Dietary Patterns

Identification and Health Implications in the Swedish Population

ERIKA AX
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Abstract

We eat foods not nutrients. What is more, we eat them in combinations. Consequently, capturing our complex food habits is likely an advantage in nutrition research. The overall aim of this doctoral thesis was therefore to investigate dietary patterns in the Swedish population—nutrient intakes, nutritional biomarkers and health aspects.

Prostate cancer is the most common cancer among men in the developed world. However, the impact of dietary factors on disease risk is largely unknown. In Study I we investigated the association between a Mediterranean- and a Low-carbohydrate-high-protein dietary pattern and prostate cancer risk, in a cohort of elderly Swedish men. The latter (but not the former) was associated, inversely, with prostate cancer risk when taking validity in food records into account.

Diet is one of our main exposure routes to environmental contaminants. Hence, such exposure could act as a mediating factor in the relation between diet and health. In Study II we investigated the association between; a Mediterranean- and a Low-carbohydrate-high-protein dietary pattern, as well as the official dietary recommendations, and circulating levels of environmental contaminants, in an elderly Swedish population. The first two patterns were positively related to levels of both persistent organic pollutants and heavy metals, whilst the dietary recommendations were inversely associated to dioxin and lead.

Finally, although dietary patterns are likely to influence health, little is known about current dietary patterns in Sweden. In Study III we used a data-reduction method to identify dietary patterns in a nationwide sample of the Swedish population. Two major patterns were derived; a Healthy pattern of foods generally considered healthy (e.g. vegetables, fruits, fish and vegetable-oils) and a Swedish traditional pattern (with e.g. meats, potatoes, sauces, non-Keyhole milk-products, sweet-bakery products and margarine). Derived patterns were associated to population characteristics and the Healthy dietary pattern was inversely associated to anthropometric variables in Study IV. Dietary characteristics of the patterns were well reflected in correlations to nutrient intake and (to a lesser extent) in nutritional biomarkers.

In conclusion dietary patterns for overall health should be considered, as well as other lifestyle-factors, when interpreting results in nutrition epidemiology and establishing dietary recommendations.

Keywords: Dietary Pattern, Dietary Recommendations, Dietary Survey, Environmental Contaminants, Healthy Diet Indicator, Healthy dietary pattern, Low-Carbohydrate, Mediterranean diet, Nutritional Biomarkers, Obesity, Overweight, Principal Component Analysis, Prostate Cancer, Sweden, Traditional dietary pattern

Erika Ax, Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala Science Park, Uppsala University, SE-75185 Uppsala, Sweden.

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When you change the way you look at things, the things you look at change.

Max Planck
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV  Ax E., Becker W., Andersson A., Lindroos A K., Ridefelt P., Cederholm T., Fung T.T., Sjögren P. Dietary patterns in relation to anthropometry, inflammation, and nutritional biomarkers in a nationwide population of Swedish adults (In manuscript)

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<tr>
<td>AHEI</td>
<td>Alternative Healthy Eating Index</td>
</tr>
<tr>
<td>Al</td>
<td>Aluminum</td>
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<tr>
<td>BDE</td>
<td>Brominated Diphenyl Ether</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BMR</td>
<td>Basal Metabolic Rate</td>
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<td>BPA</td>
<td>Bisphenol A</td>
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<td>BW</td>
<td>Body Weight</td>
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<tr>
<td>Cd</td>
<td>Cadmium</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CRP</td>
<td>C-Reactive Protein</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>DEHP</td>
<td>Di-2-ethyl hexyl phthalate</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>EE</td>
<td>Energy Expenditure</td>
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<tr>
<td>EI</td>
<td>Energy Intake</td>
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<tr>
<td>EPIC</td>
<td>European Investigation into Cancer and Nutrition</td>
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<td>Ery-folate</td>
<td>Erythrocyte folate</td>
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<tr>
<td>FFQ</td>
<td>Food Frequency Questionnaire</td>
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<tr>
<td>HCB</td>
<td>Hexachlorobenzene</td>
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<td>HDI</td>
<td>Healthy Diet Indicator</td>
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<tr>
<td>HEI</td>
<td>Healthy Eating Index</td>
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<tr>
<td>Hg</td>
<td>Mercury</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>LCHP</td>
<td>Low Carbohydrate High Protein</td>
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<tr>
<td>MEHP</td>
<td>Mono-[2-ethylhexyl] phthalate</td>
</tr>
<tr>
<td>MEP</td>
<td>Monoethyl phthalate</td>
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<tr>
<td>mHDI</td>
<td>Modified Healthy Diet Indicator</td>
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<tr>
<td>MiBP</td>
<td>Monoisobutyl phthalate</td>
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<td>mMDS</td>
<td>Modified Mediterranean Diet Score</td>
</tr>
<tr>
<td>MMP</td>
<td>Monomethyl phthalate</td>
</tr>
<tr>
<td>MUFA</td>
<td>Monounsaturated Fatty Acids</td>
</tr>
<tr>
<td>NFA</td>
<td>National Food Agency</td>
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<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>OC</td>
<td>Organochlorine</td>
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<tr>
<td>OCDD</td>
<td>Octachlorodibenzo-p-dioxin</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PAL</td>
<td>Physical Activity Level</td>
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<tr>
<td>Pb</td>
<td>Lead</td>
</tr>
<tr>
<td>PBDE</td>
<td>Polybrominated Diphenyl Ether</td>
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<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
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<tr>
<td>PCB</td>
<td>Polychlorinated Biphenyl</td>
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<tr>
<td>P-folate</td>
<td>Plasma folate</td>
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<td>PIVUS</td>
<td>Prospective Investigation of the Vasculature in Uppsala Seniors</td>
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<tr>
<td>POP</td>
<td>Persistent Organic Pollutant</td>
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<tr>
<td>p,p'-DDE</td>
<td>p,p'-Dichlorodiphenyldichloroethylene</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated Fatty Acids</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SHR</td>
<td>Subhazard Ratio</td>
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<tr>
<td>SFA</td>
<td>Saturated Fatty Acids</td>
</tr>
<tr>
<td>TNC</td>
<td>Trans-nonachlor</td>
</tr>
<tr>
<td>ULSAM</td>
<td>Uppsala Longitudinal Study of Adult Men</td>
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<tr>
<td>WC</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHR</td>
<td>Waist to Hip Ratio</td>
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<tr>
<td>WHHR</td>
<td>Waist Hip to Height Ratio</td>
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Introduction

Dietary patterns in nutrition epidemiology

Nutrition research has traditionally had a reductionist focus, where foods or nutrients have been studied as isolated factors. This approach has yielded numerous insights in how individual dietary factor influence our metabolism. Indeed, also the role of foods and nutrients in disease prevention has become clearer. However, the increased knowledge has not had the corresponding impact on public health. Although we live longer, we are also more burdened by disease and ill-health. Seemingly, we have a novel kind of “malnutrition” today; for which the single-nutrient or food-investigations are not sufficient.

Reality is complex. We eat foods in non-random combinations and nutrients and food factors are often correlated also within foods. Due to this, effects of individual foods or nutrients are hard to separate in observational studies. This complicates interpretation of associations between diet and health-outcomes and might even lead to identification of false associations.

The traditional approach focusing on separate nutrient-factors may also miss out on small but meaningful associations –captured first when they add up in the context of a diet. Assessing multiple dietary factors one by one increases the risk of multiple testing, and associations that occur simply by chance. Moreover, since metabolism of nutrients is not isolated processes, studying single foods or nutrients does not include the interaction in uptake, metabolism and health effects between dietary components. Based on food synergy, it can indeed be argued that; whole foods are more than the sum of its parts.

Assessing foods and overall-diet, contrary to single nutrients, also includes additional features of dietary intakes such as the numerous non-nutrient factors, which we often disregard.

Consequently, dietary pattern analysis, as a more holistic approach in nutrition epidemiology, has become popular. By considering multiple aspects of the diet in combination we surpass many of the shortcomings of single nutrient investigations.

The potential of dietary patterns in disease prevention have been reviewed in multiple papers (1-9). Above all food patterns emphasizing (high intake) of
fruits and vegetables, nuts and seeds, vegetable oils, wholegrain cereals, fish and other seafood, whether a predefined “high-quality index”, a Mediterranean-diet or an empirically derived Prudent or Healthy dietary pattern have repeatedly shown health beneficial effects \(^{(2,3,6-11)}\). Opposite, dietary patterns including high intake of red and processed meats, refined grains and sugar-rich products have been associated with adverse health effects \(^{(9)}\). The potency of high- qualitative dietary patterns has also been confirmed in intervention studies \(^{(12-16)}\).

Hence, dietary pattern analysis has contributed essentially to the nutrition research field in the last decades. However, in some areas the implication of overall dietary patterns is still limited. For example, the evidence base for a healthy dietary pattern in the prevention of various cancers is low \(^{(17)}\). Similarly, associations with overweight and obesity have so far been inconclusive \(^{(18,9)}\). In other areas, such as environmental health, the dietary pattern analysis is still in an early era.

In summary the rational for studying dietary patterns comes from the idea that the reductionist approach in nutrition research today may be too simplistic. Therefore this doctoral thesis aimed at taking a more holistic approach to diet and health associations in the Swedish population by applying the dietary pattern methodology.
Background

Means of defining dietary patterns

There is no standard definition of dietary pattern analysis. However, as concluded by Kant it often implies “a dietary evaluation in which multiple dietary characteristics (foods and (or) or nutrients) are examined simultaneously or collectively rather than individually”. Dietary patterns are normally not measured directly. However, there are several ways to define dietary patterns within data of dietary intakes. The methods are typically subdivided into “a priori” methods, predefined dietary indices based on current knowledge or hypothesized of diet-disease relationships and “a posteriori”, data derived dietary patterns identified in a population and from the data at hand. Their application depends on the aim of the assignment. Dietary indices are generally used to measure adherence to dietary guidelines or diets with hypothesized health implications. Individual’s adherence to the indices can also be further assessed in relation to health outcomes. Data derived patterns, on the other hand, identify current dietary practices, an objective on its own, but also useful where hypothesis of relations between specific dietary components and disease are limited. Recently, reduced rank regression, a hybrid method, has been proposed as an alternative method which determines combinations of foods that best explains disease specific response variables (20), however, since not included in this thesis this method will not be further addressed.

A priori defined dietary indices

Indices are combined measurements of individual variables where each variable contribute with a different dimension. Using indices to handle several variables at once is a practical way to avoid statistical issues related to correlated data. In nutrition epidemiology indices defining dietary patterns are often used to measure a population’s adherence to dietary guidelines and to evaluate the implication of dietary advices on non-communicable diseases. Several indices has been developed in this purpose e.g. those based on the US Dietary Guidelines for Americans: the Healthy Eating Index (HEI) (21), later reformed by Harvard Scientists to the Alternative Healthy Eating Index (AHEI) (22), the Swedish NNR-score based on the Nordic Nutrition Recommendations (23) and the Healthy Diet Indicator (HDI) developed from the World Health Organization (WHO) recommendations (24). In addition, the
Mediterranean Diet Score (25) and the DASH diet (14) are additional examples of predefined high-qualitative dietary indices based on hypotheses of healthy dietary patterns.

Dietary pattern indices can be based either on food or nutrient intakes or a combination of both. Most indices, as those mentioned above, include multiple foods and (or) nutrients to measure overall quality of an individual’s diet. There are also indices focusing on for example quantities of macronutrients as the Low Carbohydrate High Protein (LCHP) index (26), or the variety in food choices as in the dietary variety score (27). Adherence to predefined dietary patterns is assessed on an individual level. The dietary intake of each participant is normally compared with a cutoff or range of desirable intake, for each variable in the index, and scored according to a preset scale. An individual’s adherence to the dietary pattern is then reflected in the total summary score for the index.

A posteriori identified dietary patterns

Exploratory analyses of food data can be used to empirically identify dietary patterns in a population. This approach ignores previous knowledge of healthy or less favorable foods and nutrients and leaves to the statistics to determine the current dietary patterns in a population, from the data at hand. These so called data derived patterns are identified with multivariate statistical techniques primary factor analysis, usually principal component analysis (PCA), or cluster analysis. This thesis focuses on PCA derived dietary patterns; however, a brief description of cluster analysis is included.

PCA is a data reduction method that reduces the dimensions in large data sets to summary variables (components) that are constructs of, and based on, correlations between the true intakes. In PCA components are mathematically transformed (rotated) to uncorrelated variables. The assumption is that the variance in the data is the interesting thing, and by deriving and keeping the principal components –the major dietary patterns –we can ignore the “blur” from subsequent components.

Several studies have reported identifying a Healthy or Prudent and a less healthy often denoted Western-dietary pattern (8, 28). The derived patterns are not mutually exclusive. Hence, an individual’s overall dietary habits are explained by the combination of a person’s score on each dietary pattern. The score reflects a gradient of a person’s agreement with the derived pattern, which can be further assessed in relation to health outcomes.

In cluster analysis individuals are aggregated into relatively homogenous mutually exclusive groups with similar diets. Diverse methods can be applied to identify clusters based upon individual differences in mean intake most often K-Means or Ward’s methods are used (8). Larger clusters represent dietary habits shared by many, whilst small clusters represent more specific food consumption. Cluster derived dietary pattern might be easier to
grasp, since each individuals are grouped only in one cluster. However, since there is no gradient, cluster analysis is less useful (have lower power) when assessing relations between dietary patterns and health outcomes \(^{(9)}\).

Diet and health

This doctoral thesis focuses on the analysis of dietary patterns and relations to health. However, it does not prioritize one area of health, but assesses health-issues relevant for the Swedish adult population today where there is limited knowledge of the implication of dietary patterns.

Diet and prostate cancer risk

Prostate cancer is the second most common cancer among men worldwide \(^{(29)}\). In Sweden prostate cancer is the most common male cancer \(^{(30)}\). The World Cancer Research Fund (WCRF) estimates that a third of the most common cancers could be prevented by keeping a healthy weight, being physically active and eating healthy. This is supported by results from the European prospective investigation into cancer and nutrition (EPIC), where an index measuring adherence to the WCRF-recommendations on diet, physical activity, and weight management for cancer prevention, showed cancer protective effects \(^{(32)}\). Protective associations were significant for most cancers, however not for prostate cancer \(^{(32)}\).

Little is known about diet in the etiology of prostate cancer. The most recent report from the WCRF (the Continuous Update Project Report on Diet, Nutrition, Physical Activity, and Prostate Cancer) downgraded the evidence for dietary factors previously considered as probable modifiers of disease risk. The evidence for increased risk with diets high in calcium or dairy products is today graded as limited-suggestive. Similarly, the evidence for foods containing lycopene or selenium previously graded as having probable protective effect is now graded as limited-no conclusion \(^{(33)}\). The only factors that today are categorized as probable modifiers (increase risk) of prostate cancer are body-fatness (for advanced prostate cancer) and adult attained height (as a marker for developmental factors leading to greater linear growth) \(^{(33)}\). For individual dietary pattern which was included as a new exposure in the latest report, the evidence is too limited to draw any conclusion \(^{(33)}\).

A Mediterranean dietary pattern has been proposed in prostate cancer prevention \(^{(34, 35)}\). However, this hypothesis has not been confirmed in studies assessing the association between Mediterranean diet scores and prostate cancer risk \(^{(36-38)}\). Although, the Mediterranean diet has been associated to decreased incidence and mortality from overall cancer \(^{(6)}\).
Opposite, the LCHP diet has been associated with an increased risk of total cancer mortality among men (39, 40). However, when investigating prostate cancer incidence or mortality specifically, studies fail to identify any clear association (39, 41, 42).

Bosire et al. assessed adherence to different quality indices and found an inverse association between the HEI-2005 and the AHEI-2010 and prostate cancer (38). Recently Möller et al. assessed adherence to a score based on the Nordic Nutrition Recommendations and found no significant association (23).

Data derived western-style dietary patterns, high in red and processed meat and (or) refined grains has shown to increase risk of prostate cancer in some (43-46), but not in all studies (47-49).

In summary although there is a growing body of literature supporting the role of dietary patterns in the development of multiple health conditions, including cancer. The impact of overall dietary habits on prostate cancer incidence is still unsettled.

Diet and environmental contaminants

We are daily exposed to low doses of environmental contaminants. This low-level, so called background exposure of chemical substances occurs to a large extent through our diet (50, 51).

Persistent organic pollutants (POPs) are a large group of lipophilic substances which are semi-volatile and highly resistant to degradation (51, 52). Consequently, these substances spread easily and accumulate in the environment. Although their use has been regulated since decades they can still be detected even in places where they have never been used. POPs include e.g. dioxins, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and numerous organochlorines (OC). These substances originate primarily from industrial processes, where they are purposely produced or produced as byproducts, and from the agricultural section where they are used as pesticides.

Plastic associated chemicals including phthalates and bisphenol A (BPA) are another group of chemicals in our surroundings. They are not persistent but ubiquitously and we are everyday exposed to them via a range of consumer products. Intake of food and beverages are an important source due to their migration from food packaging (53).

In addition, metals can enter the food chain from the environment and although many are essential high exposure, especially to heavy metals such as lead, cadmium and mercury, might be detrimental (51).

The long-term health effect of our background exposure to environmental contaminants is rather unknown. However, some contaminants are considered endocrine disrupters, altering the hormonal system, which may cause damage to the immune and reproductive system; several substances have
also shown developmental and carcinogenic effects \cite{51, 54}. In addition, recent studies indicate a role of many of these substances in the development of major chronic disease e.g. type 2 diabetes, obesity and cardiovascular disease \cite{55-59}.

The associations between dietary habits and measures of exposure to environmental contaminants are scarce. Most studies use consumption statistics in combination with food analyses to approximate exposure from the diet. Few studies actually measure circulating levels of contaminants in individuals and relate them to food intake. Consequently, the inter-individual exposure variation in levels of contaminants in relation to dietary patterns is largely unknown. This, although environmental contaminant exposure could contribute to the health effects associated with specific dietary patterns.

A limited number of studies have investigated a posteriori defined dietary patterns and specific environmental contaminant exposure \cite{60-62}. However, only one study have used a predefined dietary pattern and assessed relations to environmental contaminants. This study found no associations between a Mediterranean diet and OC-pesticide exposure \cite{63}. Another resent Spanish study on intake of animal products and serum levels of POPs concluded that animal products was a significant exposure source to POPs but also that analysis of dietary pattern in relation to POP exposure would be valuable \cite{64}.

Hence, studies assessing the implication of dietary patterns on environmental contaminant exposure, preferable including exposure to multiple contaminants, are wanted.

**Dietary patterns, nutrition, inflammation and anthropometry**

Adherence to high-qualitative dietary indices has generally shown the expected favorable, disease preventing effects in observational studies \cite{9}. However, they are optimized to capture healthy dietary patterns and study participants are categorized into dietary patterns that might be more or less representative for their total dietary habits. From a public health point of view, studying current dietary patterns, what people actually eat rather than what they should eat, and relations to health outcome is at least as relevant. Schwerin et al. derived dietary patterns by PCA already in the beginning of 1980 \cite{65} and concluded that certain eating patterns were associated with better nutritional health \cite{66}. Schwerin also proposed that dietary pattern analysis would prove useful for examining associations between patterns of food intake and specific health concerns \cite{66}. It took a couple of decades until the real breakthrough of data derived dietary pattern research, but today dietary patterns have been identified in multiple populations \cite{8, 9}.

Associations between a posteriori defined dietary patterns and multiple health outcomes have been documented \cite{8, 9}. Especially, data on dietary patterns and cardiovascular disease (CVD) have been rather uniform \cite{2, 9}. Die-
Dietary patterns have also been related to biomarkers of obesity (67), and low grade inflammation (68). However, reviews on empirically derived dietary pattern and body mass index (BMI) have so far been inconclusive (18, 19). Studies of associations between diet and obesity are complicated by selective misreporting in dietary data (69, 70). Failure to account for misreporting could be one explanation for inconsistent results in analyses of associations between dietary patterns and overweight and obesity, as indicated in previous studies (71, 72). Moreover, the commonly used BMI has limitations as a proxy for overweight and obesity since it does not take fat distribution into account. Measurements such as waist circumference (WC), waist-to-hip ratio (WHR) and recently waist-to-hip-to-height ratio (WHHR) might be more useful since taking abdominal obesity into account. These measurements have also shown to be superior in predicting CVD risk (73).

Dietary recommendations aim to promote good health and prevent diet-related disease. They are based on scientific evaluations of human nutritional needs and diet for prevention of major chronic disease. In addition, dietary habits and cultural aspects of the population they target are also considered. Hence, population based studies of current dietary patterns, reflecting how foods are commonly consumed in combination are valuable. Today few studies have investigated associations between data derived dietary patterns and objective nutritional biomarkers (17, 74). Such information is valuable to evaluate potential health benefits or risks of identified patterns.
Aims

The overall aim of this doctoral thesis was to investigate health aspects of different dietary patterns in the Swedish population—including nutrient intakes, biomarkers of nutrition and health, and selected health outcomes.

The first part (Study I and II) investigates \textit{a priori} dietary indices, and the second part (Study III and IV) identifies, evaluates and applies \textit{a posteriori} derived dietary patterns.

Study specific aims were to

**Study I**
- Investigate the association between a Mediterranean dietary pattern and a Low-carbohydrate high-protein dietary pattern and prostate cancer risk, in a cohort of elderly Swedish men

**Study II**
- Investigate the association between dietary patterns with postulated health implications; a Mediterranean dietary pattern, a Low-carbohydrate high-protein dietary pattern and the official dietary recommendations, and circulating levels of multiple environmental contaminants in an elderly Swedish population

**Study III**
- Identify dietary patterns \textit{a posteriori}, by principal component analysis in a nationwide sample of the Swedish population
- Describe the identified dietary patterns in aspect of food and nutrient contribution
- Investigate associations between identified dietary patterns and population characteristics

**Study IV**
- Investigate the association between \textit{a posteriori} derived dietary patterns and anthropometric variables and a marker of inflammation
- Evaluate the association between \textit{a posteriori} derived dietary patterns and nutritional biomarkers
Methods

Study populations and study design

The ULSAM cohort (Study I)

The first study in this thesis is a follow-up study of dietary patterns and prostate cancer risk. The study was based on data from the Uppsala Longitudinal Study of Adult Men, the ULSAM cohort. The cohort was initiated in 1970 with the primarily aim to identify risk factors for cardiovascular disease and type 2 diabetes in middle aged men. All men born between 1920 and 1924 and at the time being living in Uppsala municipality were invited to participate, 82 percent accepted (n=2322). The cohort has been reinvestigated repeatedly. The 70-year investigation, which served as baseline for this study, was conducted between August 1991 and May 1995. All participants who were invited to the first investigation (at age 50), still alive and living in the Uppsala region (n=1681), were invited. Seventy-three percent accepted (n=1221) and 68 percent (n=1138) completed a food record. The latter was the inclusion criteria for the present study. The physical investigation included among other things; blood sampling and anthropometric measurements. Participants also filled in a medical questionnaire and a questionnaire including lifestyle habits such as physical activity and living conditions. More information about the ULSAM study is available online; www.pubcare.uu.se/ULSAM

In this study, we excluded men with self-reported type 2 diabetes since presumably they had changed their dietary habits following dietary advices. Hence, subsequent food records would not reflect their previous habitual diet. Men that reported extreme energy intakes (<3200 (n=4) or >18 000 kJ/day (n=1)) were also excluded. Men with previously diagnosed prostate cancer were excluded after the ascertainment of dietary patterns but prior to investigation of associations between dietary patterns and prostate cancer. The complete study population consisted of 1044 men. Follow-up on prostate cancer diagnosis ended 31st of December 2007.

The PIVUS cohort (Study II)

The second study, which cross-sectionally investigated associations between predefined dietary indices and blood levels of environmental contaminant exposure, was based on the Prospective Investigation of the Vasculature in
Uppsala Seniors, PIVUS. The PIVUS study was initiated in 2001 with the primary aim to evaluate the predictive power of vascular function on cardiovascular disease. A secondary aim was to evaluate circulating blood levels of environmental contaminants and their relation to health. At baseline, a random sample of 70-year old men and women in Uppsala were invited (n=2025), and 1016 (50.1%) agreed to take part. Participants underwent an extensive physical examination; including e.g. fasting blood sampling and anthropometric measurement. Participants also filled out a structured lifestyle questionnaire including e.g. questions on physical activity. All participants gave blood samples for analyses of environmental contaminants and 861 (84.7%) completed the food record. Body fat was measured by dual-energy X-ray absorptiometry (DXA) scan one or two years after the baseline investigation.

Seventeen individuals were excluded due to incomplete dietary data. Reported daily energy intake was within acceptable range, approximately 3000 to 14000 kJ among women and 3800 to 17000 kJ among men; hence there were no exclusions due to extreme energy intakes. The final study population consisted of 844 participants (50 % women). To read more about the PIVUS study visit: www.medsci.uu.se/pivus

Riksmaten adults 2010-11 (Study III and IV)

The third and fourth study in this thesis, identified, characterized and assessed a posteriori derived dietary patterns in the national dietary survey Riksmaten adults 2010-11. Riksmaten is a Swedish nationwide recurrent food survey, performed by the National Food Agency (NFA). Riksmaten adults 2010-11, were carried out between May 2010 and July 2011. All Swedish residents aged 18 to 80 were eligible to participate. The project was coordinated by Statistics Sweden on behalf of the NFA. Sampling was made by proportional allocation based on vital statistics and in strata of gender, age and region for the main sample (n=3995). For an additional sample who also were invited to participate in a parallel biomonitoring study, sampling was done according to affiliation to Swedish Occupational and Environmental Medicine Centers (n=1008). In total 53 individuals died or moved out of the country after the sampling was made; hence the true sample size was 4950. Participation rate was 46% for any of the included parts, 30% for the biomonitoring study (n=300, 52% women) and 36 % for the food record (n=1797, 56% women). The latter was the inclusion criteria in these two projects. Demographic data was collected from the Swedish population register. Information on additional covariates e.g. smoking-status and physical activity, was collected in a web-based questionnaire.

Individuals were excluded from our analyses if reporting extreme energy intakes ((approximately in kJ per day), women <2000 kJ (n=5) or >15000 kJ (n=5) and men <3400 (n=6) or >17000 kJ (n=8)). In addition 25 women who
reported being pregnant and 18 women who were currently breastfeeding were also excluded, since presumably not following their usual diet. The final study population consisted of 952 women and 778 men, of whom 147 women and 130 men also participated in a biomonitoring study. Detailed description of the study population and methods, together with the result from the Riksmaten adults 2010-11 dietary survey is available online: www.livsmedelsverket.se/matvanor-halsa--miljo/kostrad-och-matvanor/matvanor---undersokningar/riksmaten-2010-11---vuxna

Ethics

The two cohort studies ULSAM, PIVUS and the dietary survey Riksmaten 2010-11 were all approved by the Regional Ethical Review Board of Uppsala. Participation was voluntary and all individuals gave their informed consent before participating. Personal data was handled confidential.

Exposure assessment

Dietary assessment

PIVUS and ULSAM populations

In both ULSAM and PIVUS dietary intakes were assessed by self-report in a pre-coded seven-day optical readable food record. The food record has been evaluated against weighted records (correlations of energy intake and most energy yielding nutrients 0.4 to 0.6) and validated by 24-h urinary nitrogen excretion with acceptable agreement. Quantities were reported in household measurements or for selected foods, guided by pictures, as portion-sizes. Additional consumptions, not pre-coded, could be reported in free-text.

The dietary data was analyzed in commercial software based on food composition data from the Swedish NFA (SLV version 1990) including approximately 1500 items. Energy and nutrient intakes were derived from the system.

Riksmaten adults 2010-11

In Riksmaten dietary intake was assessed by self-report in a four-day estimated web-based food record (Livsmedelsystemet, application 04.1). Written information included a portion guide with photographs for estimation of portion sizes. Participants who were not able to self-report in the web-based food record could report by telephone to interviewers. The web-based food record was connected to a survey specific NFA food composition database (Livsmedelsdatabasen version Riksmaten adults 2010-11), which included
approximately 1900 food items. Dietary intakes and energy and nutrient content was derived directly from the system. An official version of the food record is available online http://www.slv.se/sv/grupp1/Mat-och-naring/kostrad/Test-matvanekollen/.

Evaluation of dietary data

Misreporting is a recognized problem in dietary assessments. Non-random misreporting might lead to misclassification in dietary exposure variables and attenuate, blur or even alter associations between diet and health (69, 76, 77).

To get an appreciation of the validity of the reported energy intake (EI), EI can be compared to energy expenditure (EE). Energy requirements can be stated as multiples of basal metabolic rate (BMR), EE:BMR, which is also known as the physical activity level (PAL). If, assuming weight stability then EI=EE. Hence, EI:BMR=PAL. However, absolute agreement between EI:BMR and PAL cannot be expected due to day to day variation in EI, BMR and PAL. The Goldberg equation can be used to identify an upper and a lower cutoff (confidence limits) for reasonable energy intake (EI) in relation to estimated EE taking errors and variation in included measurements into account (78). In this way the Goldberg equation can be applied to identify low- (with EI:BMR below the lower cutoff) and high- (with EI:BMR above higher cutoff) energy reporters. Further, in aim to limit the effect of unreliable dietary data and misclassification in the exposure variable individuals falling outside the acceptable range can be excluded before repeating the statistical analyses in the subpopulation of acceptable energy reporters (for simplicity from here on referred to as “acceptable reporters”).

In ULSAM and PIVUS BMR was estimated, based on age, gender and body weight (BW), with the age adjusted Schofield’s formula (for age group 64-70 years). In Riksmaten the standard, age-group specific, equation for estimating BMR was used (79). An individual’s PAL was predicted from questions of physical activity habits as described in detail in Appendix 1. In ULSAM and PIVUS an individual 95% confidence interval (CI) for PAL (i.e. EI:BMR) was estimated and compared to reported-EI:BMR. In Riksmaten a combined PAL, representing the mean PAL estimated from reported leisure- and work-time physical activity, was used; 1.67 for both men and women. The calculated 95% CI was then 0.93-3.01 for the whole population, and individuals with reported-EI:BMR outside of this range were considered acceptable reporters.

In this thesis exclusion of low (and the smaller proportion of) high energy reporters were primarily done in sensitivity analyses, to confirm the results in data of acceptable reporters conceivably less affected by non-random misreporting in the dietary assessment. In ULSAM 490 individuals (45.5%) were considered misreporters of energy intake; 488 low- and 2 high energy reporters. Leaving a subpopulation of acceptable reporters n=566. In PIVUS
205 individuals (24.3%) were characterized as misreporters of energy intake. 198 low- (whereof 107 women) and 7 high energy reporters (1 woman), hence 639 individuals were categorized as acceptable reporters. In the Riksmaten study population 156 women (16.5%) and 159 men (20.7%) were identified as low- and one woman as high energy reporter. Additional individuals in Riksmaten lacked information on BW (n=16) and their energy intake could not be evaluated, hence, they were also excluded from sensitivity analyses. In total, 788 women and 610 men constituted the groups of acceptable reporters in Study III and IV.

Assessment of dietary patterns

Adherence to dietary indices (Study I and II)
Participant’s adherence to pre-specified indices in study I and II were measured by comparing reported intakes with the predefined scores. To limit the effect of extraneous variation in energy intake on specific food or nutrient intakes all foods and nutrients were energy adjusted prior to the scoring process. This was done either by using energy densities (energy %) or by adjusting reported intakes by the residual method (g/d), as described by Willett (80).

The cutoffs in the scoring models were based on the intakes in the same population (or subpopulation, in sensitivity analyses of acceptable reporters). This was done to ensure good discriminating power between participants on the included variables. Hence a relative adherence to the dietary patterns was assessed. Moreover, scoring cutoffs and adherence to the score were defined separately for men and women in PIVUS.

We used previously published dietary indices with proposed health associations (2, 4, 6, 24). In ULSAM adherence to and associations with prostate cancer risk were assessed for a modified Mediterranean diet score (mMDS) and a LCHP diet score. In PIVUS the same indices were used and in addition a modified Healthy Diet Indicator (mHDI) based on the WHO dietary recommendations were assessed and related to circulating levels of environmental contaminants. Outline of the dietary indices are presented in Table 1.

Modified Mediterranean Diet Score
The Mediterranean diet score considers components typical of the traditional Mediterranean diet, referring to the diet kept by the Čertan Greeks and nearby populations in the 1950’s and early 60’s. Their diet consisted of high intakes of fruits and vegetables, olive oil, nuts, legumes, whole-grain cereals and fish, and moderate amount of alcohol (mainly having wine with meals), and their intake of dairy products and red meat was low (81, 82). Several Mediterranean dietary scores have been developed during the years and the Mediterranean diet has repeatedly shown beneficial health effects in diverse populations (6).
We applied the score defined by Trichopoulou et al. (25) with some modification to adapt the index to Swedish conditions (Table 1). Due to very low intake in the current population; pulses were incorporated into the vegetable score and nuts and seeds were disregarded. The cereal variable was extended to included potatoes, thereby capturing the contribution of potatoes to complex carbohydrate intake; in line with earlier publications (81). Polyunsaturated fatty acids (PUFA) replaced monounsaturated fatty acids (MUFA) when estimating dietary fat quality. Olive-oil consumption was very moderate in Sweden in the beginning of the nineties, and MUFA and saturated fatty acids (SFA) are highly correlated in a traditional Swedish diet. Alcohol intake was considered in agreement with the Mediterranean diet if reported intake ranged between 5 and 25 g/d for women and 10 and 50 g/d for men, as previously defined (25). In ULSAM (were information was available) AST/ALT <2.0 was a prerequisite for moderate drinking. For remaining variables the median of the dietary characteristic in the population served as a cut off, identifying and scoring (1p) the half of the population with the most characteristic/Mediterranean-like consumption of each included variable: fat quality, vegetables, fruits, cereals, fish (1p if above median intake) and meat and dairy products (1p if below median intake). The mMDS could take a total value of between 0 and 8 points.

Low Carbohydrate High Protein Score

In recent years, keeping a diet low in carbohydrates and high in protein has been encouraged to promote weight loss (83). Indeed, low carbohydrate diets have also gained ground among the general population. However, concern about the long-term health effects have been raised and in a recent a meta-analysis the LCHP diet was positively associated with all-cause mortality (4).

To identify adherence to a LCHP diet participants were divided into deciles of carbohydrate and protein intake (g/d). Participants in the highest decile of carbohydrate intake were assigned the lowest score (1p), the score increased (1p per decile) with descending deciles, hence, those in the lowest decile were assigned the highest score (10p). The reverse was applied for protein intake. The carbohydrate score- and the protein score variables were summed up and the total LCHP score took a value between 2 and 20 points (Table 1).

In additional analyzes in Study II the LCHP score was modified in aim to enhance the significance of fat intake independent from protein intake, as previously described (39). Deciles of fat intake (g/d) were scored in line with protein intake and added to the carbohydrate and protein scores. This modified LCHP score including fat intake could take a value between 3 and 30 points.
Modified Healthy Diet Indicator

The HDI was developed by Huijbregts et al. to measure the adherence to the WHO dietary recommendations for prevention of major chronic disease \cite{24}. The HDI has been inversely related to mortality \cite{24}. We applied a modified HDI (Table 1), previously adapted by Sjögren et al., to conforming to the recommendations from the Swedish NFA \cite{77,84}. In addition our mHDI was population based, using cutoffs from the current population. The score included variables for: macronutrient composition, dietary fiber, cholesterol, fruits and vegetables and fish intake. Individuals, whose intake matched the desirable intake range (or cutoff) was given 1 point (else 0). For sucrose intake a negative score (-1) was given if exceeding pre-specified maximum intake level. The mHDI could take a value between -1 and 8 points.

Table 1. Outline of dietary indices\textsuperscript{a}

<table>
<thead>
<tr>
<th>modified Mediterranean Diet Score</th>
<th>Cut-off</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUFA/SFA (ratio)</td>
<td>&gt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Vegetables and legumes (g/d)</td>
<td>&gt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Fruit (g/d)</td>
<td>&gt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Cereals including potato (g/d)</td>
<td>&gt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Fish (g/d)</td>
<td>&gt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Meat and meat products (g/d)</td>
<td>&lt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Milk and milk products (g/d)</td>
<td>&lt; median</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td>Alcohol \textsuperscript{b} (g/d)</td>
<td>Women 5-25</td>
<td>1 (else: 0)</td>
</tr>
<tr>
<td></td>
<td>Men 10-50</td>
<td>1 (else: 0)</td>
</tr>
</tbody>
</table>

Range: 0 to 8 points

Low Carbohydrate High Protein Score

<table>
<thead>
<tr>
<th>Carbohydrate intake g/d</th>
<th>Lowest to Highest decile</th>
<th>10 to 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake g/d</td>
<td>Lowest to Highest decile</td>
<td>1</td>
</tr>
</tbody>
</table>

Range: 2 to 20 points

modified Health Diet Indicator

| SFA (% of energy)        | < median | 1 (else: 0) |
| PUFA (% of energy)       | approx 5-10| 1 (else: 0) |
| Protein (% of energy)    | approx 10-15| 1 (else: 0) |
| Carbohydrates (% of energy) | approx 50-70 | 1 (else: 0) |
| Sucrose (% of energy)    | > median | -1 (else: 0) |
| Fiber (g/MJ)             | > median | 1 (else: 0) |
| Fruit and vegetables (g/d)| > median | 1 (else: 0) |
| Cholesterol (mg/d)       | < median | 1 (else: 0) |
| Fish (g/d)               | > median | 1 (else: 0) |

Range: -1 to 8 points

\textsuperscript{a}All dietary intakes were energy adjusted, either by the residual method or evaluated as g/MJ or % of energy

\textsuperscript{b}In ULSAM an additional prerequisite was AST/ALT <2.0 (data not available in PIVUS)
Data derived dietary patterns (Study III and IV)
In Riksmaten adults 2010-11 PCA was used to identify the principal components that best explained the variation in the dietary data and hence constituted the major dietary patterns in the population.

Preparing data for identification of dietary patterns
The PCA was based on linear correlations between crude reported food intakes in grams per day. The food composition database included 1900 items. Reported items were grouped into 35 food groups as described below. Merging registered food items into food groups was done based on culinary use and nutrient composition. However, to keep the quality aspects of otherwise similar foods and not ignore the impact of prudent food choices, milk products were categorized in two groups; in accordance or not in accordance with the Nordic Keyhole-label (the symbol identifies options containing less fat and less sugar (85)) and bread was separated into refined bread or bread rich in wholegrain and fiber (> 5% fiber). Some additional foods were kept in separate groups since they represent distinct food choices or nutritional characteristics (e.g. butter, margarine and vegetable oils) or simply not appropriate to combine with any other foods (e.g. potatoes, coffee, tea).

Evaluation of retrieved components
PCAs were performed in men and women separately. PCA outputs were evaluated based on eigenvalues (>1.25), scree plots and interpretation of retrieved components, and then repeated with the number of components to keep specified. Identified components were rotated with varimax rotation creating orthogonal, uncorrelated, factors. These factors constitute the dietary patterns. Individuals were given a score on each of the retained factors, to reflect the individual agreement with each dietary pattern and create variables that could further be assessed in relation to health outcomes. These dietary pattern scores were based on the sum of the products of the regression weights (so called loadings) multiplied with the reported intakes of the specific food groups. Hence, a high factor score for a given pattern indicates a high intake from food groups that loaded strongly positively on that factor and low intakes of food groups loading negatively on the same factor.

Naming of derived patterns
Three dietary patterns were derived in women and two in men. The naming of the patterns was based on the interpretation of the factors founded on nutritional and domestic-cultural knowledge. The first two patterns had similar loadings in both men and women. Loadings can be interpreted as correlations between the food groups and retrieved components. The first pattern loaded positively on foods generally considered healthy such as vegetables, fruits and berries, fish and seafood, eggs, hot and cold cereals and vegetable
oils and negatively on foods considered less healthy such as refined bread, fast food and soda. Hence this pattern was named the Healthy pattern. The second pattern was characterized by strong loadings for foods recognized as components of a traditional Swedish diet e.g. meat and processed meats, potatoes, sauces, non-Keyhole milk products, sweet bakery products and margarine. This pattern was named the Swedish-traditional pattern. The third pattern identified only in women loaded positively on bread and cheese, rice, pasta and food grain meals, substitute products for meat and dairy and snack-foods, and negatively on potatoes. This pattern was called the Light-meal pattern. Dietary patterns are described in more detail in the results section.

Assessment of outcome
Prostate cancer (Study I)
Prostate cancer diagnoses, up to 31st of December 2007, were identified in the Swedish Cancer Register. For tumor specific analyses, in the subpopulation of acceptable energy reporters, tumor characteristics at diagnosis were collected from medical records and classified as low- or high-risk disease (details are given in Paper I). Deaths were confirmed in the Swedish national Cause of Death register.

Environmental contaminants (Study II)
As previously described (86) POPs were analyzed in blood plasma by high resolution chromatography/high resolution mass spectrometry. The detection rate was overall high. The following POPs were included in our study: p,p′-dichlorodiphenyldichloroethylene (p,p′-DDE), hexachlorobenzene (HCB), trans-nonachlor (TNC), octachlorodibenzo-p-dioxin (OCDD), the PBDE BDE47 and the PCBs 118, 126, 153, 169, 170 and 209. The six PCBs were chosen since previously shown to be representative markers of overall PCB exposure (87). OCDD was considered a marker for overall dioxin exposure (86).

Serum levels of BPA and phthalate metabolites were measured by high performance liquid chromatography/tandem mass spectrometry (HPLC–MS/MS) (88). Four metabolites which showed detectable levels in almost all participants were included in this study: mono-[2-ethylhexyl] phthalate (MEHP), monoethyl phthalate (MEP), monoisobutyl phthalate (MiBP) and monomethyl phthalate (MMP).

Cadmium, lead, mercury and aluminum, were analyzed in whole blood using a doublefocusing inductively coupled plasma-sector field mass spectrometry instrument (ICP-SFMS) (89). Additional details on the analyses are given in Paper II.
Demographic and lifestyle characteristics (Study III)
In Riksmaten adults 2010-11 demographic data on age, gender, educational level, income and living area, were retrieved from the Swedish population register. Education was categorized as high if university or college degree, else low. Income was either above (high) or below (low) gender specific median income. Living area was coded as urban, if living in a larger city, else rural region.

A web-based questionnaire was used to collect information on residential and lifestyle factors. Living in single household was identified and coded as yes or no. Individuals were considered as either current smokers or non-smokers. Leisure-time and work-time physical activity were assessed separately in web-based questions as described in detail in Appendix 1.

Anthropometry (Study IV)
BW (kg), height (cm) and waist- and hip-circumference (cm) were self-reported in a web-based questionnaire. Instructions for making the latter two measurements were included in the questionnaire. BMI was defined as the ratio between BW and the quadratic term of height (kg/m^2). WHR was calculated as WC divided by hip circumference. WHHR was defined as the WHR divided by height.

CRP and nutritional biomarkers (Study IV)
Blood sampling of participants in the Riksmaten biomonitoring study was, for practical reasons, non-fasting.

C-reactive protein (CRP), ferritin and folate was analyzed in plasma on a ci8200 Abbott Architect (Abbott, US). CRP was analyzed by turbidimetric method and ferritin and folate concentrations by chemiluminescent microparticle immunoassay. Erythrocyte folate was analyzed in whole blood with ascorbic acid by the competitive principle and regents from Roche Diagnostics (Roche Diagnostics Scandinavia AB). Total 25-hydroxy vitamin D (D2 and D3) was measured by LC-MS in plasma with EDTA on a Hewlett-Packard 1100 liquid chromatograph coupled to a Hewlett-Packard mass spectrometer (Agilent Technologies). Fatty acid composition was measured in serum phospholipids, by gas chromatography with Thermo TR-FAME (Thermo Electron Corporation, USA) and Agilent Technologies system (GC 6890N, Autosampler 7683, and Agilent ChemStation). Details are given in Manuscript IV.
Statistical methods in brief

Cox proportional hazard regression (Study I)
Cox proportional hazard regression was used to estimate relative risk of prostate cancer associated with adherence to the predefined dietary patterns. Additional analyses; separating low- and high-risk disease and explanatory analyses adjusting for intake of nutrients considered as probable modifiers of prostate cancer risk by the WCRF (i.e. selenium, calcium and lycopene) (90), were performed in acceptable reporters only. (Note, in an updated project report evidence for these nutrients risk modifying effects have all been downgraded (33)).

Competing risk (Study I)
In Study I we examined the possibility of competing risks modifying the associations between dietary patterns and prostate cancer-risk. A competing risk is defined as an event that precludes or alters the possibility for the event under study. Mortality due to other causes than prostate cancer was assessed as a competing risk in this setting.

Competing risk analyses were performed according to the Fine and Gray model (stcrreg command in STATA). In addition we did a graphical inspection of the cumulative incidence estimates of prostate cancer, considering death without prostate cancer diagnosis both as a competing risk and as a censoring event. We also conducted logistic regression analysis on survivors up to 2003, to reduce the effect of total mortality as a competing event.

Multivariate linear regression (Study II)
In Study II the association between dietary patterns and environmental contaminants were assessed in multivariate linear regressions. A multivariate analysis refers to a statistical model with two or more dependent variables (two or more outcomes) as compared to multivariable or multiple analyses where there are two or more independent variables or predictors. Separate analyses were conducted for each diet score (independent variable), using all 20 contaminants as outcome variables simultaneously. The multivariate model allowed us to test the 20 associations between each dietary pattern and contaminant levels at once in a global test, thereby avoiding multiple testing issues. Interactions between gender and dietary patterns were also assessed in global tests.

Principal component analysis (Study III)
PCA is a data reduction method that reduces the dimensions of the observed data to unobserved components, taking as much of the variance as possible into account when retrieving each component. The PCA was performed based on linear correlation between 35 food groups (defined as described above), using the “pca” command in STATA. Intakes were included as
grams per day. The procedure is described in more detail above (Assessment of dietary patterns).

**Classic linear regression and correlation analyses (Study III and IV)**
Associations between empirically derived dietary patterns and demographic data, lifestyle factors, food intake (g/day) and nutrient densities (E% or per MJ) were examined in quintiles of dietary pattern scores (highest quintile for highest score) and tested for trends in linear regression analyses, with the score quintiles applied as continuous variables. The same approach was used for examination of relations between derived dietary patterns and anthropometric data and CRP in study IV. Correlations between dietary pattern score and energy intake was tested in pairwise correlation. Spearman rank correlation was used to assess relations between dietary patterns and energy adjusted nutrient intakes continuously (Study III), since most nutrient intakes were non-normally distributed. In Study IV partial correlation analysis was used to assess relations between dietary patterns and nutritional biomarkers in the biomonitored subpopulation.

**Sensitivity analyses**
In all three study populations the reported dietary intake in the food records were evaluated by the Goldberg equation (as described above). In subsequent sensitivity analyses low and high energy reporters were excluded and analyses were repeated in the subpopulations of acceptable reporters.

**Statistical software**
All analyses were performed in STATA statistical software (Intercooled STATA 11.0 for Windows; Stata Corp, College Station; TX, USA), except for the graphical assessment of competing risk which were performed in R (R Development Core Team 2009, R Foundation for Statistical Computing, Vienna, Austria). Significance level was set to 0.05.
Results

Population characteristics
The study populations are described briefly in Table 2 and commented on below. Additional information on the populations and subpopulations, including dietary intakes are given in the corresponding paper or manuscript.

The ULSAM men
The ULSAM men were slightly overweight with a mean BMI of 26.1 (3.4) and 62 percent were regularly physically active (Table 2). Acceptable reporters were slightly healthier than men categorized as misreporters of energy intake; with lower BMI and WC and lower frequency of the metabolic syndrome.

Spearman correlations between dietary patterns and macronutrients and selected food groups are presented in Table 3. Correlations between the mMDS and the LCHP score were r=-0.24 in the whole study population and r=-0.20 in acceptable reporters.

One hundred and thirty three cases of prostate cancer were diagnosed during median follow-up of 13 years. Seventy-two of these cases were registered in acceptable reporters; 20 low-risk diseases and 50 high-risk diseases, for two of the cases there were no information on disease grade.

The PIVUS population
The PIVUS population was also somewhat overweight, mean BMI 27.0 (4.3), and about a fourth was physically active on a regular basis (Table 2). The subgroup of acceptable reporters was slightly healthier with a mean BMI of 26.3 (3.9), and 8 percent smokers, 11 percent diabetics and 19 percent who fulfilled the criteria for the metabolic syndrome, compared to 9, 12 and 23 percent in the full study sample. However, level of education and physical activity was similar in both groups.

Spearman correlations between dietary patterns and macronutrients and selected food groups are presented in Table 3. Correlations between the indices were r=0.62 for the mMDS and the mHDI, r= -0.14 for the mMDS and the LCHP and r=-0.43 for the mHDI and the LCHP.

Levels of contaminants have been reported previously (88, 89, 91). Levels of POPs were overall comparable to what has been reported from other non-
occupationally exposed European populations \(^{(91)}\). However, although the PCB congener-exposure patterns were similar to the pattern in elderly individuals participating in the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 \(^{(87)}\), levels of PCBs were generally higher in the present study than in NHANES \(^{(91)}\). Levels of BPA and detected phthalate metabolites were similar to what has been found in other studies \(^{(88)}\).

Riksmaten adults 2010-11

Mean age in Riksmaten adult 2010-11 was 48 (17) years and mean BMI 25.4 (4.3) \((\text{Table 2})\), 47 percent were overweight or obese. Misreporters of energy intake had higher BMI 27.7 (5.1), were more likely to be overweight or obese 71 percent, and less likely to be regularly physically active on their spare-time; 46 percent compared to 51 percent in the whole study sample.

<table>
<thead>
<tr>
<th>Table 2. Background characteristics of the study populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ULSAM</strong></td>
</tr>
<tr>
<td>Nb. of subjects</td>
</tr>
<tr>
<td>Women n (%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)) mean (sd)</td>
</tr>
<tr>
<td>Regular physical activity(^a) n (%)</td>
</tr>
<tr>
<td>Smoker n (%)</td>
</tr>
<tr>
<td>High education(^b) n (%)</td>
</tr>
<tr>
<td>Energy (kJ) mean (sd)</td>
</tr>
<tr>
<td>Low-energy reporters n (%)</td>
</tr>
</tbody>
</table>

\(^a\)Leisure-time physical activity was defined separately for each population, details are given in Appendix 1

\(^b\)High if university or college degree else low
Table 3. Correlations between predefined dietary patterns and dietary variables in ULSAM and PIVUS

<table>
<thead>
<tr>
<th></th>
<th>ULSAM</th>
<th></th>
<th>PIVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mMDS</td>
<td>LCHP score</td>
<td>mHDI</td>
</tr>
<tr>
<td></td>
<td>Rho</td>
<td>p</td>
<td>Rho</td>
</tr>
<tr>
<td>Carbohydrates ( % of energy)</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>-0.73 &lt;0.001</td>
</tr>
<tr>
<td>Protein ( % of energy)</td>
<td>-0.14</td>
<td>&lt;0.001</td>
<td>0.70 &lt;0.001</td>
</tr>
<tr>
<td>Fat ( % of energy)</td>
<td>-0.32</td>
<td>&lt;0.001</td>
<td>0.44 &lt;0.001</td>
</tr>
<tr>
<td>Fruit and vegetables (g/d)</td>
<td>0.46</td>
<td>&lt;0.001</td>
<td>-0.22 &lt;0.001</td>
</tr>
<tr>
<td>Cereals incl. potatoes (g/d)</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>-0.06 0.04</td>
</tr>
<tr>
<td>Fish (g/d)</td>
<td>0.48</td>
<td>&lt;0.001</td>
<td>0.06 0.07</td>
</tr>
<tr>
<td>Meat and meat products (g/d)</td>
<td>-0.26</td>
<td>&lt;0.001</td>
<td>0.36 &lt;0.001</td>
</tr>
<tr>
<td>Milk and dairy products (g/d)</td>
<td>-0.42</td>
<td>&lt;0.001</td>
<td>0.27 &lt;0.001</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>0.11 &lt;0.001</td>
</tr>
</tbody>
</table>

*Spearman correlations between dietary patterns and energy percentages of macronutrients or energy adjusted intakes of selected food groups, assessed in the full study population of ULSAM (n=1044) and PIVUS (n=844)
Main findings

Dietary patterns and prostate cancer (Study I)

There were no statistical significant associations between dietary patterns and prostate cancer risk in the full ULSAM study population (Table 4). In sensitivity analyses, restricted to acceptable reporters, the LCHP score was inversely related to prostate cancer; hazard ratios (HR) 0.77 (0.61; 0.96) per 1 SD increment in score, adjusted for energy intake, smoking, regular physical activity and level of education (Table 4). HRs did not markedly differ in analyses stratified on disease grade (results not shown).

Competing risk analyses

Results from competing risk analyses performed in acceptable reporters did not differ substantially from results in cox-regression analysis; multivariable adjusted (as above) sub-hazard ratio (SHR) 0.75 (0.59; 0.96) for 1 SD increment in score and SHR 0.45 (0.20; 0.98) for high compared to low LCHP adherence. The logistic regression analyses on survivors up to 2003 (n=438 acceptable reporters, 34 cases) indicated an inverse association between adherence to the LCHP diet and prostate cancer, although not significant; high vs. low adherence multivariable adjusted OR 0.40 (0.12; 1.32). In the graphical assessment the Kaplan Meier curve did not substantially deviate from the cumulative incidence of prostate cancer (graphs are displayed in Paper I).

Collectively this implies that our results were not substantially influenced by competing risk.

Explanatory analyses

Including selenium intake (μg/day) in the cox-regression analysis, attenuated the association between the LCHP score and prostate cancer risk, high vs. low adherence; HR 0.70 (0.28; 1.73).
Table 4. *Hazard ratios for prostate cancer diagnosis in relation to adherence to dietary patterns*†

<table>
<thead>
<tr>
<th></th>
<th>Continuous</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>p-for trend(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole study population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mMDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of men (cases)</td>
<td>1044 (133)</td>
<td>231 (31)</td>
<td>674 (88)</td>
<td>139 (14)</td>
<td></td>
</tr>
<tr>
<td>Energy adjusted HR (95 % CI)(^b)</td>
<td>0.83 (0.67; 1.03)</td>
<td>1.0</td>
<td>0.92 (0.61; 1.39)</td>
<td>0.69 (0.36; 1.29)</td>
<td>0.28</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)(^c)</td>
<td>0.81 (0.65; 1.02)</td>
<td>1.0</td>
<td>0.90 (0.59; 1.39)</td>
<td>0.71(0.37; 1.36)</td>
<td>0.32</td>
</tr>
<tr>
<td>LCHP score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of men (cases)</td>
<td>1044 (133)</td>
<td>169 (27)</td>
<td>705 (86)</td>
<td>170 (20)</td>
<td></td>
</tr>
<tr>
<td>Energy adjusted HR (95 % CI)(^b)</td>
<td>0.90 (0.77; 1.06)</td>
<td>1.0</td>
<td>0.79 (0.51; 1.22)</td>
<td>0.75 (0.42; 1.33)</td>
<td>0.31</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)(^c)</td>
<td>0.89 (0.76; 1.05)</td>
<td>1.0</td>
<td>0.76 (0.48; 1.19)</td>
<td>0.72 (0.40; 1.31)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Acceptable reporters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mMDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of men (cases)</td>
<td>566 (72)</td>
<td>116 (14)</td>
<td>377 (49)</td>
<td>73 (9)</td>
<td></td>
</tr>
<tr>
<td>Energy adjusted HR (95 % CI)(^b)</td>
<td>1.00 (0.75; 1.34)</td>
<td>1.0</td>
<td>1.04 (0.57; 1.88)</td>
<td>0.93 (0.40; 2.16)</td>
<td>0.91</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)(^c)</td>
<td>1.01 (0.75; 1.37)</td>
<td>1.0</td>
<td>1.10 (0.59; 2.04)</td>
<td>1.04 (0.43; 2.49)</td>
<td>0.90</td>
</tr>
<tr>
<td>LCHP score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of men (cases)</td>
<td>566 (72)</td>
<td>97 (19)</td>
<td>375 (43)</td>
<td>94 (10)</td>
<td></td>
</tr>
<tr>
<td>Energy adjusted HR (95 % CI)(^b)</td>
<td>0.81 (0.66; 1.01)</td>
<td>1.0</td>
<td>0.60 (0.35; 1.03)</td>
<td>0.55 (0.25; 1.17)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)(^c)</td>
<td>0.77 (0.61; 0.96)</td>
<td>1.0</td>
<td>0.55 (0.32; 0.96)</td>
<td>0.47 (0.21; 1.04)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\(^a\)Risk estimates presented as hazard ratios derived by Cox proportional hazard regression analyses, with 95% CI.
\(^b\)Adjusted for energy intake
\(^c\)Adjusted for energy intake, smoking, regular physical activity and level of education
\(^d\)In low-, medium- and high-adherent groups
Dietary patterns and environmental contaminants (Study II)

Significant associations were found between all three dietary patterns and circulating levels of environmental contaminants in global tests (mMDS p=0.001, LCHP score p=0.002 and mHDI p=0.004 adjusted for energy intake, gender, smoking and education). These overall tests for associations remained in fat mass (DXA) adjusted models and in sensitivity analyses including only acceptable reporters. Associations between each dietary pattern and circulating levels of specific environmental contaminants are summarized below and displayed as predicted % change in geometric mean value per interquartile range (IQR) increase in dietary pattern score Figure a-c. Details are published in Paper II.

There were no interactions between dietary patterns and gender in associations with circulating levels of environmental contaminates in the PIVUS population. Adjusting analyses for fat-mass had no major impact on the results. Results from fat-mass adjusted analyses and sensitivity analyses can be found in the supplementary material to Paper II.

The Modified Mediterranean Diet Score
In summary higher adherence to the mMDS was associated with higher levels of PCBs, the pesticide remnant TNC and mercury (Figure a). In sensitivity analyses (including only acceptable reporters) relations to PCB 118, 153 and 209 as well as to TNC and mercury remained whilst other associations were attenuated and no longer statistically significant.

The Low Carbohydrate High Protein Score
The LCHP dietary pattern showed positive associations with circulating levels of PCB 118 and 153, the pesticide remnants p,p'-DDE, HCB and TNC as well as lead and mercury (Figure b). In sensitivity analyses results for PCB 118 and HCB persisted, the strength of the association with mercury was attenuated and all other associations remained of the same magnitude however without statistical significance. When adding fat intake as a separate variable to the LCHP index only associations with HCB and lead remained.

The Modified Healthy Diet Indicator
High adherence to the mHDI was inversely related to circulating levels of OCDD and lead (Figure c). Positive associations were found for levels of PCB 118, TNC and mercury, the latter non-significantly. When restricting analyses to acceptable reporters in sensitivity analyses inverse association with OCDD and lead remained significant, coefficients for mercury, TNC and PCB 118 were slightly stronger but non-significant.
Figure a. Forest plot displaying predicted percent change in geometric mean value per IQR increase in mMDS.
Figure b. Forest plot displaying predicted percent change in geometric mean value per IQR increase in LCHP score
Dietary patterns among Swedish adults (Study III)

Three dietary patterns were identified in women and two patterns in men, explaining 19% and 13% of the total variance, respectively. The first two patterns were similar in men and women; a Healthy pattern and a Swedish-traditional pattern, whilst the third Light-meal pattern was specific for the female population in Riksmaten. Loadings for each dietary pattern are presented in Table 5 and summarized below. The interpretation of the patterns in sensitivity analyses including only acceptable reporters was the same as in the full Riksmaten study sample. Lifestyle and nutrient characteristics associated with the patterns are summarized in brief below. Correlations between dietary patterns and nutrients are also displayed in Figure d-g. Additional details on food intake and the nutrient profiles of the patterns are given in Manuscript III.
Table 5. Dietary patterns and rotated (varimax-rotation) factor loadings, only loadings greater than ±0.15 for are shown.

<table>
<thead>
<tr>
<th>Food groups(^a)</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
<td>Swedish-Traditional</td>
</tr>
<tr>
<td>Fish and seafood</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Meat and processed meat</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Milk-products, non-Keyhole(^b)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Potatoes</td>
<td>0.35</td>
<td>-0.18</td>
</tr>
<tr>
<td>Vegetables</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Fruit and berries</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Fast food</td>
<td>-0.25</td>
<td>-0.18</td>
</tr>
<tr>
<td>Rice, pasta and food grains</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Refined bread(^c)</td>
<td>-0.30</td>
<td></td>
</tr>
<tr>
<td>Fiber-rich bread(^e)</td>
<td>0.25</td>
<td>0.27</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>0.20</td>
<td>0.23</td>
</tr>
<tr>
<td>Sweet bakery Products</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Desserts</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Sweet condiments</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Sweets and candy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salads (main dish)</td>
<td>-0.19</td>
<td></td>
</tr>
<tr>
<td>Soup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sauces, dressing</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Substitute products(^d)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Margarine</td>
<td>0.37</td>
<td>0.20</td>
</tr>
<tr>
<td>Vegetable-oil</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Crisp and snacks</td>
<td>-0.17</td>
<td></td>
</tr>
<tr>
<td>Nuts and seeds</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td>0.17</td>
<td>-0.37</td>
</tr>
<tr>
<td>Tea</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Soda</td>
<td>-0.30</td>
<td></td>
</tr>
</tbody>
</table>

Variance explained\(^e\) | 7.6 | 6.0 | 5.4 | 7.3 | 6.0

\(^a\)Food groups with loadings <0.15 on all derived patterns are not listed (i.e. poultry, cream and cream-fraiche, milk-products with Keyhole\(^b\), savoury bakery products, butter, juice and alcoholic beverages). Food groups are thorough defined and exemplified in the supplemental material to Manuscript III.
For milk-products, the Swedish NFA Keyhole symbol identifies options that contain less fat and less sugar; fat content has to be limited to maximum 0.7% and for flavored products there is an additional limit for sugars, maximum 9%.

Fibre-rich bread had a minimum of 5% fibre; unspecified Swedish crisp bread was also included in this category since most crisp breads have higher fibre content. Bread with fibre content less than 5% was considered refined.

Substitute products; used as substitutes for dairy products, meat and fish etc. includes for example soy- and oat-milk, soy protein and quorn.

Total variance explained by the derived components; in women 19% and, in men 13.3%.

The Healthy pattern
The first pattern, explaining the largest part of the variation, loaded positively on vegetables, fruits and berries, fish and seafood, eggs, cereals and vegetable oils and negatively on foods considered less healthy such as fast food, refined bread and soda (Table 5). In men additional strong positive loadings included fiber-rich bread and tea.

The Healthy pattern was directly associated with e.g. age in both genders, and with education and income in women only. Women with high Healthy pattern score were more likely to live in single households. Both men and women with high Healthy pattern score were less likely to be smoking and more likely to be physically active on their spare time. Women were however also more likely to have a sedentary work.

There was a significant positive correlation between the Healthy pattern and energy intake in men (r=0.26), but not in women. In summary, the Healthy pattern showed a favorable nutrient profile with e.g. positive correlations to fiber intake, omega-3 fatty acids and total PUFA, and negative correlations to added sugar, details are displayed in Figure d-e. Correlations to residual adjusted micronutrient intakes in both women and men revealed significant positive correlations for most vitamins and minerals assessed, as shown in Figure f-g.

The Swedish-traditional pattern
The second pattern loaded positively on traditional Swedish foods such as potatoes, meat and processed meat, sauces, non-Keyhole milk products, sweet bakery products, sweet condiments, desserts and margarine (Table 5). In women this pattern loaded also on fiber-rich bread and cereals and in men on refined bread and coffee. Negative loadings were found for fast food in both men and women and salads (as a main dish) in women, and vegetable oils in men.

High dietary agreement with this pattern was e.g. associated with higher age, lower education and living in rural areas. Women with high Swedish-traditional pattern score had lower income whilst men were more likely to live alone and to have a work including moderate physical activity (not sedentary); however they were less physically active on their spare time.

The Swedish-traditional pattern was correlated to higher energy intake in both men and women (r=0.38 and r=0.51). In summary this pattern was posi-
tively correlated with e.g. total carbohydrates, added sugar, total fat and SFA and negatively with protein and dietary fiber (the latter in men only) (**Figure d-e**). Correlations to energy adjusted intakes of micronutrients are displayed in **Figure f-g**.

**The Light-meal pattern**
The third interpretable pattern derived in women loaded positively on fiber-rich bread, cheese, rice-, pasta- and food grain-dishes, substitute products for meat and dairy products, sweets and candies, snacks, nuts and seeds and tea, but negatively on potatoes and coffee (**Table 5**).

High Light-meal pattern score was associated with younger age, lower BMI, living in urban areas, not smoking and having a higher education.

The Light-meal pattern was positively correlated to energy intake (r=0.41). Correlations were also positive for energy percentage of total carbohydrates as well as added sugars and dietary fiber as shown in **Figure d**. Correlations were negative for e.g. protein and alcohol. Correlations to energy adjusted micronutrients were mostly negative (**Figure f**).
**Figure d.** Spearman rank correlation between dietary patterns and macronutrients (E%, except for fiber g/MJ) in women

**Figure e.** Spearman rank correlation between dietary patterns and macronutrients (E%, except for fiber g/MJ) in men
Figure f. Spearman rank correlation between dietary patterns and energy adjusted micronutrient intakes in women

Figure g. Spearman rank correlation between dietary patterns and energy adjusted micronutrient intakes in men
Dietary patterns, anthropometry, inflammation and nutritional biomarkers (Study IV)

**Dietary pattern and anthropometry**

The Healthy dietary pattern score was inversely associated with anthropometric measurements in age and energy adjusted analyses. In fully adjusted analyses, adjusting also for education and leisure-time physical activity (below referred to as multivariable analyses), the Healthy dietary pattern was inversely associated with BMI, WC, WHR and WHHR in women and with BMI and WC in men (Table 6). In women BMI was 1.3 units lower comparing the fifth quintile (highest score) of the Healthy dietary pattern score with the first quintile (lowest score), in multivariable analyses (p=0.011). For the same comparison in men BMI was 1.0 unit lower, however this difference did not reach statistical significance (p=0.06). WC was 3.5 cm lower in women (p=0.016), and 3.6 cm in men (p=0.024), comparing fifth to first quintile of dietary pattern score. The WHR differed with 0.02 units (p=0.016) and the WHHR with 0.015 units (p=0.015) comparing the extreme quintiles of the Healthy dietary pattern in women. There were no statistical significant associations between the Swedish-traditional or the Light meal dietary patterns and measures of body anthropometry in multivariable analyses. Associations between the healthy dietary pattern and BMI as well as WC were slightly stronger in sensitivity analyses including only acceptable reporters (details are given in Manuscript IV).
<table>
<thead>
<tr>
<th>Quintile of Healthy dietary pattern score</th>
<th>Q1</th>
<th>Q3</th>
<th>Q5</th>
<th>β-crude</th>
<th>p</th>
<th>β²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 (21.5; 27.5)</td>
<td>24.2 (22.3; 26.7)</td>
<td>24.2 (22.1; 27.2)</td>
<td>-0.06</td>
<td>0.55</td>
<td>-0.30</td>
<td>0.012</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>83 (76; 93)</td>
<td>85 (78; 92)</td>
<td>86 (78; 93)</td>
<td>-0.04</td>
<td>0.90</td>
<td>-0.82</td>
<td>0.012</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84 (0.78; 0.90)</td>
<td>0.85 (0.80; 0.91)</td>
<td>0.85 (0.81; 0.90)</td>
<td>-0.0006</td>
<td>0.74</td>
<td>-0.005</td>
<td>0.024</td>
</tr>
<tr>
<td>WHHR</td>
<td>0.50 (0.47; 0.54)</td>
<td>0.52 (0.48; 0.55)</td>
<td>0.51 (0.49; 0.54)</td>
<td>&lt;0.0001</td>
<td>0.97</td>
<td>-0.003</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (23.1; 28.2)</td>
<td>25.5 (23.3; 27.8)</td>
<td>24.8 (22.6; 27.2)</td>
<td>-0.11</td>
<td>0.3</td>
<td>-0.24</td>
<td>0.050</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>94 (85; 102)</td>
<td>97 (89; 104)</td>
<td>94.5 (88; 101)</td>
<td>0.21</td>
<td>0.51</td>
<td>-0.89</td>
<td>0.016</td>
</tr>
<tr>
<td>WHR</td>
<td>0.93 (0.89; 1.00)</td>
<td>0.95 (0.91; 1.00)</td>
<td>0.94 (0.91; 0.99)</td>
<td>-0.0004</td>
<td>0.88</td>
<td>-0.004</td>
<td>0.23</td>
</tr>
<tr>
<td>WHHR</td>
<td>0.52 (0.49; 0.55)</td>
<td>0.53 (0.50; 0.56)</td>
<td>0.53 (0.50; 0.56)</td>
<td>0.001</td>
<td>0.46</td>
<td>-0.009</td>
<td>0.64</td>
</tr>
</tbody>
</table>

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHHR, waist-hip to height ratio

²Median (interquartile range, p25; p75)

Regression coefficient adjusted for age, energy intake, education and leisure-time physical activity
Dietary patterns and inflammation

Results from multivariable regression analyses between dietary patterns and CRP-levels were all non-significant. Excluding participants with suspected clinical infection (CRP > 5mg/L or 10mg/L) did not change the results. Results were also consistent in sensitivity analyses of acceptable reporters.

Dietary patterns and nutritional biomarkers

Correlation coefficients for dietary patterns and nutritional biomarkers, adjusted for age, energy intake and supplemental use, are presented in Table 7. Results were largely consistent in sensitivity analyses of acceptable reporters, although some correlations were no longer significant.

Table 7. Nutritional biomarkers, levels and adjusted correlation coefficients between nutritional biomarkers and dietary pattern scores

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (iqr)</td>
<td>Healthy</td>
<td>Swedish-trad.</td>
<td>Median (iqr)</td>
<td>Healthy</td>
<td>Swedish-trad.</td>
</tr>
<tr>
<td>Vitamin D (nmol/L)</td>
<td>65 (53; 77)</td>
<td>-0.03</td>
<td>-0.12</td>
<td>61 (50; 75)</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>P-folate (nmol/L)</td>
<td>14 (11; 18)</td>
<td>0.26**</td>
<td>-0.15</td>
<td>13 (10; 17)</td>
<td>0.14</td>
<td>-0.26**</td>
</tr>
<tr>
<td>Ery-folate (nmol/L)</td>
<td>450 (390; 500)</td>
<td>0.15</td>
<td>-0.18*</td>
<td>480 (420; 550)</td>
<td>0.08</td>
<td>-0.11</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>21 (54; 94)</td>
<td>-0.08</td>
<td>-0.22*</td>
<td>142 (96; 223)</td>
<td>-0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>5.7 (4.6; 6.8)</td>
<td>0.29***</td>
<td>-0.03</td>
<td>5.6 (4.9; 6.8)</td>
<td>0.16</td>
<td>-0.27**</td>
</tr>
</tbody>
</table>

Ery-folate, erythrocyte folate; P-folate, plasma folate; Swedish-trad, Swedish-traditional

*P<0.05, **P<0.01, ***P<0.001

a Partial correlations adjusted for age, energy intake and supplements (nutrient specific supplemental or multivitamin use). Vitamin D was also adjusted for sampling season.

b Values > 90 nmol/L were excluded

c Individuals with CRP >5 mg/L were excluded

d Percentage of alpha-linolenic acid, docosahexaenoic acid and eicosapentaenoic acid
Discussion

In Nutrition Epidemiology we study aspects of diet and its influence on health and disease. With epidemiological methods and tools we analyze data in samples of the target population with the objective to be able to make inference of diet-disease associations in the population. Necessarily, we also aim to make inference of the causality i.e. that the dietary factor is not simply associated with, but may cause the disease.

Interpreting results in epidemiological studies are generally done based on evaluation of causality criteria’s for a true causal association between diet and outcome of interest. In brief to make an evaluation of causality the internal validity, hence the absence of systematic bias; selection bias, information bias; generally misclassification, and confounding needs to be addressed. Moreover the precision of the estimation, the extent of random error, is evaluated. This tells us with what certainty we can draw conclusions from the results.

In addition “one study is no study”; we also have to put our results in relation to previous studies and the current knowledge in the research field.

Interpretation and considerations

Dietary patterns and prostate cancer (Study I)

In ULSAM a relatively low-carbohydrate high-protein dietary pattern, but not a Mediterranean-like diet was inversely associated with prostate cancer incidence when excluding misreporters of energy intake.

Dietary patterns and prostate cancer in previous studies

The association between a LCHP diet and prostate cancer is scarcely investigated. However, in a study from the north of Sweden no association between a LCHP diet and prostate cancer was found (41). Similarly, two studies investigating the association between a LCHP diet and prostate cancer death also reported null-findings (39, 42). The reason for our contrasting results can only be speculated on.

The LCHP diet inferred a diet relatively low in carbohydrates and sucrose (Table 3) (details on dietary intakes are published in Paper I). The role of carbohydrate intake in prostate cancer development is inconclusive. Refined
carbohydrates have been suggested to increase disease risk (92-94). Still, others report that glycemic index and glycemic load do not seem to be strong predictors for prostate cancer incidence (95, 96). An explanatory factor suggested for the inverse association between refined grains, low glycemic index or load diets and prostate cancer is the carbohydrate regulation of insulin metabolism (97, 98).

High adherence to the LCHP diet was also associated with higher intake of meat and meat-products. High meat intake has been postulated to increase prostate cancer risk (99), but a review and meta-analysis from 2010 do not support any association (100). Moreover, in a recent Swedish study an inverse association between a high meat intake and prostate cancer risk was indicated (36). Our explanatory analyses indicated a role of selenium in the inverse association between the LCHP diet and prostate cancer. In Sweden the main dietary sources for selenium are foods of animal origin; meat, fish and eggs (101). These foods were consumed to a greater extent by men with high LCHP adherence in our study. The role of selenium and especially selenium intake in the etiology of prostate cancer remains inconclusive. Most definitely factors such as baseline selenium status, levels of intake and variation in intake and status are important aspects, which complicate the interpretation of existing studies. In the updated WCRF report evidence for an increased risk of prostate cancer with low plasma selenium concentrations is categorized as limited-suggestive (33).

A few studies have used a posteriori methods to derive dietary patterns. Jackson et al. found a refined carbohydrate dietary pattern to be associated with increased risk of prostate cancer in Jamaican men (44). Walker et al. found that a dietary pattern high in both refined grains and meat products were directly associated to prostate cancer in Canadian men (45). Similarly a Western dietary pattern was directly associated to prostate cancer in Australian men (43). All three studies were case-control studies. Two prospective studies, on the other hand, did not find any association between empirically derived dietary pattern and prostate cancer (47, 49). Direct comparisons with our results are hampered primarily by the differences in dietary pattern methodology.

Our results imply that the Mediterranean-like dietary pattern do not have the same impact on prostate cancer risk as on e.g. CVD risk, the latter which has been rather well documented (2, 6, 12, 13). A suggestive protective effect of the Mediterranean diet on cancer in general has been reported (5, 6, 102). Mediterranean dietary factors have been postulated to be prostate cancer protective (34, 35). However, this has so far not been confirmed. On the contrary, our results are in line with previous studies which also failed to show any protective effect of Mediterranean dietary patterns on prostate cancer risk (36-38).
Study specific considerations

Prostate cancer is a disease of age and it has been postulated that all men who live long enough will be diagnosed with the disease. For health conditions that increase strongly with age changes related to the nature of the surviving cohort and competing risks might impact on the relative risks of the disease (103).

In our setting, death from any other cause then prostate cancer was considered a competing event, preventing a prostate cancer diagnosis. Since the LCHP diet score has been directly related to mortality in the same cohort (and the mMDS inversely so) we postulated that differential competing risk could bias our results. Differential competing risk could lead to that prostate cancer to a larger extent was underdiagnosed in individuals with high LCHP adherence. This would then give the impression of a protective effect of a LCHP dietary pattern. We consider this potential bias in several ways, but our results still show a consistent inverse association between the LCHP diet and prostate cancer in acceptable reporters.

Changing food habits might distort associations between baseline diet and disease in longitudinal studies. Although elderly might be less prone to the changing food matrix of the society, we cannot rule out the possibility that participants deliberately or unconsciously made dietary changes e.g. due to health concerns.

Misclassification in dietary pattern adherence may relate to methodological aspects of e.g. constructing a dietary index which is discussed in detail below (6.2.3). However, the chain is never stronger than its weakest link, and measuring dietary intakes is unquestionably a challenging task. Self-reported dietary intakes are regardless of method of assessment subject to information bias, which may lead to misclassification. In aim to reduce misclassification of participant’s dietary patterns in ULSAM we identified and excluded low and high energy reporters. Pros and cons of this approach are discussed in detail in the end of this section (6.2.3).

We cannot exclude that factors which we were not able to take into account or appropriately adjust for have biased our results. We were for example not able to consider genetic predisposition for prostate cancer. Noteworthy though, hereditary prostate cancer occurs earlier in life and the old age of the participants and exclusion of men with previously diagnosed prostate cancer probably limited such bias.

The impact of diet on prostate cancer might differ in different stages of the disease and by disease grade and prognosis. Although, our results did not implicate an interaction between dietary pattern and disease grade, stratified analyses in our study were likely limited by few incident cases.
It might be that due to the long latency period of prostate cancer, the critical window for diet to impact disease risk occurs earlier in life. Hence, focusing on diet at 70-years of age might be of little relevance and we might need to measure diet in younger years.

The diet of high LCHP adherent individuals in ULSAM was not extreme but only moderately low in carbohydrates (43E%) and moderately high in protein (17E%), similar to what has been reported in other population based studies (26, 40, 41). Hence, our results cannot be extrapolated to more extreme versions of low-carbohydrate diets.

Strengths of this study relate to its population based, age standardized set-up with complete follow-up and, in acceptable reporters confirmed relevant non-Prostate Specific Antigen (PSA) detected prostate cancer cases. Since the ULSAM men most likely were too old to have been subject to PSA testing the risk of diagnostic bias is limited. Adherence to the mMDS was associated with higher education and higher educated individuals might be more prone to visit the doctor. Noteworthy though, this would above all lead to identification of low grade diseases and our results showed no indication of such a scenario.

The small study population and hence, limited number of cases was partly compensated for by a relatively long follow-up centered on the period in life where most prostate cancer cases are recorded.

Dietary patterns and environmental contaminants (Study II)

In this study of elderly Swedish men and women dietary patterns were cross-sectionally associated with circulating levels of environmental contaminants. Adhering to a Mediterranean-like diet or a diet relatively low in carbohydrates and high in protein might contribute to higher background exposure especially of POPs and heavy metals. The official dietary recommendations were positively associated with a few contaminants however; this pattern was also negatively associated with levels of dioxin and lead.

Environmental contaminants and diet in previous studies

The content of environmental contaminants in foods, depend on the foods characteristic, their hierarchy in the food chain, the origin of the product, breeding-, cultivation- or production process and packaging etc. POPs are fat-soluble and resistant to degradation; hence these substances accumulate in our environment, in fat tissue and through the food chain.

Our main exposure route for many of these compounds is therefore through intake of foods of animal origin. High protein and high fat foods;
fish, dairy products, meat and meat products has been shown to contain the highest levels of these compounds \(^{(104)}\). The associations between the LCHP diet and pesticide remnants and PCBs are therefore not surprising. Nor are the associations between the mMDS, PCBs, TNC and mercury. Consumption of fish in Sweden is complicated by high levels of POPs in fish from the Baltic Sea and mercury in fish from inland lakes \(^{(104-106)}\). Interestingly, the mHDI, which also promotes fish intake but in combination with other dietary characteristics, e.g. limed fat intake, was merely directly associated with one PCB \(^{(118)}\) and TNC, and associations with mercury were non-significant.

In addition, the mHDI was the only dietary pattern of which adherence was inversely associated to levels of specific environmental contaminants. Levels of OCDD and lead were lower for increasing adherence to this pattern. Fish intake is thought to be our main exposure route to dioxins. Hence, consumption of less contaminated, lean or farmed fish, or considerably lower consumption of other foods normally contributing to dioxin exposure might be the explanation. This finding supports the role of dietary pattern analysis in the evaluation of dietary exposure to environmental contaminants. Although correlations between the mMDS and mHDI were quite strong \((r=0.62)\), the patterns seemingly capture overall dietary habits that differ in content of environmental contaminants. The mMDS had stronger positive correlations to fish and alcohol than the mHDI, which instead had stronger positive correlation to carbohydrates and stronger negative correlations to fat intake as shown in Table 3 (details are published in Paper II).

The LCHP diet score and the mHDI were associated with lead exposure in opposite directions. Positive relations to lead exposure could be related to high intake of meat and dairy products or alcohol consumption, in line with the results for the LCHP diet (Table 3) \(^{(104, 106)}\). However, also fruit and vegetables have shown to contain lead \(^{(104)}\).

When including a separate variable for fat intake in the LCHP score associations with environmental contaminants were attenuated. This might reflect the attenuated correlation between this dietary pattern and intake of animal products primarily high in protein and high in the food chain.

There were no significant associations between dietary patterns and phthalate and BPA exposure. However, a tendency for an association between the mMDS and MEHP, a metabolite of di-2-ethyl hexyl phthalate (DEHP) was found. DEHP is one of the main phthalates found in foods, but it is not clear which foods that are the main contributors to human exposure \(^{(53)}\).

There are a few studies which have investigated the association between data derived dietary patterns and circulating levels of environmental contaminants \(^{(60, 61)}\). Kvalem et al. found a northern coastal dietary pattern character-
ized by high intake of fish liver and seagull eggs to be closely associated with high blood concentrations of dioxins and PCBs (61). In Japanese individuals Meat-, Seafood- and Dairy- dietary patterns were all independently and positively linked to blood levels of PCBs and dioxins (60). Finally, a recent study used reduced rank regression to identify a dioxin-diet, characterized by high consumption of red and white meat, lean and fatty fish, low-fat dairy and low consumption of salty snacks and high-fat cheese in pregnant Greek women (62). One study previously assessed a predefined Mediterranean index and environmental contaminant exposure found no association between a dietary pattern of Spanish mothers-to-be and OC pesticides in umbilical cord blood of their newborns (63).

**Study specific considerations**
Importantly, lack of associations between the dietary patterns and specific environmental contaminants do not imply that we are not exposed to these substances. However, the variation in exposure is not associated to the dietary patterns assessed. For example phthalate contamination of foods originates mainly from food packaging and might therefore be wide-ranging and not necessarily isolated to the intake of specific foods or dietary patterns. Although predefined, the dietary patterns assessed were not developed to capture the exposure to environmental contaminants, but chosen based on their proposed health implications.

However, null-findings might also indicate methodological shortcomings. Blood samples were taken before and not adjacently after the completion of the food records, hence blood levels do not reflect the period reported in the food record. Although dietary data are believed to represent dietary habits, for e.g. phthalates that have short half-life and presumably are less related to specific foods, associations to habitual dietary intakes might be more challenging to capture (compared to persistent contaminants). Repeated blood sampling could have improved the ranking of individuals, above all, on habitual phthalate and BPA exposure.

Contamination of blood samples during quantification of the environmental contaminants cannot be fully excluded. However, there is no reason to believe that this should be anything else than random and most likely attenuate associations.

The results in sensitivity analyses, performed only in acceptable reporters, did not deviate substantially from in the full study population. This may indicate that misreporting was sufficiently handled by the energy adjustment of dietary intakes. It might also be that misreporting of energy intake is not associated with dietary characteristics affecting the exposure to environmental contaminants.

Measurements of circulating levels of environmental contaminants also include exposures from other sources than the diet. It might be that other
sources of exposure, which we were not able to correctly adjust for in our analyses, have influenced the observed relations.

This study had a relatively low participation rate (50.1%). However, the representativeness of the cohort has previously been assessed by comparing cardiovascular disorders and medications between participants and 100 non-attendees. The results indicate that PIVUS is a fairly representative sample of the total population regarding most cardiovascular disorders and medication \(^{107}\). Still, generalizing our results to other populations might be unjustified due to the local impact on concentrations of contaminants in different foods. Moreover, the extrapolation of our results to other generations are also limited, since circulating levels of many substances reflects lifetime exposure, and there are time trends in the use of these contaminants.

Strengths of this study include its population based and age standardized set up, limiting selection bias and birth cohort effects and increasing the validity of our results. Multivariate linear regression analyses with global tests for overall significant associations limits the risk of chance findings due to multiple testing and allow for inclusion of relevant covariates.

This is a cross-sectional study with no time interval to confirm cause-and-effect relationships. However, reverse causality—that exposure levels would induce dietary habits is unlikely.

Above all this study is unique since including the dual complexity of dietary habits and circulating levels of multiple environmental contaminants.

**Dietary patterns, nutrition, inflammation and anthropometry**  
**(Study III and IV)**

We identified two dietary patterns common to both men and women in Riksmaten adults 2010-11; a Healthy pattern and a Swedish traditional pattern. In addition a third Light-meal pattern was derived in women. Derived dietary patterns were associated with nutrient intakes and (to a lesser extent) nutritional biomarkers in expected directions. Dietary patterns were also related to multiple lifestyle characteristics and the Healthy pattern was inversely associated to concurrent anthropometric measurements.

**PCA derived dietary patterns in previous studies**

The two major dietary patterns derived in our study resemble patterns derived in other populations. These patterns are often referred to as “Prudent” or “Healthy” and “Western” or sometimes “Traditional” dietary patterns.

Although, diversities in loadings for specific foods exist, as can be expected due to culture and country specific dietary habits and methodological differences, the interpretations of the patterns are similar. The Healthy or
Prudent pattern usually load on fruit and vegetables, fish, wholegrain products or fiber rich bread, low-fat dairy and sometimes nuts and seeds and vegetable oils. The Western or Traditional pattern most commonly load on meat and processed meat, refined cereals, sweet bakery products and high-fat dairy. However, there are some important differences between our Swedish-traditional pattern and the more frequently described Western dietary patterns. Our pattern loaded negatively on fast food and it did not load on soda, butter or snacks, contrary to what is typical seen as strong positive loadings for the Western dietary patterns.

The Swedish-traditional and Healthy patterns in this study are comparable to the Traditional- and Health-conscious pattern, previously derived in a Canadian population (108) and also recently in the Danish national survey on diet and physical activity (109). However, the third pattern identified in Riks-maten was not comparable to the additional patterns identified in these populations; in the Canadian study a High-energy density pattern (loading on salty snacks, sauces, salad dressings, soda, other bread and high-fat dairy) (108), and in the Danish study a Fast-food pattern (loading on pizza, hamburgers, crisps, sugar-sweetened beverages and sweets) (109). A more extensive comparison with previously published PCA-derived dietary patterns can be found in Manuscript III.

Associations between data derived dietary patterns and lifestyle and demographic factors is frequently reported (8). A healthy pattern is, similar to in our study, often associated with higher education and income, and with healthy habits such as exercising and not smoking (8). The Traditional pattern in the Canadian and the Danish studies were positively associated with male gender and age, and the Health-conscious with female gender, age and education (108, 109). In the Swedish Mammography cohort dietary patterns were associated with age, energy intake, BMI and education (110). Moreover in the EPIC-Potsdam population, derived dietary patterns were associated to BMI, education, smoking and physical activity and vitamin and mineral supplement use (111), to give some examples.

Overall, results on dietary pattern and overweight and obesity have been inconclusive, partly due to difficulties in synthesizing results owing to methodological differences (18, 19). The results in our follow-on study, investigating cross-sectional associations between dietary patterns and anthropometric measurements, are however in line with other studies, supporting an inverse association between a Healthy or similar Prudent dietary pattern and concurrent BMI (109, 112), and weight gain over time (113-115). In the Danish national sample the Health-conscious pattern was cross-sectionally inversely associated with BMI in men (109). The Traditional pattern was not associated with BMI class, but male overweight participants had significantly higher traditional pattern score than did normal weight men (109). Corresponding patterns
in the Canadian population was not associated with BMI \(^{(108)}\). Western dietary patterns has been directly associated with BMI and weight gain in some \(^{(112,113,116)}\), but not in all studies \(^{(117)}\).

We did not find any association between dietary patterns and CRP-levels. Western dietary patterns have been directly associated with low-grade inflammation and opposite, Prudent or Healthy patterns have indicated inverse associations, though exclusively in observational cross-sectional data \(^{(68)}\).

Correlations between dietary patterns and nutrient intakes were in expected directions. In the national Danish sample the Health-conscious dietary pattern and the traditional pattern showed similar correlations to macronutrients as in our study \(^{(109)}\). An additional feature of the Danish study was the correlation between derived patterns and an index based on the food based dietary guidelines. As expected, the Health-conscious pattern showed positive, and the Traditional pattern negative correlations with the index \(^{(109)}\). Beaudry et al. reported a Health-conscious dietary pattern, similar to our Healthy pattern, to be positively correlated to indicators of nutrition quality \(^{(108)}\). The traditional dietary pattern in the same study was also favorable in relation to micronutrients contribution (contrary to the traditional pattern in our study) but did less well in relation to a score for macronutrient composition \(^{(108)}\). In the Swedish Mammography Cohort, a Healthy pattern showed good stability over time and was, similar to in our study, positively correlated to e.g. intakes of protein and dietary fiber, folic acid and also to Vitamin C, B\(_6\) and \(\beta\)-carotene \(^{(118)}\). The Western-Swedish pattern identified in the same study showed positive, although less stable, correlations to saturated fat and vitamin B\(_{12}\) \(^{(118)}\).

Documented association between dietary patterns and micronutrient biomarkers are few, however, when assessed results are in the expected directions \(^{(9,17,119)}\). In the Health professional follow up correlations to plasma folate were similar as in our study; positive to a prudent and negative to a western dietary pattern \(^{(67)}\). A review of the ability of dietary pattern methods to assess nutrient adequacy concluded that factor derived dietary patterns showed modest to good validity correlations for intake of to selected nutrients \(^{(74)}\).

**Study specific considerations**

Riksmaten adults 2010-11 is a cross-sectional study based on self-reported dietary and anthropometric data. This implies some limitations to our study. It might be that overweight and obese individuals change their diet in aim to control their body weight or avoid further weight gain. Hence, interpreting data on cross-sectional relations between diet and overweight is limited by the lack of a time interval between exposure and outcome measurements. Moreover relations between diet and measurements of overweight and obesity are easily confounded by information bias such as misreporting dietary
intake, anthropometric variables and other lifestyle factors\textsuperscript{(70)}, also in studies of dietary patterns\textsuperscript{(71, 72)}.

However, the interpretation of the dietary patterns derived in sensitivity analyses, including only acceptable reporters, was consistent with the patterns identified in the full study population. Moreover, associations between the Healthy dietary pattern and anthropometry were similar, only slightly stronger in sensitivity analyses. Validity in food records is discussed further below (6.2.3).

Validity in self-reported BW and anthropometric data might be questioned. Self-reported BW and BMI are seemingly under-estimated in most populations\textsuperscript{(120)}. However, a recent Swedish study confirms the usability of web-based self-reported BW in adults, with a correlation between self-reported and measured weight of $r=0.98$ ($p<0.001$)\textsuperscript{(121)}. Similar results have been reported for paper-based self-reported BW in earlier studies\textsuperscript{(122)}. Self-reported and self-assessed waist and hip circumference have also shown reasonable to good validity\textsuperscript{(123)}, especially when (as in our study) instructions for making the assessment is included\textsuperscript{(124)}. However, some degree of information bias is likely.

BMI is traditionally used as a marker for overweight and obesity and as a risk marker for disease in epidemiological studies. However, the increased risks for e.g. insulin resistance, dyslipidemia, type 2 diabetes, and CVD are more closely related to abdominal fat accumulation\textsuperscript{(125)}. Focusing on general obesity might therefore not be specific enough to capture individuals at risk\textsuperscript{(125)}. Hence, BW and BMI have limitations since not taking fat distribution into account. Measurements that include fat distribution; WC, WHR and WHHR, have shown to be superior predictors of CVD risk\textsuperscript{(73, 125)}.

In this study the Healthy dietary pattern was consistently inversely associated with all anthropometric variables. The consistency between the measurements is central; partly because they are all common markers for obesity and overweight and partly since they are based on different self-reported anthropometric measurements. The consistency between the results for different measurements of adiposity might imply acceptable validity of the measurements.

However, considering the associations between dietary patterns and other lifestyle factors, we cannot rule out the possibility that our results are confounded by such variables.

Although an association between dietary patterns similar to those described in our study, and chronic inflammation has been reported\textsuperscript{(68)}, we did not identify any association. Since CRP as well as nutritional biomarkers was measured only once and in a small subpopulation the impact of random error might limit the analyses. In addition blood samples were non-fasting, which might limit correlation analyses between nutritional biomarkers and dietary
patterns. However, when significant, correlations were overall in expected directions.

Data derived dietary patterns in national dietary surveys are scarce but valuable. Unfortunately the participation rate in the Riksmaten adults 2010-11 was low, only 36 percent for the dietary survey. Participation was especially low among young men and non-native Swedes. Participants had higher education than non-participants. However, percentage of overweight and obese (47 percent) are in line with the numbers for the Swedish population (49 percent 2010 and 2011) (126). Still, the dietary patterns derived in this study, and hence also the associations to anthropometry etc., might not be fully representative for the general Swedish population.

Strengths of this study include the detailed dietary data, the assessment of multiple anthropometric measures in parallel and analyses of nutritional biomarkers.

Methodological considerations

A priori methodology

Dietary indices have shown to be more strongly related to disease risk, than individual food factors (1). However, the usefulness of a priori defined patterns has been questioned due to unresolved methodological issues (9, 17). Some considerations related to the construction and the application of dietary indices in Study I and II are discussed below.

Variables, cutoffs and scoring

Dietary indices can take different forms and there are multiple indices for measuring adherence to the same dietary patterns (e.g. Mediterranean-diet scores or scores measuring the adherence to the official dietary recommendations). The components included in an index are generally determined by its aim, still somewhat arbitrary (127).

Cutoffs for scoring may also differ between studies. Most often if the aim is to measure adherence to dietary recommendations cutoffs derived from the recommendations are applied. However, if the aim is to assess associations with health outcomes population based cutoffs might be preferable in aim to distinguish well between the participants on the included variables. The latter is important to ensure a spread in the summary score and enabling assessment in relation to health outcomes.

The Mediterranean-diet score was developed to measure adherence to a Mediterranean-diet. However, due to the population based cutoffs in our score, and the minor modifications made to the original index, it would be
more correct to refer to this dietary pattern as a Mediterranean-like diet. A drawback of the population based cutoffs is that high adherence might not represent Mediterranean (healthy) levels of intake. Hence, the actual denotation of a Mediterranean diet in a Swedish population might be questionable (127). For example it might be that our Mediterranean-like diet was not “Mediterranean enough” to be prostate cancer protective. Although our results are in line with previous studies assessing the association between a Mediterranean diet and prostate cancer, these studies were all performed in non-Mediterranean populations (37, 38). Möller et al. made a nice work assessing several versions of Mediterranean dietary indices without detecting any associations (36). They also included a comparison between intakes related to a Mediterranean diet in a Swedish and a Greek population. Considerably lower intake of fruit and vegetables and higher intake of dairy product were seen in the Swedish population. Nonetheless, Möller et al. concluded that a Mediterranean diet score with study specific cutoffs was useful for assessing a Mediterranean-like diet in a non-Mediterranean population (36).

The HDI, based on the WHO dietary recommendations was modified to capture adherence to the official dietary recommendations in Sweden. The defined mHDI was, however, also population based to capture relative adherence to the recommendation, thus prioritizing the discriminating power of the index. Hence, the absolute adherence to the recommendations per se is not measured nor assessed in relation to environmental contaminant exposure.

Similarly, a relative adherence to a LCHP diet did in our study populations not equal an extreme low-carbohydrate high-protein diet. Hence, caution should be taken in the extrapolation of our results to more extreme versions of low-carbohydrate diets. The LCHP score is a crude overall measure of a dietary macronutrient composition which does not take food sources into account. Hence, on an individual level the high LCHP diet is likely to take many different appearances.

**Dietary pattern adherence as exposure variables**

Predefined dietary patterns were assessed as continuous variables to keep the maximum information in a continuous rank-variable and limit the risk of misclassification in arbitrary categories. However, in Study I dietary pattern adherence was also grouped as low-, medium- or high adherence to capture the extremes of the dietary pattern and relations to prostate cancer incidence. This also reflect risk relations more interpretable and comparable between patterns. The use of both approaches is relevant since manners of grouping dietary pattern adherence have been shown to influence results (128).

The dietary indices when assessed in parallel in a population are not mutually exclusive. Hence a high mMDS does not per se equal a low LCHP diet and above all adherence to the mHDI and the mMDS are likely to overlap. The latter was also indicated by the relatively high correlation between the
two scores in the PIVUS cohort (0.62). However, the indices do capture somewhat different dietary patterns, which also differed in relations to circulating levels of environmental contaminants (Study II).

**Explanatory analyses**

Potentially, dietary pattern analyses could mask (or dilute) specific association between a single dietary constituent and outcome, if an observed association is due to the intake of a single nutrient or food. In our explanatory analysis in Study I selenium intake seemed to be a mediator in the association between the LCHP diet and prostate cancer risk in acceptable reporters. However, it did not explain the extensive risk reduction seen among those with high adherence to the LCHP diet. Explanatory analyses of the impact of different features in a dietary pattern might be considered necessary for assessing the inference and relevance of dietary pattern analysis. However, such analyses are not unproblematic and often mean departing from the DP approach (127).

**A posteriori methodology**

There are several more or less arbitrary choices made in the process of deriving dietary patterns empirically. Subjectivity and other methodological considerations in the assessment of a posteriori derived patterns have been emphasized by several researchers (129-131). Some issues relevant for PCA and the patterns derived in Riksmaten adults 2010-11 are discussed below.

**Food groups, numbers and units**

Normally dietary data includes a range of items that first has to be merged into a reduced number of representative food groups. This process is not always described although grouping of the items might influence the derived patterns and their interpretation. We based our grouping on culinary use and nutrient content. For example we categorized milk-products in two separate groups (according to and not according to the Keyhole) to keep the different nutritional aspects of these foods and allow the dietary patterns to reflect specific food choices. The numbers of food groups included in the PCA also have implications for the patterns generated. As shown by McCann et al. when the number of food groups included in the PCA decrease the explained variance of derived patterns increase (132).

Inconsistency between different studies also refers to the unit of the food groups included. Often servings or as in our study, grams per day is used. Some researchers advocate energy adjusted intakes or energy contribution from each food group. However, eating behavior, food preferences and consumption is not based only on physiological energy demands. Schwerin et al. motivated that it is therefore more relevant to consider quality of foods consumed rather than its caloric content when studying eating patterns (65).
Moreover, energy contribution would give little or no impact to some widely consumed foods or beverages such as e.g. coffee, tea and diet-soda (and water if included). Smith et al. compared four different input variable quantifications and concluded that there were strong similarities between the patterns derived in presence and absence of energy adjustment (133). Hence, energy adjustment did not seem to add any benefit when deriving dietary patterns with PCA based on food diary data (133). Similar conclusions have been reported from PCAs based on food frequency questionnaire (FFQ) data (134, 135).

**Number of factors derived**

Number of factors derived is normally based on eigenvalues and scree plots but in the end to a large extent based on interpretation of the components. Eigenvalues gives an appreciation of how good the factor is at distinguishing the data. Eigenvalues > 1 signifies that the factor explains more of the variance in the correlations than is explained by a single variable (8). Usually a cutoff at eigenvalue above 1 or 1.25 is used. Normally 2-3 patterns are identified, although some researchers have derived 7-8 or up to 25 patterns (8). We used the scree plot for guidance, 1.25 as a limit for eigenvalues but derived patterns based on the interpretability of the factors.

**Explained variance**

The dietary patterns derived in the Riksmaten adults 2010-11 explained only a limited amount of the total variance in dietary intakes; 7.6, 6.0 and 5.4 percent respectively in women and 7.3 and 6.0 percent in men. This is relatively low, but similar to what has been reported in some other studies (108, 111, 115).

However, as noted above, decreasing number of food groups included in the PCA increases the variance explained if the same number of factors are derived (132). If the correlations are generally low, the explained variance will be low (65). It is possible that the large numbers of registered items in our food record when merged to fewer food groups will, due to the inevitable heterogeneous groups, give lower correlations between groups—and therefore lower explained variance of retained factors. However, explained variance is considered a poor criterion for determining how many factors to derive (65). McCann et al. also showed that increasing the variance explained by the derived patterns did not appear to improve estimates of risk associated with the patterns (132).

**Naming of the patterns**

Naming the derived patterns is usually done based on the food loadings on the derived factors. This can be done quantitatively based on foods with high loadings or qualitatively, including the nutritional value of the derived pattern. Patterns are sometimes denoted based on cultural or geographical food
habits, as our Traditional-dietary pattern. Some patterns are also named based on characteristics of individuals with high agreement to the factor (8). Although naming of the patterns is done to get a brief accessible description of the pattern and facilitate comparison between populations, this is rarely straightforward. Food patterns with different labels can be very similar and opposite despite similar naming loadings on specific food items do vary (28).

**Reproducibility and validity of data derived dietary patterns**

Inconsistency in methodology and incomplete description of how dietary pattern are derived limits comparisons between studies. Interpreting results in relation to specific health outcomes is therefore challenging. Cross country reproducibility have been questioned, and thereby the impact of the dietary pattern analysis as a method in nutrition epidemiology (129). However, dietary habits are to some extent country and culture specific and some differences in retrieved patterns can be expected. Nonetheless, as concluded by Hu et al. this does not necessarily refute the validity of dietary pattern analysis (131). Moreover, the extent to which similar patterns are identified in different populations despite differences in methodology might be an implication for reproducibility (8, 9).

Most studies that have applied PCA to identify dietary patterns have used FFQ for assessing dietary intake. Although food records are preferable in capturing day to day variation as compared to FFQ, long term day to day variation is less well covered. It might be that PCA based on food records from limited number of days are more influenced by foods eaten in direct combination i.e. within a meal. However, reproducibility, and validity of derived dietary patterns using FFQ and diet records has shown to be relatively good (119, 136, 137). Still, few studies have reported validation data on nutrient composition of data derived dietary patterns (74).

**Misreporting in food records**

Assessing dietary intake data is a delicate task. Reported dietary intakes will to some degree always deviate from the true usual intake. Misreporting due to difficulties recalling or reporting intakes correctly, changed eating behavior during observation or avoidance to report specific intakes, can be expected (138, 139).

The objective of identifying and excluding low and high energy reporters from analyses between dietary patterns and health was to increase validity in the exposure variable by limiting misclassification due to non-random misreporting in the food records. If misreporting was exclusively random it would presumably attenuate associations. However, misreporting, above all underreporting, has repeatedly been shown to be associated with e.g. higher BMI, “dieting”, dietary changes, lifestyle and socioeconomic factors (138, 140). This was also noted in our study populations (5.1). Those who underreport
energy also tend to report healthier food habits \(^{(76)}\), and underreporting has been associated to healthy food patterns derived in cluster analyses \(^{(71, 141)}\). Collectively, this can lead to attenuated, inflated or even reversed associations between diet and health in observational studies \(^{(69, 71, 72, 76, 77)}\).

Nonetheless, how to best take misreporting in dietary assessments into account, lack consensus. We evaluated misreporting using the Goldberg equation \(^{(78)}\), as described above \((4.3.2)\). However, the equation has embedded assumptions and uncertainties \(^{(78, 138)}\) which needs to be addressed.

Primarily, the PAL values we used were estimated values, based on questionnaires on physical activity habits \((\text{Appendix 1})\) hence some degree of misclassification is expected. However, if individuals are systematically categorized as being more physical active their energy needs will be overestimated and hence they will to a larger extent be categorized as low energy reporters. This could have contributed to the rather extensive underreporting in ULSAM. Although the physical activity questions have shown good validity for ranking individuals \(^{(142)}\), their assigned activity levels might still be systematically overestimated.

Another contributing factor to the extensive underreporting identified in ULSAM and PIVUS might be a possible systematic underestimation of portion size in the food record-book, as indicated in the evaluation study \(^{(75)}\). Another explanation suggested is the limited space for reporting snacking and intakes between meals \(^{(143)}\).

Furthermore, calculated BMR might not be sufficiently accurate to determine energy needs. However, in large studies, using measured BMR in the Goldberg equation provides no additional advantages \(^{(138)}\). The Goldberg equation also assumes weight stability –which might not be a correct assumption to make.

The Goldberg equation identifies low- and high energy reporters’, assuming that misreporting food intake is reflected in energy intake. This assumption might not hold true since some foods might be under- whilst other foods might be over reported and misreporting is likely cross levels of energy intake. Hence, residual misreporting in the population of acceptable energy reporters is likely. Likewise, some individuals with relatively accurate reported food intake are probably excluded using this approach. In addition the cutoffs forces categories of low-, acceptable- and high- energy reporting, although underreporting is continuously.

Although our objective when excluding misreporters was to improve the validity in the exposure variable and limiting systematic bias, stratifying on a proxy for quality in dietary reports might introduce selection bias. If certain assumptions of the context hold true, the exclusion of low and high energy reporters would imply stratifying on a collider –which might introduce bias \(^{(144)}\). However, in
general results in sensitivity analyses were in line with, however more pronounced than, in the full-study samples.

Concluding remarks
This doctoral thesis adds to the scarce data on dietary patterns and prostate cancer risk. It contributes with unique hypothesis-generating data of associations between dietary patterns and exposure to multiple environmental contaminants. In addition this thesis gives new valuable knowledge of current dietary patterns in the Swedish population, nutritional characteristics of those patterns and relations to nutritional biomarkers, anthropometric measurements and lifestyle factors.

Using data from the ULSAM population neither a diet relatively low in carbohydrates and high in protein nor a Mediterranean-like diet was associated with prostate cancer risk. However, the Low-carbohydrate high-protein dietary pattern was inversely associated with prostate cancer when taking validity in food records into account. This implies the need to consider the validity in dietary data in observational studies. How this is best to be done is a research area by itself, nonetheless alternative methods for taking underreporting into account are warranted. Since selection bias in subgroup analysis of acceptable energy reporters cannot be excluded, our results should be interpreted with caution until confirmed in other well-designed setups.

Diseases that increase with age are more prone to be influenced by competing risks. However, after thorough assessment it seems unlikely that our results would be due to such bias.

The null-finding between a Mediterranean-like dietary pattern and prostate cancer is in contrast to what has been proposed, but in line with other studies that also report lack of an association. However, all were performed in non-Mediterranean populations. To consider the effect of more extreme low carbohydrate high protein or high-fat dietary pattern on prostate cancer would be intriguing. Likewise the impact of a low carbohydrate high protein dietary pattern on prostate cancer taking carbohydrate quality and food sources of macronutrients into account is highly relevant, and such studies are desired.

In the PIVUS population of elderly Swedish men and women predefined dietary patterns were related to circulating levels of multiple environmental contaminants. A Mediterranean-like dietary pattern and a relatively low-carbohydrate high-protein diet implied higher levels of e.g. several PCBs, pesticides and heavy metals. Opposite, a dietary pattern measuring adherence to the official recommendations was associated with a lower burden of dioxin and lead exposure.
The results are intriguing for several reasons. Primarily it suggests a role for dietary pattern analysis in environmental health and the mapping of environmental contaminant exposure through our diet. Additionally, it adds to the complex puzzle of diet for health, since contrary to our results a Mediterranean-like dietary pattern has repeatedly been associated with favorable health effects. In speculation, the health benefits of a Mediterranean-like diet may counteract the potential detrimental effect of the environmental contaminants.

This is one of the first studies assessing predefined dietary patterns and association with circulating levels of environmental contaminants. To our knowledge, this is the first study to include multiple dietary indices and a range of different kinds of environmental contaminants in the same population. Hopefully our results can be hypothesis-generating and encourage future studies to take a holistic approach on diet and environmental contaminant exposure. In addition, studies assessing dietary patterns and environmental contaminant exposure in relation to major non-communicable diseases are desired.

We identified two main dietary patterns in Riksmaten adults 2010-11; a Healthy pattern and a Swedish traditional pattern. The Healthy pattern loaded on foods generally considered healthy e.g. fruit and vegetables, fish and vegetable oils. The favorable characteristics of this dietary pattern were well reflected in macronutrient composition and dietary intake of micronutrients, and fairly well in selected nutritional biomarkers. The Swedish-traditional pattern loading on meat, potatoes, sauces and sweet bakery products and desserts were less healthy in aspect of macronutrient composition and micronutrient intake. Relations to nutritional biomarkers differed somewhat between men and women, but were overall in expected directions. The identification of these two dietary patterns indicates that, in the Swedish population, intakes of foods generally considered to be healthy are correlated. Considering the characteristics of the Swedish-traditional dietary pattern, the identification of this pattern similarly indicates that the consumption of less favorable foods are also to some extent consumed by the same individuals. Supporting this notion the Healthy dietary pattern was also inversely associated with concurrent anthropometric measurements.

An additional Light-meal pattern was derived exclusively in women. High agreement with this pattern implied a high intake of above all total carbohydrates, added sugar and dietary fiber. This pattern was associated with lower micronutrient intakes but not significantly correlated to nutritional biomarkers.

These empirically identified dietary patterns were associated to multiple lifestyle characteristics. As previously has been shown a healthy diet is seemingly more accessible for parts of our community, related to education,
social environment or personal resources. This emphasize that relevant demographic and lifestyles factors should be accounted for in assessment of diet-disease relationships. Nonetheless, this knowledge could also serve as basis for subpopulation-specific dietary interventions and pinpointed efforts for implementing healthy dietary and lifestyle habits.

Reality is still complex. A dietary pattern with documented health benefits, protective for e.g. CVD might not be preferable in prostate cancer prevention, or for lowering exposure to environmental contaminants. The reproducibility of dietary patterns per se, whether a priori or a posterior defined, and relations to health aspects in different populations should be studied further. Moreover, risk benefits of dietary patterns for overall health must be considered, as well as other lifestyle factors, when interpreting results and establishing dietary recommendations. Since as indicated by the ancient Greek word *diaeta*, diet, implies "way of living".
Conclusions

Study I
In a population based cohort of elderly Swedish men we concluded that:
- A Mediterranean dietary pattern was not associated with prostate cancer risk
- A Low-carbohydrate high-protein dietary pattern was related to a decrease in prostate cancer risk in acceptable energy reporters

Study II
In a Swedish population of elderly men and women we found that:
- A Mediterranean-like diet was associated with higher levels of PCBs, the pesticide remnant TNC and mercury
- A relatively low-carbohydrate high-protein diet was associated with higher levels of PCB 118 and 153, pesticide remnants as well as lead and mercury
- Following the official dietary recommendations was associated with higher levels of PCB 118 and TNC, however also with lower levels of dioxin and lead.

Study III
In a nationwide sample of the Swedish population we identified
- A Healthy dietary pattern loading positively on foods generally associated with potential health benefits, reflected also in a favorable nutrient intake profile
- A Swedish-traditional dietary pattern loading on foods with potentially less favorable health effects reflected also in correlations to nutrient intake
- In women only; a Light-meal pattern with positive correlations to intake of carbohydrates but negative to most micronutrients
- The identified dietary patterns were associated to demographic and lifestyle factors implying the role of diet as a part of a lifestyle

Study IV
In a nationwide sample of the Swedish population we found that
- A Healthy dietary pattern was inversely associated with concurrent anthropometric data
• Neither a Swedish-traditional nor a Light-meal pattern was associated with anthropometric data.
• None of the three dietary patterns were associated to CRP-levels.
• The nutrient profiles of the dietary patterns and the appreciation of the dietary patterns as healthy or less favorable were fairly well reflected in nutritional biomarkers.
Svensk sammanfattning


Kostmönsteranalyser delas ofta in i två kategorier; "a priori" fördefinierade index och "a posteriori" datadrivna kostmönster identifierade med statistiska metoder i den aktuella studiepopulationen.


Syftet med denna avhandling var därför att ta sig an dessa frågeställningar och utvärdera kostmönster i relation till olika hälsoaspekter i den svenska befolkningen. I de två första studierna undersöktes hälsoaspekter av fördefinierade (a priori) kostmönster medan de två sista arbetena identifierar, karaktäriserar och analyserar hälsoutfall relaterade till datadrivna (a posteriori) kostmönster.

Prostatacancer är den vanligaste cancersjukdomen hos män i västvärlden. Även om en rad kost- och livsstilsfaktorer har studerats i relation till denna cancerform så vet vi fortfarande väldigt lite om kostens inverkan på sjukdomsrisken. Syftet i Studie I var därför att studera sambandet mellan två fördefinierade kostmönster och risken för prostatacancer. Studien baserades på data från ca 1100 70-åriga män som registrerat sin kost under sju dagar. Efter en uppföljning på i snitt 13 år visade våra resultat inget samband mellan en Medelhavslikkost eller en Lågkolhydrat-högprotein (LCHP) kost och prostatacancer risik. Däremot var en LCHP kost kopplad till minskad risk när vi exkluderer män som underrapporterat i kostregistreringen.

De få studier som tidigare studerat LCHP-kost i relation till prostatacancer har inte visat några samband, varken till prostatacancerdiagnos eller mortalitet. Forskare har föreslagit att en Medelhavskost skulle kunna minska risken för prostatacancer, men våra resultat är i linje med tidigare studier som inte heller visar på någon skyddande effekt.

Våra analyser antydde att ett högre selenintag hos män som följde en LCHP-kost kunde vara en bidragande orsak till den riskminskning som sågs.


även till kvicksilver. En LCHP-kost var direkt kopplad till POPar, framför-
allt pesticidmetaboliter, men även till kvicksilver och bly. Det tredje kostin-
dexet mätte följsamheten till de officiella kost- och näringsrekommendation-
erna, och att följa dessa var kopplat till högre nivåer av ett par POPar, men
också till lägre dioxinnivåer och lägre nivåer av bly.

Denna tvärnittsstudie är en av de första som studerar sambanden mellan
kostmönster och cirkulerande nivåer av miljögifter. Den är framförallt unik
för att den inkluderar flera kostindex och uppmätta nivåer av ett antal olika
miljögifter parallellt. Våra resultat ska framförallt ses som hypotesgener-
rande och sambanden mellan kostmönster och miljögiftsexponering bör stu-
deras vidare. Relationen mellan kostmönster och miljögiftsexponering bör
även studeras i andra populationer och i yngre generationer, då exponerings-
källorna delvis varierar mellan regioner och generationer. Det senare som ett
resultat av reglering och tidsbrott i dess användande.

Resultaten i Studie II är dock högst intressanta då de visar på viken av att
studera kosten som helhet baserat på kostmönsteranalyser. Resultaten visar
också på komplexiteten i sambanden mellan kost och hälsa, eftersom en
Medelhavslik kost, som återkommande visat positiva hälsoeffekter, här var
associerad till högre nivåer av miljögifter.

För att identifiera befintliga kostmönster i den Svenska befolkningen an-
vände vi i Studie III och IV data från den nationella kostundersökningen,
Riksmaten vuxna 2010-11. Data från ca 950 kvinnor och 850 män som fyllt i
en fyra-dagars webbaserad kostdagbok inkluderades. Med datareduktions-
teknik (principal komponent analys) identifierade vi två huvudsakliga kost-
mönster hos både män och kvinnor (Studie III); ett Hälsosamt kostmönstret
som karaktäriserades av livsmedel som generellt anses hälsosamma (frukt
och grönsaker, fisk, vegetabiliska oljor etc.) och ett Traditionellt kostmönstret
som karaktäriserades av livsmedel som normalt anses reflektera en tradition-
ell svensk kost (kött och potatis, säs, margarin och fikabröd). Ett tredje
Lätt-måltider-mönster, karaktäriserat av livsmedel som oftast förtärs som
lättare måltider (te, fullkornsbröd, ost), men också ersättningsprodukter för
kött och mjölk, samt godis och snacks, identifierades hos kvinnor.

Det Hälsosamma kostmönstret var kopplat till ett högre intag av bland
annat kostfiber, omega-3 fett, totalt intag av fleromättat fett samt flertalet
vitaminer och mineraler, och även till ett lågt intag av tillsatt socker. Det var
också positivt korrelerat till framförallt plasma-folat och biomarkörer för
omega-3 fett intag. Det Svensk-traditionella kostmönstret var kopplat till ett
högre intag av tillsatt socker och mättat fett och omvänt korrelerat till bio-
markörer för folat och omega-3. Lätt-måltider mönstret innebar ett högre
totalt intag av kolhydrater, framförallt tillsatt socker men också kostfiber.

Män och kvinnor med ett mer Hälsosamt kostmönster var överlag äldre,
mer fysiskt aktiva och icke-rökare. Hos kvinnor var detta kostmönster kopp-
lat till högre utbildning och högre inkomst. Det Svensk-traditionella kost-

I studie IV fann vi att det *Hälsosamma kostmönstret* var förknippat med fördelaktiga antropometriska variabler; mindre midjeomfång, lägre BMI (body mass index, kg/m²) och lägre midja-höft-kvot. Inget av de identifierade kostmönstren var kopplat till inflammations markören C-reaktivt protein.

Slutsatserna från Studie III och IV begränsas till viss del av dess tvärsnittliga karaktär samt att deltagandet i vissa subgrupper av den svenska befolkningen var lågt. Likväl har de kostmönster vi identifierade i Riksmaten vuxna 2010-11 många likheter med kostmönster som har identifierats i andra populationer; ofta benämnda Hälsosamma eller ”Förståndiga” (Prudent) respektive Traditionella eller vanligen ”Västerländskt” (Western). Vissa skillnader finns dock, framförallt karaktäriseras det västerländska kostmönstret ofta även av snabbmat, läsk och snacks vilket vårt Svensk-traditionella kostmönster inte gjorde. Våra resultat tyder dock på att intag av hälsosamma livsmedel till viss del samvarierar i den svenska befolkningen och att intag av mindre hälsosamma livsmedel också delvis tycks konsumeras av samma individer.
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Assessment of physical activity

Since the assessment of physical activity has not been described in detail in each paper, the information is given below.

**Physical activity in ULSAM**

Leisure-time physical activity was assessed in four questions in the medical questionnaire, each which could be answered yes or no:

1. Do you spend most of your time reading, watching TV, going to the cinema or doing other, mostly sedentary, activities?
2. Do you often go walking or cycling for pleasure?
3. Do you do any active sport or heavy gardening for at least 3 hours every week?
4. Do you regularly perform hard physical training or competitive sport?

The questions were used to categorize individuals as sedentary, moderately active, regularly active or athletic. The categorization was made as follows; if question 4 was answered affirmatory the individual was categorized as athletic, else if question 3 was answered affirmatory the individual was categorized as regularly active, else if question 2 was answered affirmatory then the individual was considered moderately active. If only question 1 was answered affirmatory then the individual was categorized as sedentary. Each level was allocated a group specific PAL; sedentary PAL 1.4, moderately active 1.5, regularly active 1.6 and athletic 1.7. This PAL value was used in the evaluation of reported energy intakes in relation to energy expenditure, as described below. For background characteristics and inclusion as a covariate in the statistical model physical activity was further merged into regular physical activity yes or no. Participants were considered to have a regular pattern of physical activity if categorized as regularly active or athletic in the questionnaire. These physical activity categories have been used before and validated against activity counts measured by an accelerometer showing good discriminating capacity (142).
Physical activity in PIVUS
Physical activity was assessed in two questions regarding time spent in moderate and vigorous activity each week:

1. How many times per week do you devote yourself to moderate exercise for at least 30 minutes (e.g. walking, cycling, playing golf, gardening etc.)?
2. How many times per week do you devote yourself to vigorous exercise for at least 30 minutes (e.g., running, swimming, playing tennis or football, etc.)?

Time spent at each activity level was summarized to hours and multiplied with an assigned metabolic equivalent (MET) value, 4 for moderate and 8 for vigorous physical activity. Remaining time was multiplied by a MET value of 1.5 (e.g. sitting, reading, eating etc.). MET values were derived with inspiration from Ainsworth et al. \(^{145}\). Total MET hours per week were summarized and divided by 7 days and then by 24 hours to provide an individual PAL. The approximated PAL ranged from 1.5 to 1.7.

Regular physical activity as defined in background statistics was defined as $\geq 3.5$ h per week hard or moderate physical activity.

Physical activity in Riksmaten
Physical activity was assessed in association with the web-based food record. One question considered leisure-time physical activity and one work-time physical activity:

1. Considering the last 12 months, how physically active have you been on your spare-time? If your activity varies a lot between e.g. summer and winter, try to give an average for the last 12 months.
   a. Sedentary spare-time (reading, watching TV. Walking, cycling etc. less than 2 h/week)
   b. Moderate activity (At least 2 h/week, but without sweating, e.g. cycling, walking, working in the garden, fishing, bowling of playing ping-pong)
   c. Moderate, regular activity (1-2 times a week, running, swimming, playing tennis or badminton or similar)
   d. Regular physical activity and work-out (At least 3 times/week and at least 30 minutes each session)

2. Considering the last 12 months, which of the following most closely match with how physically active you normally are during work-time. If you are not working (e.g. are on parental leave, unemployed, retired or similar) please state what best describes your everyday situation. If your activity varies a lot between e.g. summer and winter, try to give an average for the last 12 months.
   a. Predominantly sedentary work (e.g. paperwork, light assembly work)
b. Light but mobile work – I walk around but do not carry or perform heavy lifts (e.g. industrial workers, shop assistants, nurses, housework/domestic work without small children)

c. Moderately heavy work – I walk around, carrying and lifting heavy lifts (cycling mail carriers, industrial workers, janitors, nursing assistant, housework/domestic work with small children)

d. Heavy work – My work includes heavy lifts and heavy work (heavy agricultural supplies or forestry work, fishing with heavy equipment, heavy construction work)

The physical activity levels defining the answers have previously been allocated PAL values and successfully validated against double labeled water (146). The mean PAL in the Riksmaten population was 1.67.

Leisure-time physical activity was merged into sedentary (if a or b) and regular (if c or d) and work-time physical activity was coded as sedentary (if a or b) and moderate (if c or d), for background statistics.
References


50. Darnerud PO, Atuma S, Aune M, Bjerselius R, Glynn A, Grawe KP, et al. Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on


101. Agency NF. Riksmaten 2010-11, Livsmedels- och näringsintag bland vuxna i Sverige (Riksmaten 2010-11, Intake of Foods and Nutrients


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)