr>
<td>Incidence rate (95% CI)*</td>
<td>6.8 (6.2–7.5)</td>
<td>5.9 (5.1–6.9)</td>
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<tr>
<td>Univariate HR (95% CI)</td>
<td>1.16 (1.06–1.27)</td>
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<tr>
<td>Model A HR (95% CI)</td>
<td>1.17 (1.07–1.27)</td>
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<tr>
<td>Model B HR (95% CI)</td>
<td>1.10 (1.00–1.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model C HR (95% CI)</td>
<td>1.11 (1.01–1.21)</td>
<td>0.03</td>
</tr>
</tbody>
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Model A. Adjusted for low-dose aspirin medication.
Model B. Adjusted for low-dose aspirin medication, systolic blood pressure, body mass index, smoking status, diabetes, glomerular filtration rate (estimated by cystatin C), and prevalent cardiovascular disease.
Model C. Adjusted for the covariates in model B and C-reactive protein.
*Incidence rates are given per 100 person-years.

Figure 1  Regression spline of the unadjusted association between urinary 15-keto-dihydro-prostaglandin F$_{2\alpha}$ (0.168, 0.282, and 0.503 nmol/mmol Cr). The black line shows estimated hazard ratios and the dotted line indicates 95% confidence intervals. The knots were entered at the 10th, 50th, and 90th percentiles corresponding to urinary 15-keto-dihydro-prostaglandin F$_{2\alpha}$ concentrations at 0.168, 0.282, and 0.503 nmol/mmol Cr.

Figure 2  The Nelson–Aalen plot of cumulative incidence of cardiovascular mortality by participants above vs. below median urinary 15-keto-dihydro-prostaglandin F$_{2\alpha}$. Below median corresponds to urine 15-keto-dihydro-prostaglandin F$_{2\alpha}$ ≤ 0.28 nmol/mmol Cr and above median to ≥ 0.28 nmol/mmol Cr.
Participants with a combination of high urinary 15-keto-dihydro-PGF₂α and high C-reactive protein concentrations had a highly significant two-fold increased risk of total mortality compared with participants with low urinary 15-keto-dihydro-PGF₂α and low C-reactive protein concentrations (Table 3). This association did not substantially change when adjusting for cardiovascular risk factors.

No effect modification of prevalent CVD (P = 0.94), diabetes (P = 0.91), smoking (P = 0.93), low-dose aspirin treatment (P = 0.46), or C-reactive protein (P = 0.36) was observed for the associations between urinary 15-keto-dihydro-PGF₂α and total mortality.

**Discussion**

This is the first study to explore the associations between the inflammatory mediator PGF₂α and mortality in a community setting, and it shows that PGF₂α formation in older men is associated with cardiovascular and total mortality up to 12 years later. The associations could primarily not be explained by any other common cardiovascular risk factor, indicating that PGF₂α may add important additional information on detrimental cardiovascular risk. The physiological role of PGF₂α is well known in the field of reproductive endocrinology, where it has essential mediator roles during luteolysis, ovulation, sperm transportation, pregnancy establishment, cervix dilation, and parturition in humans and different animal species. Recently, studies have emerged that indicate a possible role of PGF₂α also in the field of atherogenesis and CVDs. The notion that prostanooids are important players in atherogenesis is not novel; other prostanooids such as thromboxane A₂ and PGI₂ (prostacyclin) have established roles of being cardiovascular mediators by their ability to modify vasoactivity and homoeostasis diversely. The specific role of PGF₂α in atherogenesis is still rather unknown. Recent clinical studies have, however, uncovered that urinary 15-keto-dihydro-PGF₂α concentrations (which is considered to be an accurate way to estimate PGF₂α formation systemically) is related to several important cardiovascular risk factors namely type 1 and type 2 diabetes mellitus, obesity, smoking, and low intake of vitamins. Further, increased intima-media thickness in the carotid artery, corresponding to enhanced total atherosclerotic load in the artery system, is independently associated with increased urinary 15-keto-dihydro-PGF₂α concentrations. These studies may all together indicate a possible role for the inflammatory, vasoconstrictive mediator PGF₂α, as an important factor related to atherogenesis and subsequently cardiovascular mortality. The independent associations between 15-keto-dihydro-PGF₂α and cardiovascular mortality found in this study further confirms this hypothesis.

The associations between urinary 15-keto-dihydro-PGF₂α and cardiovascular mortality could primarily not be explained by high-sensitive C-reactive protein, according to the multivariate analyses. Speculatively, the results may indicate that C-reactive protein and 15-keto-dihydro-PGF₂α measurements in part reflect different...
Certain aspects of inflammation. C-reactive protein is primarily an acute phase protein synthesized in the liver by the signal of activated pro-inflammatory cytokines. There is an unclear consensus whether C-reactive protein represents a cardiovascular risk factor with bioactive properties related to atherogenesis or rather a risk marker of general chronic inflammation. Despite this, C-reactive protein is currently shown to be an important and consistent predictor of cardiovascular morbidity and mortality, especially in middle-aged subjects. For older age groups, however, the predictive value of C-reactive protein is far less studied, and evaluated clinical studies have shown inconsistent outcomes. Prostaglandin F$_{2\alpha}$, on the other hand, has well-known potent bioactivity by primarily being a vasoconstrictor at sites of inflammation and is essentially inhibited by aspirin and other non-steroidal anti-inflammatory drugs. Despite these well-known biological vasoactive properties of PGF$_{2\alpha}$, to our knowledge, this is the first study to evaluate the role of PGF$_{2\alpha}$ formation and cardiovascular mortality risk. Further, the finding that a combined increase of 15-keto-dihydro-PGF$_{2\alpha}$ and C-reactive protein seemed to be more strongly associated with mortality than an increase in each biomarker alone strengthens the theory that PGF$_{2\alpha}$ and C-reactive protein may reflect different features of inflammation. Further studies are needed to evaluate the value of 15-keto-dihydro-PGF$_{2\alpha}$ in addition to C-reactive protein and other cytokines and inflammatory mediators in cardiovascular risk prediction.

Urinary 15-keto-dihydro-PGF$_{2\alpha}$ was not associated with cancer-specific mortality in the continuous or categorical models in this setting of older men. This may indicate that despite convincing evidence in the literature that PGs and cyclooxygenases are important players in cancer pathology and angiogenesis, PGF$_{2\alpha}$ formation specifically does not play a major role in the pathology leading to cancer mortality in this age group. Clinical studies reflecting the role of PGF$_{2\alpha}$ in cancer are sparse, but data from different cancer cell lines including endometrial carcinomas, colorectal cancer, and renal cell carcinomas have suggested a role of PGF$_{2\alpha}$ in cancer pathogenesis. Results from a clinical study evaluating urinary 15-keto-dihydro-PGF$_{2\alpha}$ in patients with prostate cancer could, however, not find any cross-sectional relation between cancer prevalence and 15-keto-dihydro-PGF$_{2\alpha}$ concentrations. This is somewhat in line with the results in this longitudinal study considering that the major type of cancer in this cohort is prostate cancer. On the other hand, a combination of high urinary 15-keto-dihydro-PGF$_{2\alpha}$ and high-sensitive C-reactive protein was independently associated with a two-fold risk of cancer mortality, again strengthening the theory that PGF$_{2\alpha}$ and C-reactive protein perhaps reflect different aspects of inflammation.

This study also showed that urinary 15-keto-dihydro-PGF$_{2\alpha}$ was independently associated with total mortality, representing a heterogeneous endpoint. One interpretation may be that this association is in part driven by the association between urinary 15-keto-dihydro-PGF$_{2\alpha}$ and CVD mortality since CVD is a major cause of death in this age group. Another interpretation may speculatively be that increased urinary 15-keto-dihydro-PGF$_{2\alpha}$ concentrations signal a state of increased inflammation and vasoconstriction which may be important in the pathogenesis leading to death by different causes, including accelerating atherosclerosis as discussed above, functional decline, or other crucial morbidity. Studies have shown that other inflammatory biomarkers in settings of very old adults may represent age-related functional decline in general, or other chronic conditions possibly related to mortality.

The strengths of this study include the community-based study design, which to our knowledge is the only community cohort with estimations of urinary 15-keto-dihydro-PGF$_{2\alpha}$. In addition, this study has also detailed clinical and biochemical characterization of cardiovascular risk factors including C-reactive protein measurements. The study is longitudinal with a relatively long follow-up time and a very low loss to follow-up due to the high-quality Swedish registry data. However, the problems of generalizing these results to women, other age groups, and other ethnic groups have to be acknowledged. Further, the results may be related to or depend on variables that we were unable to adjust for. It cannot be ruled out that the results of this study to some extent are related to reverse causation; that is, high urinary 15-keto-dihydro-PGF$_{2\alpha}$ is rather a consequence of prevalent disease with related low-grade inflammation at baseline.

### Conclusion

This is the first study to show that formation and excretion of the inflammatory mediator PGF$_{2\alpha}$ were independently associated with mortality and specifically cardiovascular mortality 10 years later. The results are in line with the emerging evidence of the importance of PGF$_{2\alpha}$ as a cardiovascular risk factor and suggest that PGF$_{2\alpha}$ may carry risk information beyond the established cardiovascular risk factors. However, the clinical utility of measuring urinary 15-keto-dihydro-PGF$_{2\alpha}$ for risk prediction purposes needs to be further evaluated.

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### Conflict of interest:

none declared.

### References


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PGF$_{2\alpha}$ and mortality 243


