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# Food, Fatty Acids and Antioxidants Intake
# and their Associations with Atopic disease in Adults

Dissertation

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# INDEX OF CONTENTS

**Abbreviations List**

AA: Arachidonic acid

ALNA: Linolenic acid

aOR: Adjusted odds ratio

BHR: Bronchial hyperresponsiveness

BMI: Body Mass Index

BLS: Bundeslebensmittelschlüssel

CI: Confidence intervals

COX: Cyclooxigenase

CSF: Colony stimulating factor

DHA: Docosahexanoic acid

DHAA: Dehydroascorbic acid

ECRHS: European Community Respiratory Health Survey

EPA: Eicosapentaenoic acid

FA: Fatty acids

FFA: Free fatty acids

FFQ: Food Frequency Questionnaire

GLA: γ-linolenic acid

IF: Interferon

Ig: Immunoglobulin

IL: Interleukin

Kcal: Kilocalories

LA: Linoleic acid

LDL: Low density lipoprotein

LOX: Lipoxygenase

LT: Leukotrien

MIF: Migration inhibitory factor

MONICA: MONItoring of Trends and Determinants in CArdiovascular

DiseasesMUFA: Monounsaturated fatty acids

NK: Natural killer cells

NFκB: Nuclear factor kappa

NO: Nitric oxide

OR: Odds ratio

PAF: Platelet Activating Factor

P/S ratio: Polyunsaturated FA to saturated FA ratio.

PG: Prostaglandin

PL: Phospholipase

PUFA: Polyunsaturated fatty acids

ROS: Reactive oxygen species

SFA: Saturated fatty acids

TGF: Transforming growth factor

TNF: Tumoral necrosis factor

TX: Thromboxan

# 1 Introduction

## 1.1 Epidemiological Background

The prevalence of atopic diseases continues to rise in industrialised countries. In the search for possible causes, attention has been focused on factors related to Western lifestyle, including dietary habits. [1-2]

It was suggested that the observed increase in the consumption of polyunsaturated fatty acids (PUFA) during the 20th century, due to the wider use of fat from vegetable origin, might have contributed to the observed increase in allergy prevalence.[2-3] The supply of omega-6 fatty acids such as linoleic acid may increase arachidonic acid intake, which enhances the formation of pro-inflammatory cytokines and of immunoglobulin E (IgE).[2-4-5-6] Available epidemiological evidence is often gender specific;[7-8-9] whether these gender differences might be related to known sex-specific dietary habits or not is highly speculative. Margarine may contain several-fold higher amounts of n-6 fatty acids than butter.[9] Thus, in a study conducted in adult women, dietary intake of n-6 fatty acids was positively associated with hay fever.[9] A European ecological study found no associations between polyunsaturated fatty acids consumption and sensitisation, but supported the hypothesis that a high intake of monounsaturated fatty acids (MUFA) may lead to the development of atopic disease.[10] Epidemiological studies conducted in children revealed an inverse association between high fish consumption, which provides long chain omega-3 fatty acids, and the prevalence of asthma and bronchial hyperresponsiveness, thus inferring that a decreased omega-6 to omega-3 ratio attenuates the inflammatory immune reaction.[8-11]

A number of studies have reported an association between dietary antioxidants, asthma and atopy.[12] The National Health and Nutrition Examination Study (NHANES) demonstrated negative associations between the prevalence of wheeze and serum levels of vitamin C, niacin, zinc and copper. [13-14]

Investigators pinpointed marked changes in the United Kingdom population's diet occurring since the 1960's, with a negative trend in fresh food consumption, particularly the consumption of fresh green vegetables. Based on that fact, it was hypothesized that the recent increase in asthma and atopy might be associated with the declining dietary

intake of fresh fruit and vegetables, being the consequently low antioxidants intake the plausible biological explanation.[15] Further evidence available from a European ecological study revealed a protective effect of high fruit consumption on allergic sensitisation prevalence.[10] Additionally, current results from a cross-sectional study confirmed that the intake of some vegetables may decrease the prevalence of adult asthma.[16] Among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms at young ages and higher lung function in children and adults.[17-18]

In addition, the Nurses' Health Study demonstrated a negative association between asthma and food containing vitamin E.[19] Also, a recent study showed a negative association between serum IgE levels as well as allergen skin prick test sensitisation and the intake of foods rich on vitamin E.[20]

Moreover, evidence from a nested case control study confirmed a significantly higher risk of bronchial hyper reactivity among those with the lowest intake of vitamin E and vitamin C, carbohydrate and fiber, while the lowest intake of saturated fats gave a ten-times higher protection. The same study group linked an increased risk of adult onset asthma with a low intake of vitamin E and vitamin C. These results were supported by direct measurements of plasma vitamins and triglycerides.[21-22] In addition, low β-carotene intakes have also been associated with allergic rhinitis.[23]

Ongoing research is focusing on the possibility that maternal antioxidants and lipid intake influences fetal immunity, and therefore the likelihood of childhood asthma and atopic disease.[24] Evidence from a recent clinical study in neonates indicates that altered membrane PUFA profiles during gestation may influence immunological function.[25] Higher maternal intake of foods containing vitamin E and zinc during pregnancy has been associated with decreased risk of developing childhood wheeze, asthma and atopic eczema.[26]

Although intake of fat, vegetable, and fruit as well as other related nutrients were associated with prevalence rates of allergic sensitisation, hay fever, and asthma in a few studies, the findings were not consistent in relation to specific nutrients.

## 1.2 Study Objectives

The amount and type of dietary fat and antioxidants consumed may be related to the prevalence of atopic disease. This is a cross sectional study using data collected in the city of Erfurt on German adults, aiming to explore whether:

1. The consumption of selected food, specifically fat, fruit and vegetable intake is related to the prevalence of atopic disease.
2. The intake of specific fatty acids shows any association with the prevalence of asthma, bronchial hyperresponsiveness, allergic sensitisation, hay fever and/or atopic eczema.
3. The amount of ingested antioxidants could be linked to atopic disease prevalence.
4. Any gender related differences between dietary intake and atopic disease prevalence are evidenced in the analysed population.

## 1.3 Mechanisms of Allergic Disease

Normally the immune system clears antigens without any adverse reactions. Three types of cells are involved in this response to antigens: B-lymphocytes, T-lymphocytes and macrophages. The lymphocytes arise from the bone marrow and are the basis for the functioning of two branches of the immune system: the humoral pathway and the cell-mediated pathway.

The humoral pathway involves antibodies (Ig). Antigen-specific antibodies are produced by the B-lymphocytes (B-cells) in response to the external antigen presented. The union of an antigen and an antibody causes the production of chemical mediators and/or direct cellular damage that triggers clinical manifestations.

Five antibody classes have been identified: IgG, IgM, and IgD antibodies protect the organism against bacteria and viruses. Secretory IgA antibodies in breast milk provide

local intestinal protection for infants against viruses and bacteria (Laurence, 1985) IgA are also present in saliva and intestinal secretions, blocking the antigen's absorption.

Allergic reactions are usually classified into four types: Types I, II and III, which are antibody dependent, and type IV that is T-cell dependent.

Type I allergic reaction involving IgE is the most common allergic reaction and has the most clearly understood immune mechanism.[27-28-29]

## 1.4 Pathogenesis of IgE-Mediated Allergic Response

The IgE antibodies play just a part in the allergic process; several other immune response pathways are involved. For example, asthma and allergic rhinitis among other allergic diseases may involve more than one immunological mechanism.

The IgE-mediated allergic response has been described in three major steps:

- Step 1. Sensitisation
- Step 2. Early Phase Reaction
- Step 3. Late Phase Reaction

### 1.4.1 Step 1. Sensitisation

The initial exposure to the allergen leads to IgE production. The antigen-presenting cells recognize and process the antigen into antigenic peptides. The peptides portions are exposed to the T-lymphocytes, thus stimulating the secretion of cytokines. The direct interaction between the T-lymphocyte and the B-lymphocyte activates the antigen-specific IgE production by the B-lymphocyte. Once released, the IgE will be bounded by high affinity $Fc\varepsilon$ receptors ($Fc\varepsilon R$) on mast cells and/or basophiles.[27-28]

### 1.4.2 Step 2. Early Phase Reaction (Immediate Hypersensitivity)

A later exposure to the same allergen causes reactivation of the sensitized IgE fixed to tissue mast cells or circulating basophiles, which in turn causes degranulation leading to the release of preformed mediators, such as histamine, tryptase and heparin, along with new synthesized cytokines, interleukines, and leukotrienes. (Figure 1)

Once released, these mediators, particularly histamine, cause a series of symptoms, such as:

- Smooth muscle constriction
- Vasodilatation
- Mucus secretion, and
- Sensory nerve stimulation.

## Immediate Hypersensitivity Reaction



1. Production of IgE by B cell in response to T cell cytokine secretion
2. Binding of IgE to FcεR on mast cells or basophils

B cell

IgE

FcεRI

Mast cell

1. Re-introduction of antigen
2. Cross-linking of bound IgE

1. Mast cell activation
2. Release of mediators

Mediators:
Histamine
Leukotrienes
Cytokines
Chemotactic functions
Enzymes

**Responses of target organs**

| Bronchi | Intestines | Blood vessels |
|---|---|---|
| Constriction | Hypermotility | Vascular leakage (tissue edema) |

**Figure 1. Immediate Hypersensitivity Reaction**

## 1.4.3 Step 3. Late Phase Reaction

The late phase reaction occurs in a variable time frame, from hours to days after the exposure to the allergen. It is characterized by the influx of inflammatory cells. (Figure 2)

The allergen also stimulates the activation of inflammatory cells (e.g., mast cells, T-cells) leading to the production of pro-inflammatory mediators (e.g., leukotrienes, cytokines). These mediators exert their action at the post-capillary endothelial cells, promoting:

- Outflow of plasma leading to localized edema;
- Adhesion of circulating leukocytes; and
- Infiltration of tissues by eosinophils, neutrophils, and basophiles.

Over the course of several hours, further inflammatory reactions will follow. The eosinophils produce mediators that cause tissue damage associated with chronic allergic reactions, e.g.: major basic protein, eosinophil cathionic protein, leukotrienes. Simultaneously TH2 lymphocytes release cytokines thus promoting IgE formation, increase of mucosal mast cells and the chemo attraction of eosinophils.[27-28]
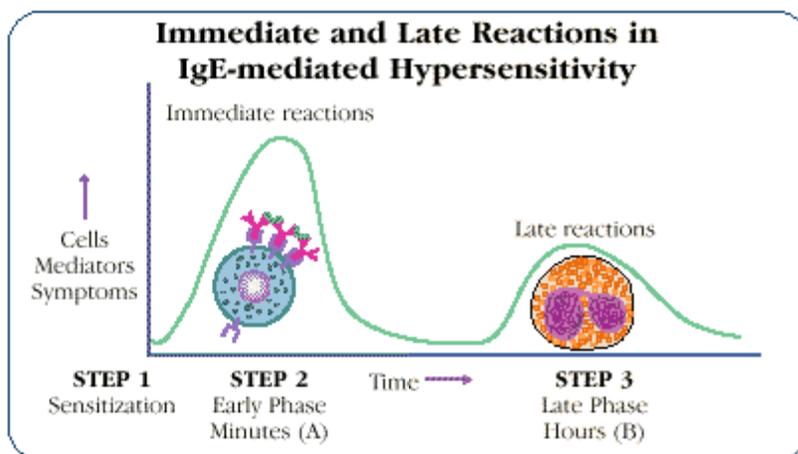


(A) Immediate hypersensitivity reactions occur within minutes of exposure to allergen in sensitized individuals. With repeat exposure to allergen, multiple IgE- FcεR-complexes are cross-linked, resulting in immediate hypersensitivity reactions (i.e., mast cells degranulate releasing histamine, leukotrienes, cytokines, and proteases).

(B) Late reactions begin 2 to 4 hours after allergen exposure and can last for 24 hours before subsiding. Inflammatory leukocytes (e.g. neutrophils, basophils, eosinophils) are involved but the late response is primarily mediated by eosinophils in atopic individuals. These inflammatory cells release cytokines and chemokines during the response.

**Figure 2. Immediate and Late Reactions in IgE-Mediated Hypersensitivity**

## 1.5 Biochemistry, Metabolism and Dietary Sources of PUFA

The classification of the PUFA into n-3 and n-6 depends on the position of the last double bond close to their methyl end. PUFA are considered essentials based on the inability of mammals to neither synthesize nor convert n-3 and n-6 PUFA and also because they are required for cell membrane integrity and a wide variety of cellular functions. Dietary PUFA are subjected to elongation and desaturation.[29-30]

The most common dietary fatty acids are linoleic acid (LA; 18:2 n-6), γ-linolenic acid (GLA; 18:3 n-6) and arachidonic acid (AA; 20:4 n-6). On the other hand, common dietary n-3 PUFAS comprise α-linolenic acid (ALNA; 18:3n-3) as well as eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexanoic acid (DHA; 22:6 n-3).[29-30-31]

The most abundant PUFA delivered by vegetable oil consumption is LA (18:2n-6) which is metabolized to AA (20:4n-6) via GLA and dihomo- γ-linolenic acid (DGLA; 20:3n-6). AA is the precursor of prostanoids and leukotrienes (LT) known as well as eicosanoid messengers. Natural sources of GLA are oils from borage, blackcurrant seed and evening primrose (Table 1).[29-30-31]

The main n-3 PUFA in vegetable oils, ALNA (18:3n-3), can not be efficiently converted to EPA (20:5n3) and DHA (22:6n3) in humans. Aging and disease conditions could also further limit the elongation and desaturation processes.  For this reason EPA and DHA are considered to a large extent, nutritionally essential and nearly exclusively derived from marine fish oils. Once ingested, PUFAS are distributed to virtually every body cell. FFA (free fatty acids) enter the cell and are converted to fatty Acyl-coenzyme A thioesters, which are substrates for elongation, desaturation, lipid synthesis, ß-oxidation, protein acylation reactions and mediator synthesis.[29-30-31]

Since PUFA cannot be synthesized by humans, the dietary PUFA content determines the proportion of PUFA in fatty acyl-CoA and membrane phospholipids. Moreover, dietary PUFA and their metabolites derived from all these reactions can affect cellular functions. PUFA exert both immunomodulatory and anti-inflammatory effects, but those of the n-3 series are considered more pronounced compared to those of the n-6 series.[29-30-31-32-33]

## Table 1 Common fatty acids and sources

| Trivial name | Short designation | Systematic name | Typical Fat Source |
|---|---|---|---|
| **Saturated fatty acids** | | | |
| Palmitic acid | 16:0 | hexadecanoic acid | Most fats and oils |
| Stearic acid | 18:0 | octadecanoic acid | Most fats and oils |
| **Monounsaturated fatty acids** | | | |
| Palmitoleic acid | 16:1n-9 | 9-hexadecenoic acid | Beef fat, some fish oils |
| Oleic acid | 18:1n-9 | 9-octodecenoic acid | Esp. olive oil, most fats and oils |
| **Polyunsaturated fatty acids,n-6** | | | |
| Linoleic acid | 18:2n-6 | 9,12-octadecadienoic acid | Most vegetable oils esp. safflower, corn, soybean |
| γ-Linolenic acid | 18:3n-6 | 6,9,12-octadecatrienoic acid | Primrose oil, borage oil |
| Dihomo- γ-Linolenic acid | 20:3n-6 | 8,11,14-eicosatrienoic acid | |
| Arachidonic acid | 20:4n-6 | 5,8,11,14-eicosatetraenoic acid | Lard |
| **Polyunsaturated fatty acids, n-3** | | | |
| α-Linolenic acid | 18:3n-3 | 9,12,15-octadecatrienoic acid | Plant leaves, canola oil, soybean oil, Flax seed oil |
| Eicosapentaenoic acid | 20:5-n3 | 5,8,11,14,17-eicosapentaenoic acid | Some fish oils |
| Docosahexanoic acid | 22:6n-3 | 4,7,10,13,16,19-docosahexaenoic acid | Some fish oils |

**1 All double bonds of listed fatty acids are in *cis* configuration**

Adapted from [29-30]

## 1.6 Immunomodulation by PUFA

Dietary PUFA interfere with a wide spectrum of physiological and pathophysiological processes, thereby affecting health as well as disease. PUFA are proved to alter plasma lipid levels, cardiovascular function, insulin action, neuronal development, and specifically the function and regulation of the immune system. A variety of molecular mechanisms have been found to explain how PUFA could interfere with immune cell function. PUFA alter eicosanoid (prostaglandin, leukotriene) synthesis, orphan nuclear receptor activation (e.g. peroxisome proliferator-activated receptors, liver X receptors) and T lymphocyte signalling by changing the molecular composition of special signalling platforms called lipid rafts.[32]

## 1.7 PUFA Effects on Lipid Messengers

Non esterified PUFA are released from membrane phospholipids to synthesize eicosanoid mediators, e.g prostaglandins (PGs), leukotrienes (LTs) and thromboxanes. The phospholipase A2 releases the predominant AA from the cell membranes which through the action of the cyclooxigenases (COX) generates PGs and thromboxanes of the 2-series, e.g. $PGE_2$ and $PGF_{2a.}$ The action of COX-1 and COX-2 is induced by activation in inflammatory cells, enhancing the production of PGs. AA metabolism via 5-lipoxygenase (5-LOX) in monocytes and/or macrophages, granulocytes and other inflammatory cells produces 5-hydroxyeicosatetraenoic acid (5-HETE) and 5-hydroperoxyeicosatetraenoic acid along with LT of the 4-series ($LTA_4$ and $LTB_4$).[30-32-33]

Eicosanoid messengers are poorly founded in lymphocytes; nonetheless these messengers impact lymphocyte function by exerting anti-inflammatory effects, such as the inhibition of lymphocyte proliferation and the production of Th1 by the action of $PGE_2$. The same $PGE_2$ also inhibits the synthesis of TNF-α, IL-1 and IL-6 by monocytes and macrophages. Additionally, $PGE_2$ exerts pro-inflammatory effects as well, for example, fever induction, increased vasodilatation, and vascular permeability. On the other hand, $LTB_4$ acts also as pro-inflammatory by increasing vascular permeability. Through its chemotactic effect over the leukocytes, LTB4 promotes the release of lysosomal enzymes and the production of oxygen radicals as well as TNF-α, IL-1 and

IL-6. In addition, $PGE_2$ inhibits 5-LOX, thus blocking the $LTx_4$ synthesis and AA also give rise to anti-inflammatory lipoxins generated via 15-LOX. Therefore, eicosanoids exert pro- as well as anti-inflammatory actions. GLA is elongated to DGLA, leading to the formation of the 1-series of PGs and the 3-series of LT. [32-33]

Compare to AA, EPA and DHA are poor COX and LOX reactions substrates. The poor metabolism is due to the configuration of EPA, which misaligns the carbon 13 by COX-1 binding with respect to Tyr-385, the residue that abstracts hydrogen from substrate FA and leads to a 7-fold oxygenation reduction relative to AA. Regardless, EPA and other C20 PUFA are in some extent metabolized by COX and 5-LOX producing eicosanoids of the 3-series of PGs and the 5-series of LT respectively. Moreover, most eicosanoids resulting from COX and LOX action on EPA are considered to be bioactive weaker than the AA metabolites. Consequently, EPA and other C20 PUFA competitively inhibit AA metabolism leading to a decreased capacity by immune cells of eicosanoids synthesis from AA. PUFA of the n-3 series also enhance the catabolism of eicosanoids by increasing the latter's peroxisomal degradation. Dietary DHA inhibits $PGE_2$ and $LTB_4$ production both by itself and by retro conversion to EPA. The ALNA intake also decreases in a minor extent the $PGE_2$ production. [30-31-32-33]

The impact of eicosanoids derived from n-6 and n-3 PUFA on inflammatory processes and particularly immune function is not easily predictable due to the parallel pro- and anti-inflammatory effects.

Recently published data pointed out that DHA and EPA (or they derivatives) inhibit COX-2 receptor in monocytes. [32-33]
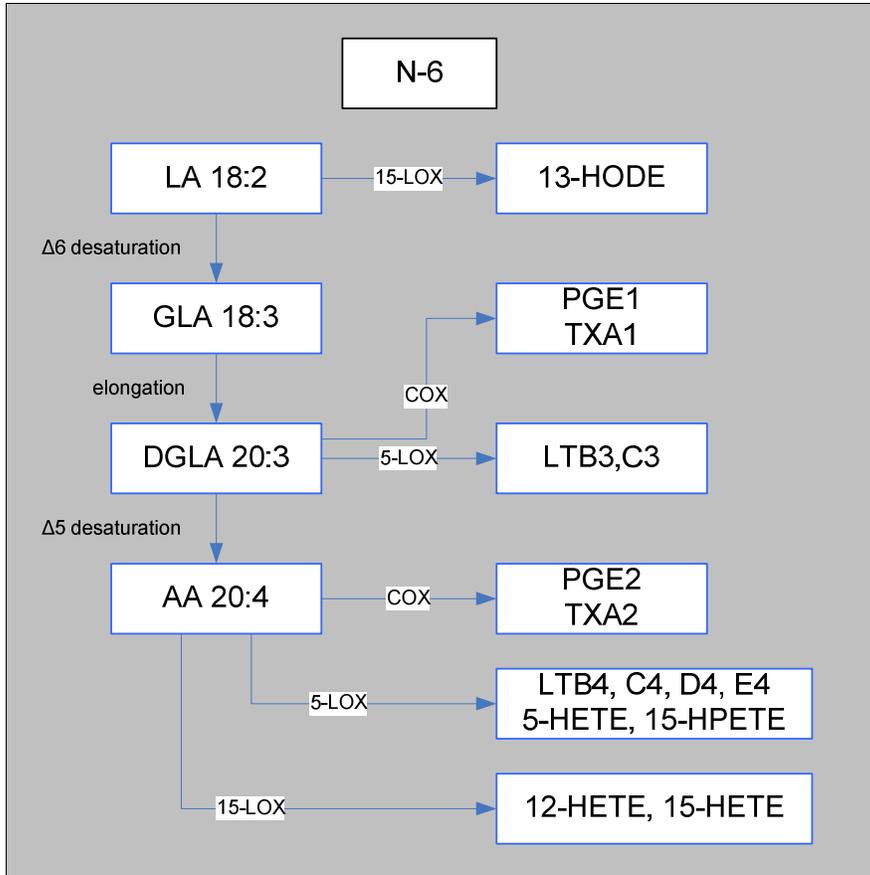
**Figure 3a.**
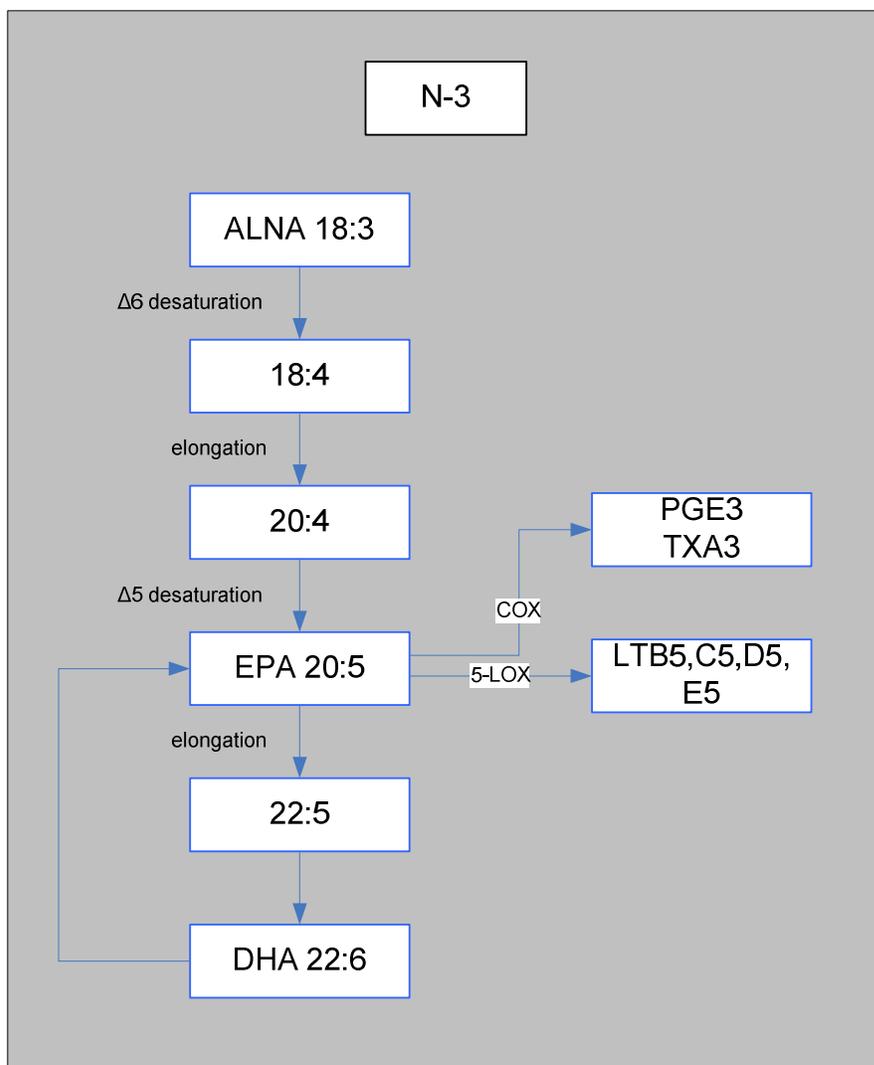
**Figure 3b.**

**Eicosanoid Synthesis from PUFA of the n-6 (a) and n-3 Series (b).**
Metabolic pathways for the synthesis of prostaglandins, thromboxanes and leukotrienes are shown. For fatty acid names see table in the text. (Adapted from [32])

## 1.8 PUFA Effects on Gene Expression

Fatty acids regulate gene function, either directly by interaction with nuclear receptors, or indirectly by altering signalling pathways initiated in the plasma membrane such as T-cell receptor (TCR) signalling. These signalling cascades regulate gene expression by altering activity transcription factors. Consequently, altered gene expression influences plasma membrane and cytoplasmic signalling by changing the cellular content and activity of involved proteins and their activators/repressors. Nuclear receptors are in a direct interaction with PUFA and their metabolites are reasonable candidates to mediate PUFA actions in the immune system.[31-32] Nuclear receptors are transcription factors that are activated by ligand binding. So-called orphan nuclear receptors attach various lipophilic metabolites including fatty acids and their derivatives, thereby regulating the gene transcription. The $\gamma$-peroxisome proliferators-activated receptor (PPAR) interferes with lymphocyte activation and promotes the macrophages differentiation. While PPAR$\alpha$ is activated by a large variety of fatty acids, PPAR$\gamma$ binds predominantly unsaturated fatty acids and some of their metabolites.[31-32] The extent of the immunomodulatory action of the PPARs continue a matter of ongoing research. [32]
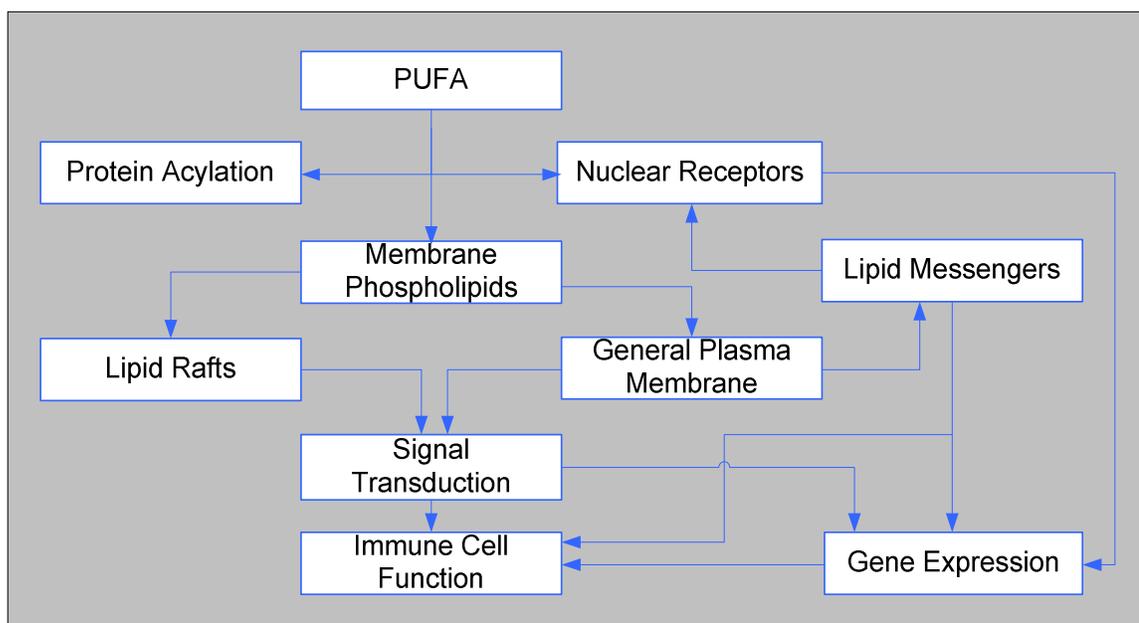


**Figure 4.  Possible Mechanisms of Immune Cell Functional Modulation by PUFA.**

## 1.9 Anti-Inflammatory Effects of Dietary Antioxidants

Oxidative stress has been defined as a disturbance in the equilibrium status of pro-oxidant/antioxidants systems in intact cells. It has been implicated in a wide range of human diseases such as cancer, eye injury, arthritis, rheumatic disorders, and particularly in a number of lung diseases, including asthma. Directly, important local antioxidants in the airways include ascorbic acid, $\alpha$-tocopherol, zinc, glutathione, and proteins. Circulating antioxidant vitamins and other nutrients have been related to several components of the immune responses, and therefore, also linked to the development of atopic disease.[13-14-15-16-17-18-19-20-34-35-36-37-38]

A complex interplay of activation and suppression mechanisms modulates the inflammatory processes. Commonly, when the antigen is rapidly disposed of, the inflammatory process is self-limited. By altered immuno-competence, the accumulation of macrophages and granulocytes lead to enhanced production of reactive oxygen species (ROS) and a number of mediators from the humoral and cellular sources specifically with cytokines and the activity of COX 2 (s. above)[30-34].
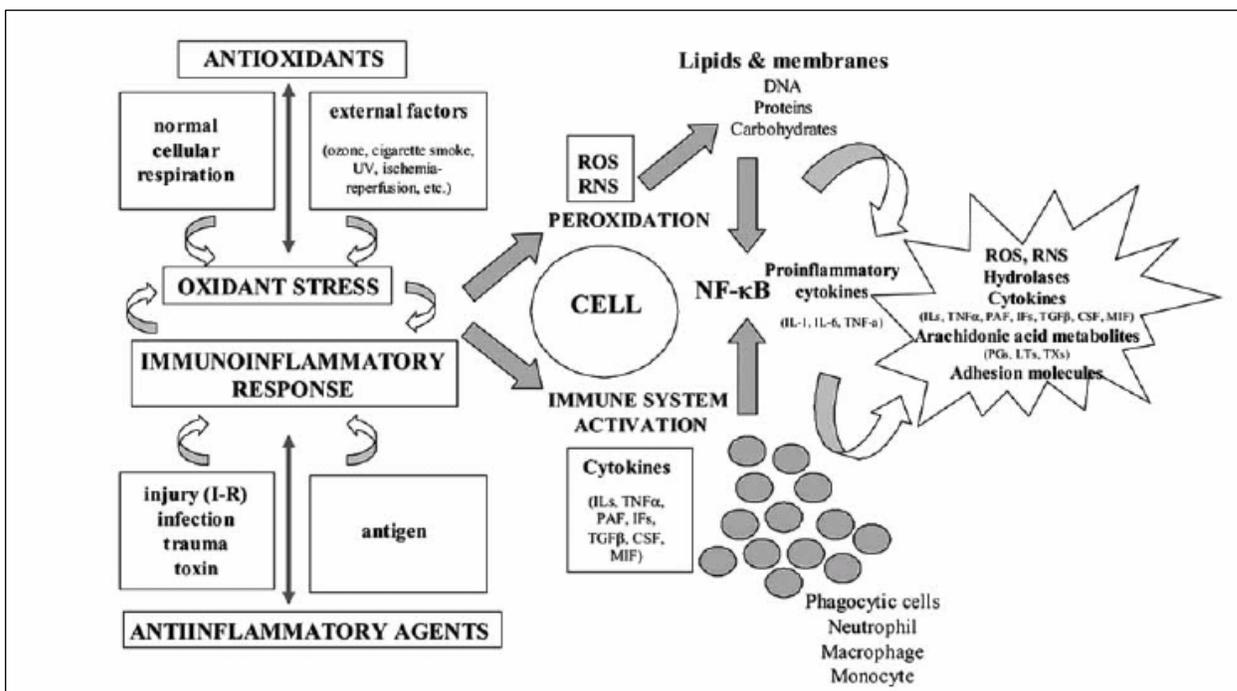


**Figure 5. Oxidant Stress and Concomitant Inflammatory Processes**[34]
I-R: Ischemia-reperfusion, ROS: reactive oxygen species, IL: Interleikin, TNF: Tumor Necrosis Factor, PAF: Platelet Activating Factor, IF: Interferon, TGF: Transforming growth factor, CSF: Colony stimulating factor, MIF: Migration inhibitory factor, NFκB: Nuclear factor kappa B, PG: Prostaglandin, TX: Thromboxane, LT: Leukotriene

## 1.10 Biochemistry, Metabolism and Dietary Sources of Antioxidants and Zinc

### 1.10.1 Vitamin A and Carotene

Lipid soluble vitamin A and a group of more than 600 carotenoids have been characterized. However, only 14 have been identified in human blood and tissue.[39] The most prevalent carotenoids in the diet include α-carotene, β-carotene (the most active form), γ-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. But only few (α-carotene, β-carotene, and β-cryptoxanthin) are converted to vitamin A and considered pro vitamin A carotenoids in foods.[39, 40]

Functions of vitamin A include vision, cellular differentiation, morphogenesis, and other related physiological processes such as growth, reproduction, and immune response. The deficiency of vitamin A impairs the humoral response to infections, the cell-mediated immunity, the NK cell activity, phagocytosis, and nonetheless the activity of T lymphocytes. Vitamin A status is affected by intakes of protein, fat, iron, zinc and vitamin E, among others.[29-30-38-39-40]

The only specific effect of carotenoids in humans is to act as a source of vitamin A in the diet however, they also have important antioxidant actions. The latter are based on the carotenoids' ability to quench singlet oxygen and trap peroxyl radicals, thereby preventing lipid peroxidation.[39] As a result, carotenoids also protect against the development of cancer, CVD, and ocular disorders. In addition, carotenoids affect cell growth regulation and gene expression. Diets low in carotenoids may lead to an increased risk of cancer and heart disease. Carotenes also are associated with enhancing the immune function; however, as a pro vitamin to vitamin A, these results may be attributed to vitamin A, which is known to enhance immunity. Some research, however, does demonstrate immune-enhancing properties that can be attributed to the β-carotene molecule itself.[39]

Good animal sources of preformed vitamin A are liver and other internal organs, eggs, dairy products, whole fish and fish oils. Primary vegetable sources of carotene include carrots, sweet potatoes, pumpkin, cantaloupe, pink grapefruit, spinach, apricots, broccoli, and most dark green leafy vegetables. (Table 2).

## 1.10.2 Vitamin C (Ascorbic Acid)

The chemical name for Ascorbic Acid is 2, 3-didehydro-l-threohexano-1, 4-lactone; other terms included hexurionic acid, cevitamic acid, l-xylosascorbic acid, and vitamin C. Currently, vitamin C is used as the generic name for all compounds exhibiting qualitatively the biological activity of ascorbic acid. Ascorbic acid is considered an essential water-soluble vitamin in the diet based on the human lack of gulonolactone oxidase, which catalyzes the last step in its synthesis from glucose.[29-30-40]

Ascorbic acid is easily oxidized to dehydroascorbic acid (DHAA), and further to inactive diketogulonic acid. Both, ascorbic acid and DHAA provide biological activity (antiscorbutic), contrary to their immediate oxidation product diketogulonic acid and isoascorbic acid. However, isoascorbic acid in biological tissues and fluids shows vitamin C-like activity acting as biological antioxidant.[29-30-40]

Vitamin C constitutes the first defence line of the redox state in plasma, only when the ascorbate is depleted, other compounds become oxidized. Ascorbate modulates the redox chemistry of iron, and scavenges superoxide anions, hydroxyl radicals, peroxyl radicals, ozone, and nitric oxide.[17-34-36-40]

Ascorbate acts together with vitamin E in lipid protection against oxidative stress by regenerating $\alpha$-tocopherol from $\alpha$-tocopheryl radicals in membranes and lipoproteins.

Vitamin C is also involved in the collagen formation, carnitine biosynthesis, neurotransmitter synthesis, and iron absorption. [29-30-40]

The vast majority of vitamin C in western diets derives from fresh foods of vegetable origin, mainly citrus fruits, green vegetables, peppers, tomatoes, berries, and potatoes (Table 2). A reduced amount is delivered by fortified products, meat, fish, poultry, and eggs.[29-30-40]

### 1.10.3 Vitamin E

Due to its lipid soluble nature, vitamin E concentrates in the interior of membranes lipoproteins and other molecules, having a crucial role as a major scavenger of free radicals in the lipid phase. Vitamin E is capable of protecting structural PUFA that are susceptible to peroxidation and prevents the propagation of lipid peroxidation.[29-30-34-40]

Additionally, tocopherols quench and react with oxygen reactive species, preserve the NO reservoir, and are involved in the reduction of iron an copper.

There are eight naturally occurring complexes with characteristics and biological activity attributable to vitamin E, divided in tocopherols and tocotrienols. The most abundant and active form among these eight isomers is α-tocopherol, but also present in foods are β-, γ-, and δ-tocopherols. Research suggests that the mixed forms found in food may be more beneficial than the isolated α -tocopherol form that is used in some supplements.

Vitamin E is necessary for maintaining a healthy immune system, and it protects the thymus and circulating white blood cells from oxidative damage.[36] Also, it may work synergistically with vitamin C in enhancing the immune function.[17]

LDL is the main carrier of tocopherol in plasma. A lack of this vitamin increases the susceptibility of lipoproteins and membranes to peroxidation. Vitamin E exerts a wide variety of functions that might limit or delay the development and/or progression of inflammatory processes such as atheroesclerosis. It also enhances the bioactivity of nitric oxide, inhibits the COX-2, diminishes platelet aggregation, and reduces the production of inflammatory mediators in the macrophages among other functions. Recently, vitamin E has been linked to the inhibition of $PLA_2$ and the subsequent regulation of AA metabolism via COX and LOX pathways.[17, 34]

Dietary sources of vitamin E include vegetable oils such as corn, wheat germ and soybean oils, margarine, nuts, and grains. (Table 2).[29-30-40]

### 1.10.4 Zinc

The dietary group IIb metal zinc (Zn) plays a crucial role in cellular metabolism and gene expression. It is a essential component of biomembranes, enzymes, and hormone receptors. It also stabilizes the nucleic acids structures and protects the integrity of sub cellular organelles. It regulates a large number of cellular processes including mitosis, apoptosis, secretion, and signal transduction as well as critical events in physiological processes as diverse as insulin release, T-cell cytokine production, wound healing, vision, and neurotransmission. Zn is present in all organs, tissues, fluids, and secretions of the body and is primarily an intracellular ion.[29-30-34-40]

Zinc is founded richly in the airways epithelium, its deficiency results in enhanced oxidative damage in the airways by causing infiltration of inflammatory cells and increased superoxide and nitric oxide production.[15-17]

Moreover, Zn deficiency results in a variety of immunologic defects. Severe deficiency is linked to thymic atrophy, lymphopenia, altered lymphocyte proliferation, and a decrease in NK cell and T4 activity. A lack of Zn shifts the Th1/Th2 balance towards Th2, thus giving rise to interleukin-4, LTB4 and $PGE_2$ levels. [41]

Meat, fish, oysters, other shellfish, liver, whole grain cereals, dry beans, and nuts are the main dietary sources of zinc. Milk and milk products also contribute to deliver zinc in the diet.[29-30-34-40] (Table 2).

**Table 2. Dietary Sources of Antioxidant Vitamins and Zinc.**

| Vitamins | Dietary Sources |
|----------|-----------------|
| **Vitamin A** | Liver, milk, cheese, egg yolk, fish oils. |
| **Carotene** | Apricot, cantaloupe melon, mango, carrot, kale, pepper, broccoli, spinach, sweet potato, squash. |
| **Vitamin C** | Citrus fruits and juices, kiwi, broccoli, green pepper, Brussels sprouts, strawberries, tomatoes, mango, papaya, potatoes. |
| **Vitamin E** | Wheat germ, grains, vegetable oils, margarine, mayonnaise, almonds, milk, peanuts, whole grain cereals, eggs. |
| **Zinc** | Shellfish, beef, red meats, whole grain cereals, nuts, legumes, fortified cereals. |

# 2 Materials and Methods

## 2.1 Study Design

This is a cross sectional study using data from the European Community Respiratory Health Survey (ECRHS) (www.erchs.org) and MONICA (MONItoring of Trends and Determinants in CArdiovascular Diseases) projects. The methods have been described in detail elsewhere and are summarised here briefly. [42-43-44]

The ECRHS represented an enormous international effort to develop a standardised protocol to allow collecting feasible data on the geographical variation of the asthma and atopic disease prevalence and their treatment in a large number of European countries. Within the framework of the MONICA Study, Erfurt data about dietary habits was collected from the study subjects. One of the objectives of this international program conducted by the World Health Organisation was to assess the extent to which trends in coronary heart disease morbidity and mortality are related to cardiovascular risk factors, such as dietary habits.[45]

## 2.2 Study Area

The city of Erfurt, in the former German Democratic Republic, with approximately 210 000 inhabitants, was selected to participate in the ECRHS because this city met one of the established criteria: The city is a pre-existing administrative boundary with a population of at least 150 000. Furthermore, the adult Erfurt population served as one of the MONICA subpopulations.[42]

## 2.3 Sources of Data

Data was collected between 1991 and 1992 from a cross sectional study that combined the European Community Respiratory Health Survey and the MONICA Study. Both studies offered high-quality data sampling to expedite the creation of a database, from where this analysis was derived.

## 2.4 Data Collection

The ECRHS survey was conducted in two stages. In stage I, subjects completed a mailed screening questionnaire that collected information about symptoms suggestive of asthma and atopic disease and their treatment (see attached questionnaire). Stage II consisted of a wider interviewer-led questionnaire with 71 items and a medical examination that consisted of determining the total and specific IgE as well as spirometry and a metacholine challenge test. Data on background factors (sociodemographic factors, living conditions, and parental atopy) were also gathered. At the same time, the MONICA survey including dietary assessment was carried out. Subjects were examined between September 1991 and June 1992. The study protocol obtained approval from the local ethics committee of the Medizinische Akademie Erfurt.[43-44]

## 2.5 Study Population

Subjects eligible for the study were adults between the ages of 20 and 64, who were residents of the Thuringian city of Erfurt in Germany. The participants were selected randomly from the residential registry. A total of 1281 persons who attended the medical examination (Stage II) were invited to participate in the dietary survey. The final study population consisted of 469 men and 333 women who conducted acceptable dietary protocols and whose measurement of total and specific immunoglobulin E (IgE) were available (Figure 6).

**Figure 6. Study Population**
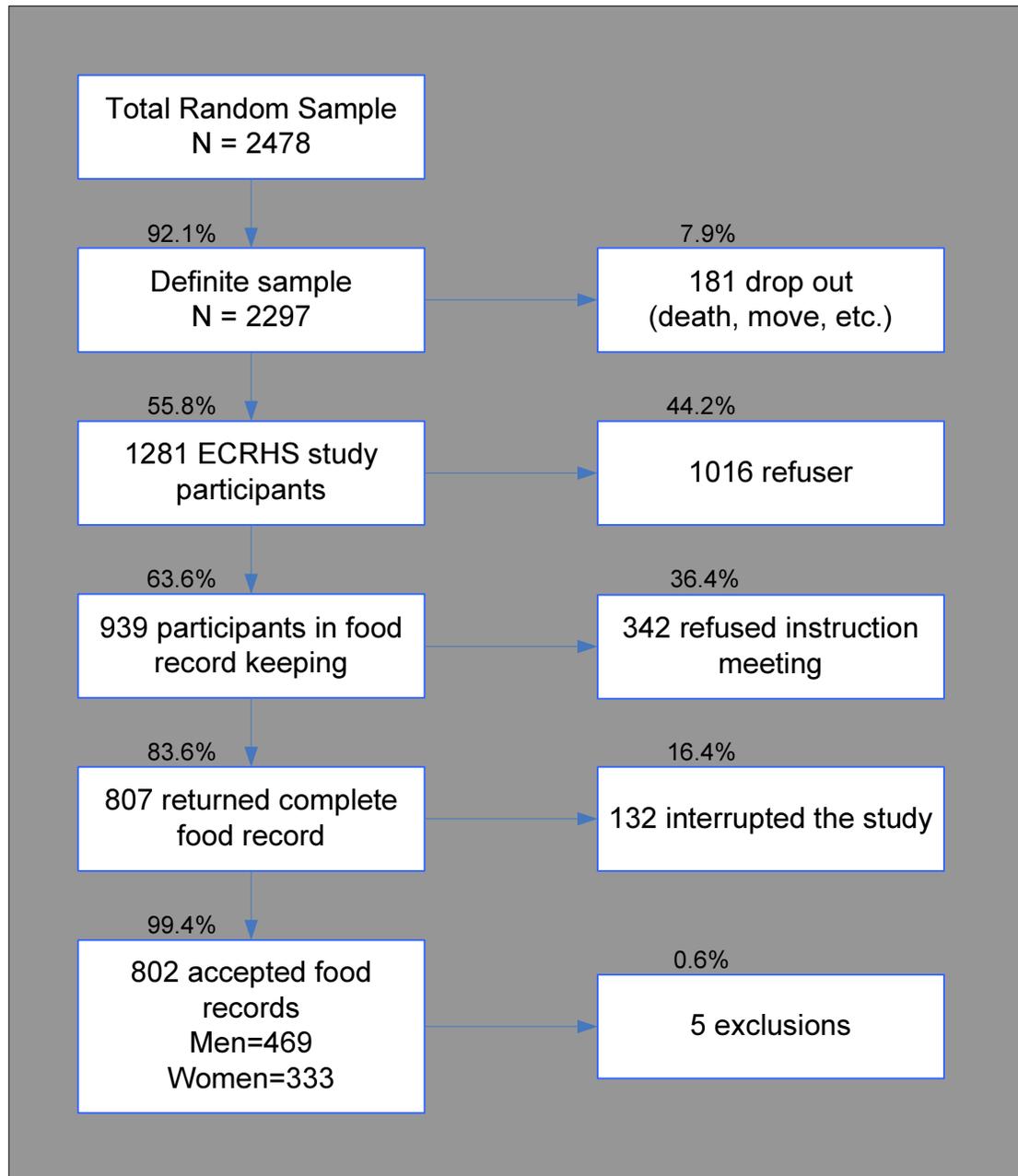
## 2.6 Dietary Assessment Methodology

Data on dietary intake was obtained using prospective three-day records. Trained nurses instructed the participants in record keeping. Food recording was supported by a combination of accurate weighing with letter scales, portion size estimation with household measures, and a booklet of portion size pictures. Supplement intakes were included in the dietary records.The participants completed the food records at home and returned them to the study nurse, who checked it briefly. Food records were rejected if not covering exactly two weekdays and one Sunday or holiday.[45-46-47]

Individual daily food consumption, energy, total fat, fatty acids, and antioxidant nutrients (vitamins A, C, E, and Zinc) were calculated from dietary records using a program developed in the GSF National Research Centre for Environment and Health based on the BLS-German national nutrient data file (Bundeslebensmittelschlüssel II.2).[47-48] Although some nutrient calculations were available from previous work, all calculations were repeated with the updated nutrient data file to obtain better quality and consistent information because this data file is constantly being expanded and corrected. For the first time, the current version of the BLS allowed the calculation not only of fat in the form of saturated (SFA), monounsaturated and polyunsaturated fatty acids but also of the specific fatty acids (arachidonic acid, for example). Therefore, the dietary data of this paper may not necessarily be identical to published data which was derived using the preceding BLS II.1.

Food intakes were presented as daily absolute amounts (g/day of consumed food). Fatty acids intake was computed as amount of the nutrient in grams pro 1000 kcal/day, and antioxidants intake was presented as mg of the vitamin pro 1000 kcal/day.

## 2.7 Outcome Definition

The following outcome variables from the ECRHS were separately considered: asthma, bronchial hyperresponsiveness, allergic sensitisation, reported hay fever, and atopic eczema.

Asthma was defined as a positive answer to the question "Have you ever had asthma?" and whether diagnosis was confirmed by a physician. (See attached questionnaire)

The Methacholine inhalation challenge test was performed using a Mefar MB3 dosimeter (Bovezzi, Italy) in all subjects with a forced expiratory volume greater than 70% of the predicted mean and greater than an absolute value of 1.5 L, who were willing to participate. Bronchial hyperresponsiveness (BHR) was defined as 20% or greater fall in baseline forced expiratory volume in one second before a maximal cumulative dose of methacholine (2 mg) was administered.[42-43] Allergic sensitisation was assessed by the measurement of specific IgE against common aeroallergens such as *dermatophagoides pteronyssinus*, *timothy grass*, cat allergen, *cladosporium herbarum*, and birch, using the Pharmacia CAP System (Uppsala, Sweden).[10] The cut-off to define sensitisation was set on $\geq$0,7 kU/l (RAST Class$\geq$2) from at least one positive specific IgE.[10-42-43] (Figure 7).

Presence of current hay fever as well as life-time atopic eczema was derived from the questionnaire on the basis of a positive answer about those conditions.
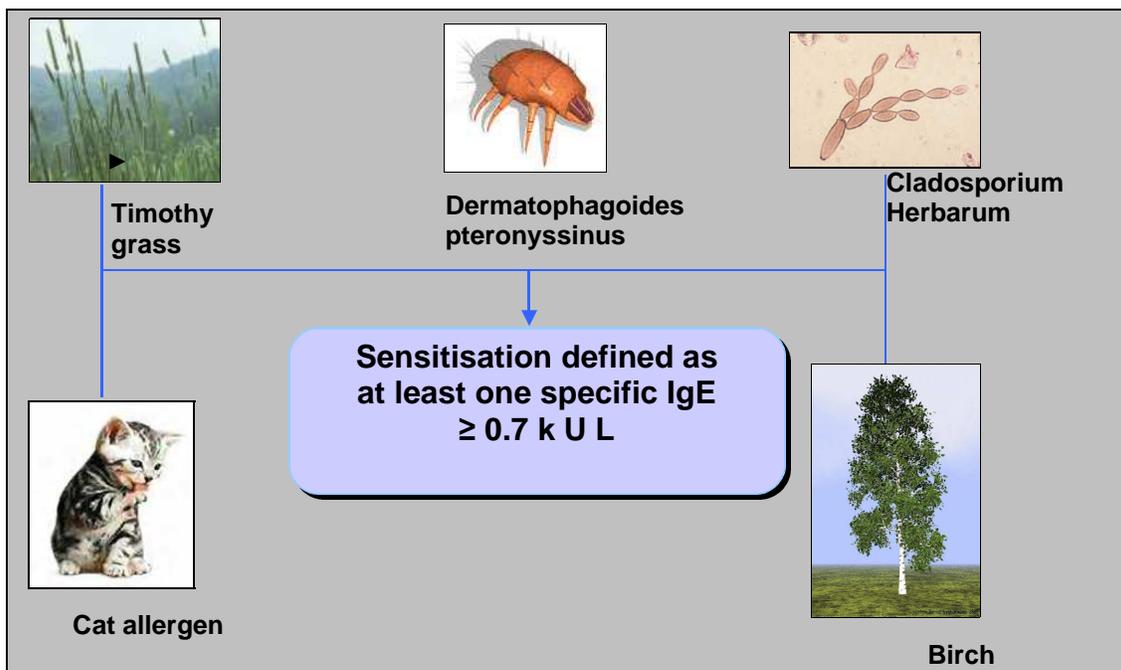


**Figure 7. Definition of Atopic Sensitisation**

## 2.8 Statistical Approach

The patterns of absolute food and nutrient consumption were described using mean, median, standard deviations, and quartiles, all stratified by sex. The Wilcoxon-Mann-Whitney Test was applied between the analysed strata. Pearson's correlation coefficients analyses between consumed fatty acids were presented.

Prevalence of the outcome variables is given. Differences between gender and age groups were determined by $X^2$ test of homogeneity. Subjects were dichotomised according to the presence of allergic disease. Multiple logistic regression models were used to analyse the association between food, fatty acids, antioxidants intake, and atopic diseases. Odds ratios and their 95% confidence intervals were computed for the second, third, and highest intake quartiles compared to the first. Linear trends were calculated. Reported odds ratios were adjusted for age group, social class (defined by educational level), genetic predisposition (parental asthma or atopy), smoking habits, and body mass index. Data analysis was performed with the SAS Software Packet, version 8.1 (SAS Institute, Cary, NC, USA).

# 3 Results

Of the 1281 persons who attended the medical examination, 62.6% participated in the dietary survey. Acceptable records on food consumption were obtained from 802 persons, 63% of whom were male (Figure 6). A Metacholine test for bronchial hyperreactivity was carried out in 613 study participants.

The prevalence of asthma, atopic sensitisation, hay fever, and atopic eczema did not differ between genders, but the bronchial hyperresponsiveness rate was higher in women (Table 3). The proportion of study participants aged between 40 and 64 years was higher in males. Differences were also observed for all educational levels in which the proportion of men was higher. There was also a higher proportion of male smokers (Table 3).

Based on its low prevalence in the study sample (less than 5 %), asthma was discharged as outcome variable for the subsequent statistical analysis (Table 3).

**Table 3. Description of the Study Population. Adults 20-64 Years from Erfurt.**

|  | Total | | Men | | Women | | p-Value |
|---|---|---|---|---|---|---|---|
|  | n | % | n | % | n | % | (X2 Test) |
| **Allergic Outcomes** | | | | | | | |
| Asthma* | 26 | 3.4 | 16 | 3.6 | 10 | 3.1 | 0.72 |
| Bronchial hyperresponsiveness ** | 122 | 19.9 | 58 | 15.8 | 64 | 26.1 | **0.002** |
| Atopic sensitisation [a] | 176 | 23.1 | 102 | 23.0 | 74 | 23.2 | 0.95 |
| Hay fever | 83 | 10.9 | 44 | 9.9 | 39 | 12.2 | 0.32 |
| Atopic eczema | 199 | 26.1 | 106 | 23.9 | 93 | 29.2 | 0.12 |
| **Age groups** | | | | | | | |
| 20-40 | 369 | 48.4 | 196 | 44.2 | 173 | 54.2 | 0.23 |
| 41-64 | 393 | 51.6 | 247 | 55.8 | 146 | 45.8 | **<0.001** |
| **Social Class** b | | | | | | | |
| Less than 10 years | 352 | 46.2 | 210 | 47.4 | 142 | 44.5 | **<0.001** |
| 10 years | 238 | 31.2 | 134 | 30.3 | 104 | 32.6 | 0.05 |
| More than 10 years | 172 | 22.6 | 99 | 22.4 | 73 | 22.8 | **0.05** |
| **Smoking Habits** | | | | | | | |
| Smokers | 251 | 32.9 | 161 | 36.3 | 90 | 28.2 | **<0.001** |
| Non-Smokers | 511 | 67.1 | 282 | 63.7 | 229 | 71.8 | **0.02** |

*Physician diagnosed asthma
**n=613
[a] Defined as at least one specific IgE concentration of $\geq 0,7$ k U/l (RAST Class $\geq 2$)
**Bold fonts:** indicate significance

### 3.1 Food consumption

### 3.1.1 Fat Intake

The data on consumption of selected food items and nutrients for men and women indicate significantly higher absolute butter and margarine intakes in men than in women (Table 4). In men margarine intake was positively associated with the presence of hay fever but not with atopic sensitisation. Those associations were not found among women, in whom only high oil intake was positively related to atopic eczema prevalence (Table 6). The fish consumption in the analysed sample was too low to assess potential effects (data not shown).

### 3.1.2 Vegetables

In men, high fresh vegetable consumption seems to be negatively linked to atopic sensitisation with a significant trend ($p<0.01$) among the intake categories, indicating a dose response relation. Correspondingly, a protective effect of moderate and normal vegetable products intake related to atopic sensitisation (odds ratio 0.40, CI 0.18 to 0.88 and odds ratio 0.33, CI 0.16 to 0.72 respectively) was found in women. Conversely, prevalence of atopic eczema was directly related to high vegetable consumption in men (Odds ratio 3.05, CI 1.55 to 5.99).

### 3.2 Fatty Acids

Fat consumption patterns showed no significant differences between women and men with the exception of alpha-linolenic, which was higher in women (Table 4). Table 5 showed Pearson's correlation coefficient between consumed fatty acids.

Statistical significance for associations between fat intake and health outcomes were mostly limited to women.

In men there were no associations between fat intake and prevalence of atopic sensitisation.

In women, a high fat intake was positively related to atopic sensitisation (odds ratio 2.42, CI 1.07 to 5.50) and hay fever (Tables 8, 10). An increasing trend in the odds ratios for allergic sensitisation was observed with increased intake of saturated and

monounsaturated fats (Table 8). This association was also found for high intakes of specific monounsaturated fatty acids, such as palmitoleic and oleic acid (odds ratio 3.04, CI 1.26 to 7.30 and odds ratio 2.47, CI 1.13 to 5.41 respectively). High intake of arachidonic acid, an n-6 polyunsaturated fatty acid with pro-inflammatory effects, was associated with allergic sensitisation (odds ratio 2.47, CI 1.13 to 5.41). Sensitisation prevalence decreased with higher polyunsaturated to saturated fatty acid ratios (odds ratio 0.39, CI 0.18 to 0.85, P 0.01).

In men, a high omega-6 to omega-3 ratio was positively related with hay fever (odds ratio 2.81, CI 1.10 to 7.16). Table 9 shows associations between fat consumption and hay fever. In women, significant odds ratios coincide with those reported above for atopic sensitisation. A high intake of total fat, monounsaturated fatty acids and oleic acid consumption were positively linked with hay fever.

Also found in women, a high consumption of the n-3 precursor, alpha-linolenic acid, was negatively associated with atopic eczema, whereas both the linoleic to alpha-linolenic acid ratio and the total omega-6 to omega-3 ratio were significantly related to atopic eczema prevalence; however, the confidence intervals of the computed odds ratios included the value one (Table 10).

No significant association between fat intake and BHR in either the strata was found (Table 7).

## 3.3 Antioxidants

No clear relationships between antioxidant nutrients consumption and allergic disease were observed. Statistically, women showed a significantly higher consumption of carotene, vitamin E and vitamin C pro 1000 kcal than men (p ≤0.0001 for all items) (Table 4).

Vitamin C and atopic eczema were positively associated in men (odds ratio 2.06, CI 1.05 to 4.06) (Table 14).

No effects were found for atopic disease outcomes and antioxidants nutrient intakes in women (Tables 11, 12, 13, 14).

## Table 4. Daily Consumption of Selected Foods and Nutrients

| | Men | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | 25th Perc. | 50th Perc. | 75th Perc. | Mean | SD | 25th Perc. | 50th Perc. | 75th Perc. | P value* |
| **Food intake (g/day)** | | | | | | | | | | | |
| Butter | 18 | 26 | 1 | 8 | 27 | 12 | 15 | 0.5 | 7 | 18 | **<0.001** |
| Margarine | 29 | 23 | 10 | 24 | 41 | 22 | 18 | 9 | 17 | 31 | **<0.001** |
| Vegetable oils | 3.6 | 6.0 | 0 | 1.2 | 4.6 | 3.2 | 4.7 | 0 | 1.6 | 4.5 | 0.30 |
| Fresh fruits | 151 | 133 | 41 | 128 | 228 | 168 | 109 | 80 | 153 | 231 | 0.05 |
| Fresh vegetables | 237 | 125 | 154 | 219 | 297 | 187 | 94 | 114 | 176 | 258 | **<0.001** |
| Vegetable products | 21 | 34 | 0.0 | 5 | 27 | 24 | 33 | 0 | 8 | 38 | 0.2 |
| **Fat intake (g/1000kcal/day)** | | | | | | | | | | | |
| Total Fat | 45 | 7 | 40 | 45 | 50 | 45 | 7 | 40 | 45 | 49 | 0.55 |
| SFA | 18 | 4 | 15 | 17 | 20 | 18 | 4 | 15 | 18 | 21 | 0.25 |
| MUFA | 17 | 3 | 15 | 17 | 19 | 17 | 3 | 15 | 17 | 19 | 0.10 |
| PUFA | 6.9 | 2.4 | 5.1 | 6.5 | 8.1 | 7.1 | 2.5 | 5.3 | 6.8 | 8.6 | 0.11 |
| Palmitoleic acid~ | 1.2 | 0.25 | 1.0 | 1.2 | 1.3 | 1.2 | 0.27 | 0.97 | 1.2 | 1.3 | 0.18 |
| Oleic acid~ | 15 | 3 | 13 | 14 | 16 | 14 | 3 | 12 | 14 | 16 | 0.10 |
| Linoleic acid+ | 5.9 | 2.3 | 4.3 | 5.4 | 7.1 | 6.1 | 2.4 | 4.4 | 5.7 | 7.5 | 0.20 |
| Alpha-Linolenic acid+ | 0.72 | 0.28 | 0.60 | 0.70 | 0.80 | 0.78 | 0.31 | 0.65 | 0.73 | 0.86 | **<0.001** |
| Arachidonic acid+ | 0.10 | 0.05 | 0.06 | 0.08 | 0.12 | 0.10 | 0.07 | 0.06 | 0.08 | 0.12 | 0.98 |
| Linoleic acid/Alpha-Linolenic acid+ | 8.3 | 2.8 | 6.6 | 7.9 | 9.4 | 8.0 | 3.1 | 6.2 | 7.6 | 9.5 | 0.07 |
| P/S ratio | 0.40 | 0.18 | 0.28 | 0.39 | 0.52 | 0.43 | 0.19 | 0.31 | 0.40 | 0.52 | 0.49 |
| Omega6/Omega3 ratio+ | 7.6 | 2.6 | 5.9 | 7.3 | 8.7 | 7.4 | 2.7 | 5.6 | 6.9 | 8.6 | 0.08 |
| **Antioxidants(mg/1000kcal/day)** | | | | | | | | | | | |
| Vitamin A | 0.76 | 0.55 | 0.99 | 0.40 | 0.76 | 0.82 | 0.60 | 1.03 | 0.42 | 0.82 | 0.43 |
| Carotene | 0.86 | 0.65 | 0.73 | 0.40 | 1.02 | 1.32 | 0.90 | 1.21 | 0.55 | 1.65 | **<0.0001** |
| Vitamin C | 36.8 | 32.2 | 23.9 | 20.7 | 46.8 | 63.5 | 56.9 | 46.4 | 38.8 | 78.3 | **<0.0001** |
| Vitamin E | 5.07 | 4.73 | 1.96 | 3.76 | 6.02 | 5.81 | 5.33 | 2.49 | 4.30 | 6.68 | **<0.0001** |
| Zinc | 4.85 | 4.75 | 9.68 | 4.16 | 5.39 | 5.09 | 4.9 | 1.09 | 4.29 | 5.72 | 0.018 |

* Wilcoxon-Mann-Whitney-Test.

SD: standard deviation, Perc: percentile, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids,
PUFA: polyunsaturated fatty acids, P/S ratio: polyunsaturated/saturated ratio.

~ monounsaturated fatty acid

+ polyunsaturated fatty acid

## Table 5. Pearson's Correlation Coefficients Between Consumed Fatty Acids Stratified for Women and Men

| Women | Total fat | SFA | MUFA | PUFA | Palmito-leic acid | Oleic acid | Linoleic acid | α- Linole-nicacid | Arachido-nic acid | Linoleic / α- Linolenic acid | PSQ | Omega6/ Omega3 | Men |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total fat | 1.00 | 0.77 | 0.9 | 0.44 | 0.74 | 0.87 | 0.39 | 0.34 | 0.16 | 0.02 | -0.03 | 0.04 | Total fat |
|  |  | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **0.000** | 0.66 | 0.56 | 0.52 |  |
| SFA | **0.74** | 1.00 | **0.56** | **-0.15** | **0.55** | **0.56** | -0.18 | **0.12** | 0.08 | **-0.36** | **-0.57** | **-0.34** | SFA |
|  | **<.0001** |  | **<.0001** | **0.01** | **<.0001** | **<.0001** | 0 | **0.03** | 0.13 | **<.0001** | **<.0001** | **<.0001** |  |
| MUFA | **0.86** | **0.45** | 1.00 | **0.36** | **0.83** | **0.95** | **0.32** | **0.25** | 0.18 | 0.01 | -0.02 | 0.02 | MUFA |
|  | **<.0001** | **<.0001** |  | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | 0 | 0.92 | 0.67 | 0.66 |  |
| PUFA | **0.46** | **-0.14** | **0.4** | 1.00 | **0.13** | **0.35** | **0.98** | **0.44** | 0.09 | **0.65** | **0.84** | **0.63** | PUFA |
|  | **<.0001** | **0** | **<.0001** |  | **0.02** | **<.0001** | **<.0001** | **<.0001** | 0.12 | **<.0001** | **<.0001** | **<.0001** |  |
| ~ Palmitoleic acid | **0.68** | **0.45** | **0.8** | **0.1** | 1.00 | **0.71** | 0.07 | **0.15** | **0.3** | **-0.16** | **-0.18** | **-0.2** | Palmitoleic acid |
|  | **<.0001** | **<.0001** | **<.0001** | **0.03** |  | **<.0001** | 0.19 | **0.01** | **<.0001** | **0** | **0** | **0** |  |
| ~ Oleic acid | **0.85** | **0.46** | **0.96** | **0.38** | **0.69** | 1.00 | **0.33** | **0.23** | **0.14** | 0.05 | -0.02 | 0.09 | Oleic acid |
|  | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** |  | **<.0001** | **<.0001** | **0.01** | 0.4 | 0.66 | 0.11 |  |
| + Linoleic acid | **0.43** | **-0.15** | **0.37** | **0.98** | 0.05 | **0.38** | 1.00 | **0.34** | 0.03 | **0.73** | **0.85** | **0.73** | Linoleic acid |
|  | **<.0001** | **0** | **<.0001** | **<.0001** | 0.33 | **<.0001** |  | **<.0001** | 0.6 | **<.0001** | **<.0001** | **<.0001** |  |
| + α -Linolenic acid | **0.43** | **0.16** | **0.34** | **0.49** | **0.27** | **0.3** | **0.38** | 1.00 | -0.01 | **-0.23** | **0.26** | **-0.21** | α -Linolenic acid |
|  | **<.0001** | **0** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** |  | 0.85 | **<.0001** | **<.0001** | **0** |  |
| + Arachidonic acid | 0.07 | -0.03 | 0.09 | 0.1 | 0.22 | 0.08 | 0.05 | -0.02 0.61 | 1.00 | 0.05 | 0.01 | -0.01 | Arachidonic acid |
|  | 0.14 | 0.59 | 0.07 | 0.03 | <.0001 | 0.08 | 0.27 |  |  | 0.33 | 0.82 | 0.86 |  |
| + Linoleic acid/ α- Linolenic acid | 0.06 | **-0.36** | 0.08 | **0.67** | **-0.2** | **0.12** | **0.74** | **-0.12** | **0.11** | 1.00 | **0.72** | **0.95** | Linoleic acid/ α- Linolenic acid |
|  | 0.23 | **<.0001** | 0.11 | **<.0001** | **<.0001** | **0.01** | **<.0001** | **0.01** | **0.03** |  | **<.0001** | **<.0001** |  |
| P/S ratio | -0.01 | **-0.56** | 0.05 | 0.84 | **-0.16** | 0.03 | **0.82** | **0.33** | 0.09 | **0.69** | 1.00 | **0.68** | P/S ratio |
|  | 0.89 | **<.0001** | 0.33 | <.0001 | **0** | 0.6 | **<.0001** | **<.0001** | 0.07 | **<.0001** |  | **<.0001** |  |
| + Omega6/ Omega3 | 0.09 | **-0.3** | **0.12** | **0.63** | **-0.21** | 0.18 | **0.72** | **-0.1** | 0.01 | **0.94** | **0.61** | 1.00 | Omega6/ Omega3 |
|  | 0.05 | **<.0001** | **0.01** | **<.0001** | **<.0001** | 0 | **<.0001** | **0.04** | 0.79 | **<.0001** | **<.0001** |  |  |

SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, P/S ratio: polyunsaturated to saturated ratio.
~ monounsaturated fatty acid
+ polyunsaturated fatty acid
**Bold fonts:** indicate significance

**Table 6 a. Associations Between Selected Food Consumption and BHR [a],  Allergic Sensitisation [b], Hay Fever, and Atopic Eczema in Men**

| Men | | | | | | |
|---|---|---|---|---|---|---|
| | | | Adjusted OR* (95% CI) | | | |
| Intake [c] | | 1st | 2nd | 3rd | 4th | P for |
| g/day | | Quartile | Quartile | Quartile | Quartile | Trend |
| **Butter** | BHR [a] | 1.00 | 0.84(0.36-1.97) | 0.79(0.35-1.80) | 0.99(0.44-2.18) | 0.69 |
| | Sensitisation [b] | 1.00 | 0.73(0.38-1.41) | 1.06(0.57-1.96) | 0.93(0.50-1.75) | 0.70 |
| | Hay fever | 1.00 | 0.79(0.35-1.75) | 0.41(0.16-1.05) | 0.47(0.19-1.18) | 0.09 |
| | Atopic eczema | 1.00 | 1.63(0.87-3.06) | 1.25(0.66-2.37) | 0.93(0.48-1.82) | 0.41 |
| **Margarine** | BHR [a] | 1.00 | 1.82(0.82-4.04) | 1.28(0.54-3.04) | 0.97(0.41-2.30) | 0.40 |
| | Sensitisation [b] | 1.00 | 0.59(0.31-1.11) | 0.62(0.33-1.17) | 0.74(0.40-1.38) | 0.09 |
| | Hay fever | 1.00 | **3.23(1.01-10.35)** | **3.25(1.02-10.39)** | 3.04(0.95-9.73) | **0.03** |
| | Atopic eczema | 1.00 | 2.01(1.07-3.79) | 1.53(0.79-2.99) | 1.00(0.50-1.98) | 0.15 |
| **Vegetable oils** | BHR [a] | 1.00 | 1.33(0.53-3.35) | 1.08(0.51-2.30) | 1.13(0.53-2.41) | 0.65 |
| | Sensitisation [b] | 1.00 | 0.54(0.25-1.17) | 0.65(0.36-1.15) | 0.65(0.36-1.16) | **0.04** |
| | Hay fever | 1.00 | 1.59(0.58-4.34) | 1.34(0.56-3.17) | 1.82(0.80-4.14) | 0.20 |
| | Atopic eczema | 1.00 | 0.40(0.17-0.92) | 0.61(0.34-1.10) | 0.96(0.56-1.67) | 0.11 |
| **Fresh fruits** | BHR [a] | 1.00 | 1.38(0.61-3.13) | 1.32(0.58-2.98) | 0.86(0.36-2.05) | 0.64 |
| | Sensitisation [a] | 1.00 | 1.24(0.67-2.29) | 0.66(0.34-1.30) | 1.03(0.54-1.95) | 0.87 |
| | Hay fever | 1.00 | 1.20(0.48-2.96) | 0.92(0.36-2.33) | 1.10(0.44-2.73) | 0.87 |
| | Atopic eczema | 1.00 | 1.12(0.59-2.13) | 1.44(0.77-2.70) | 0.80(0.40-1.58) | 0.69 |
| **Fresh Vegetables** | BHR [a] | 1.00 | 0.78(0.34-1.81) | 1.07(0.49-3.33) | 0.89(0.40-2.00) | 0.21 |
| | Sensitisation [a] | 1.00 | 0.47(0.25-0.90) | 0.60(0.33-1.10) | **0.48(0.25-0.91)** | **0.009** |
| | Hay fever | 1.00 | 0.90(0.37-2.17) | 0.76(0.30-1.93) | 0.96(0.40-2.30) | 0.72 |
| | Atopic eczema | 1.00 | 1.72(0.86-3.45) | 1.69(0.84-3.41) | **3.05(1.55-5.99)** | **0.01** |
| **Vegetable products** | BHR [a] | 1.00 | 0.76(0.35-1.66) | 0.36(0.14-0.90) | 0.98(0.47-2.06) | 0.21 |
| | Sensitisation [a] | 1.00 | 1.23(0.64-2.35) | 1.28(0.71-2.32) | 0.83(0.44-1.57) | 0.73 |
| | Hay fever | 1.00 | 2.11(0.85-5.24) | 1.52(0.62-3.69) | 1.12(0.44-2.83) | 0.28 |
| | Atopic eczema | 1.00 | 1.48(0.78-2.80) | 0.77(0.40-1.46) | 1.42(0.79-2.58) | 0.54 |

**Table 6 b. Associations Between Selected Food Consumption and BHR [a], Allergic Sensitisation [b], Hay Fever, and Atopic Eczema in Women.**

| Women | | Adjusted OR* (95% CI) | | | | |
|---|---|---|---|---|---|---|
| Intake [c] g/day | | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| **Butter** | BHR [a] | 1.00 | 1.27(0.55-2.93) | 1.07(0.45-2.53) | 1.15(0.49-2.68) | 0.68 |
| | Sensitisation [b] | 1.00 | 1.08(0.51-2.27) | 0.52(0.23-1.17) | 1.16(0.55-2.45) | 0.70 |
| | Hay fever | 1.00 | 0.92(0.34-2.46) | 0.55(0.20-1.53) | 0.94(0.36-2.46) | 0.54 |
| | Atopic eczema | 1.00 | 1.43(0.70-2.89) | 1.46(0.73-2.93) | 0.99(0.48-2.06) | 0.40 |
| **Margarine** | BHR [a] | 1.00 | 0.78(0.35-1.76) | 0.77(0.34-1.73) | 0.48(0.20-1.18) | 0.27 |
| | Sensitisation [b] | 1.00 | 1.00(0.47-2.13) | 0.96(0.45-2.04) | 0.75(0.34-1.66) | 0.75 |
| | Hay fever | 1.00 | 1.36(0.49-3.78) | 1.66(0.62-4.40) | 1.25(0.42-3.68) | 0.41 |
| | Atopic eczema | 1.00 | 0.79(0.39-1.58) | 1.33(0.68-2.57) | 0.53(0.25-1.12) | 0.60 |
| **Vegetable oils** | BHR [a] | 1.00 | 0.93(0.36-2.41) | 1.31(0.61-2.82) | 1.18(0.55-2.55) | 0.62 |
| | Sensitisation [b] | 1.00 | 1.07(0.50-2.32) | 0.55(0.26-1.17) | 0.63(0.30-1.31) | 0.20 |
| | Hay fever | 1.00 | 0.97(0.30-3.12) | 1.41(0.56-3.54) | 1.59(0.62-4.09) | 0.43 |
| | Atopic eczema | 1.00 | 2.12(1.00-4.46) | 1.45(0.73-2.88) | **2.09(1.06-4.10)** | **0.04** |
| **Fresh fruits** | BHR [a] | 1.00 | 1.23(0.62-2.44) | 0.95(0.32-2.82) | 0.99(0.75-1.31) | 0.48 |
| | Sensitisation [a] | 1.00 | 0.99(0.47-2.07) | 0.95(0.45-2.00) | 0.67(0.30-1.51) | 0.67 |
| | Hay fever | 1.00 | 1.02(0.37-2.80) | 1.24(0.47-3.26) | 0.67(0.22-2.02) | 0.98 |
| | Atopic eczema | 1.00 | 0.90(0.45-1.79) | 0.44(0.21-0.93) | 0.89(0.44-1.78) | 0.26 |
| **Fresh vegetables** | BHR [a] | 1.00 | 0.79(0.34-1.81) | 1.06(0.48-2.33) | 0.86(0.38-1.93) | 0.75 |
| | Sensitisation [a] | 1.00 | 0.51(0.24-1.11) | 0.66(0.31-1.40) | 0.80(0.38-1.67) | 0.15 |
| | Hay fever | 1.00 | 0.41(0.14-1.20) | 0.59(0.23-1.54) | 0.65(0.25-1.68) | 0.13 |
| | Atopic eczema | 1.00 | 0.86(0.43-1.72) | 0.98(0.49-1.95) | 0.67(0.33-1.38) | 0.53 |
| **Vegetable products** | BHR [a] | 1.00 | 1.21(0.48-3.09) | 2.20(1.01-4.84) | 1.88(0.86-4.10) | 0.08 |
| | Sensitisation [a] | 1.00 | **0.40(0.18-0.88)** | **0.33(0.16-0.72)** | 0.58(0.28-1.20) | **0.004** |
| | Hay fever | 1.00 | 1.35(0.51-3.59) | 0.91(0.33-2.55) | 1.27(0.49-3.31) | 0.70 |
| | Atopic eczema | 1.00 | 0.60(0.28-1.27) | 1.15(0.59-2.23) | 1.14(0.59-2.22) | 0.87 |

[a] BHR: bronchial hyperresponsiveness. Defined as 20% drop in $FEV_1$ during methacholine provocation test. n=613 (Men=368, Women=245)
[b] Defined as at least one specific IgE concentration of $\geq$0.7k U/l (RAST Class $\geq$2)
[c] Intake was categorised according to food quartile of daily consumption
*Adjusted for age group, educational level, history of parental atopy, smoking habits and body mass index
OR: Odds ratio, CI: confidence intervals.
**Bold fonts:** indicate significance

**Table 7. Associations Between Dietary Intake of Fatty Acids and Bronchial Hyperresponsiveness[a]  in Adults**

| Men | Adjusted OR with 95% CI | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Total fat | 1.00 | 0.90 | (0.41-1.99) | 0.88 | (0.41-1.92) | **0.37** | **(0.14-0.93)** | 0.05 |
| SFA | 1.00 | 0.87 | (0.39-1.95) | 0.87 | (0.38-1.96) | 0.62 | (0.26-1.47) | 0.31 |
| MUFA | 1.00 | 0.35 | (0.14-0.85) | 0.90 | (0.43-1.90) | 0.35 | (0.15-0.83) | 0.11 |
| PUFA | 1.00 | 0.65 | (0.28-1.50) | 1.26 | (0.59-2.66) | 0.57 | (0.24-1.34) | 0.49 |
| Palmitoleic acid~ | 1.00 | 0.68 | (0.30-1.50) | 0.50 | (0.22-1.13) | 0.45 | (0.20-1.02) | **0.04** |
| Oleic acid~ | 1.00 | 0.62 | (0.27-1.44) | 1.10 | (0.52-2.35) | 0.37 | (0.15-0.90) | 0.11 |
| Linoleic acid+ | 1.00 | 0.90 | (0.40-2.00) | 1.32 | (0.61-2.86) | 0.54 | (0.22-1.31) | 0.36 |
| Alpha-Linolenic acid+ | 1.00 | 0.67 | (0.30-1.53) | 0.82 | (0.37-1.78) | 0.57 | (0.25-1.29) | 0.24 |
| Arachidonic acid+ | 1.00 | 1.04 | (0.44-2.48) | 1.13 | (0.48-2.67) | 1.34 | (0.59-3.05) | 0.46 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.26 | (0.55-2.87) | 1.26 | (0.57-2.79) | 0.92 | (0.39-2.13) | 0.84 |
| P/S ratio | 1.00 | 1.04 | (0.44-2.44) | 1.69 | (0.75-3.81) | 1.12 | (0.48-2.59) | 0.55 |
| Omega6/Omega3 + | 1.00 | 1.43 | (0.62-3.27) | 1.68 | (0.75-3.80) | 0.94 | (0.39-2.26) | 0.94 |

| Women | Adjusted OR* with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 0.56 (0.24-1.28) | 0.54 (0.23-1.29) | 0.89 (0.41-1.97) | 0.81 |
| SFA | 1.00 | 0.57 (0.24-1.33) | 0.72 (0.32-1.63) | 0.70 (0.31-1.59) | 0.52 |
| MUFA | 1.00 | 0.74 (0.32-1.69) | 0.49 (0.21-1.13) | 0.73 (0.33-1.61) | 0.30 |
| PUFA | 1.00 | 1.20 (0.54-2.66) | 0.74 (0.32-1.72) | 0.74 (0.32-1.75) | 0.32 |
| Palmitoleic acid~ | 1.00 | 0.64 (0.28-1.42) | 0.37 (0.16-0.89) | 0.72 (0.32-1.64) | 0.26 |
| Oleic acid~ | 1.00 | 0.55 (0.24-1.28) | 0.63 (0.28-1.43) | 0.62 (0.28-1.40) | 0.31 |
| Linoleic acid+ | 1.00 | 1.68 (0.75-3.75) | 1.03 (0.44-2.40) | 0.73 (0.30-1.76) | 0.30 |
| Alpha-Linolenic acid+ | 1.00 | 0.80 (0.34-1.87) | 0.88 (0.39-1.96) | 1.00 (0.44-2.29) | 0.97 |
| Arachidonic acid+ | 1.00 | 1.34 (0.60-3.02) | 0.68 (0.28-1.62) | 1.12 (0.48-2.60) | 0.81 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.62 (0.73-3.60) | 0.55 (0.23-1.36) | 0.94 (0.41-2.15) | 0.48 |
| P/S ratio | 1.00 | 1.37 (0.63-2.99) | 0.88 (0.38-2.06) | 0.54 (0.23-1.29) | 0.11 |
| Omega6/Omega3+ | 1.00 | 1.87 (0.83-4.22) | 0.51 (0.21-1.27) | 0.95 (0.41-2.16) | 0.33 |

[c] Intake was categorised according to food quartile of daily consumption

[a] BHR: bronchial hypersponsiveness. Defined as 20% drop in $FEV_1$ during methacholine provocation test

*Adjusted for age, educational level, history of parental atopy, smoking habits, and  body mass index

OR: Odds ratio, CI: confidence intervals, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, P/S ratio: polyunsaturated to saturated ratio.

~ monounsaturated fatty acid

+ polyunsaturated fatty acid

**Bold fonts:** indicate significance

## Table 8. Associations Between Dietary Intake of Fatty Acids and Allergic Sensitisation in Adults

| Men | Adjusted OR with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 0.65(0.35 to 1.20) | 0.57(0.30 to 1.07) | 0.71(0.39 to 1.31) | 0.23 |
| SFA | 1.00 | 0.82(0.44 to 1.54) | 1.11(0.61 to 2.02) | 0.60(0.31 to 1.15) | 0.26 |
| MUFA | 1.00 | 0.61(0.32 to 1.14) | 0.70(0.38 to 1.30) | 0.72(0.39 to 1.33) | 0.38 |
| PUFA | 1.00 | 0.98(0.54 to 1.78) | 0.69(0.37 to 1.29) | 0.61(0.32 to 1.16) | 0.08 |
| Palmitoleic acid~ | 1.00 | 0.82(0.43 to 1.56) | 0.91(0.48 to 1.73) | 1.07(0.57 to 2.01) | 0.78 |
| Oleic acid~ | 1.00 | 0.75(0.40 to 1.39) | 0.73(0.39 to 1.37) | 0.65(0.35 to 1.23) | 0.20 |
| Linoleic acid+ | 1.00 | 0.99(0.55 to 1.81) | 0.58(0.30 to 1.11) | 0.67(0.36 to 1.27) | 0.09 |
| Alpha-Linolenic acid+ | 1.00 | 0.64(0.34 to 1.19) | 0.52(0.27 to 0.99) | 0.79(0.43 to 1.44) | 0.35 |
| Arachidonic acid+ | 1.00 | 1.21(0.66 to 2.23) | 0.80(0.42 to 1.53) | 0.65(0.33 to 1.26) | 0.11 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.00(0.54 to 1.85) | 0.65(0.34 to 1.26) | 0.88(0.47 to 1.63) | 0.46 |
| P/S ratio | 1.00 | 0.86(0.46 to 1.61) | 1.04(0.56 to 1.93) | 0.72(0.37 to 1.38) | 0.46 |
| Omega6/Omega3 + | 1.00 | 0.78(0.42 to 1.46) | 0.57(0.30 to 1.10) | 0.86(0.46 to 1.59) | 0.45 |

| Women | Adjusted OR with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 2.52 (1.12-5.68) | 1.56 (0.66-3.64) | **2.42 (1.07-5.50)** | 0.12 |
| SFA | 1.00 | 1.18 (0.51-2.76) | 2.35 (1.07-5.17) | 1,99 (0.89-4.46) | **0.03** |
| MUFA | 1.00 | 0.84 (0.36-1.99) | 1.81 (0.83-3.94) | 2.13 (0.98-4.62) | **0.02** |
| PUFA | 1.00 | 1.12 (0.54-2.34) | 0.86 (0.40-1.85) | 0.69 (0.32-1.51) | 0.28 |
| Palmitoleic acid~ | 1.00 | 3.01 (1.29-7.02) | 2.86 (1.19-6.85) | **3.04 (1.26-7.30)** | **0.02** |
| Oleic acid~ | 1.00 | 1.44 (0.63-3.30) | 1.52 (0.68-3.43) | **2.47 (1.13-5.41)** | **0.03** |
| Linoleic acid+ | 1.00 | 1.42 (0.67-3.02) | 1.45 (0.68-3.08) | 0.70 (0.31-1.60) | 0.47 |
| Alpha-Linolenic acid+ | 1.00 | 0.65 (0.30-1.43) | 1.12 (0.53-2.36) | 0.94 (0.45-1.98) | 0.81 |
| Arachidonic acid+ | 1.00 | 2.59 (1.16-5.77) | 1.97 (0.85-4.58) | **2.47 (1.07-5.72)** | 0.08 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.09 (0.52-2.24) | 0.92 (0.44-1.93) | 0.52 (0.23-1.17) | 0.12 |
| P/S ratio | 1.00 | 0.70 (0.34-1.44) | 0.51 (0.24-1.09) | **0.39 (0.18-0.85)** | **0.01** |
| Omega6/Omega3 + | 1.00 | 0.80 (0.37-1.72) | 1.22 (0.59-2.53) | 0.57 (0.26-1.28) | 0.36 |

[c] Intake was categorised according to nutrient quartile of daily consumption

[a] Defined as at least one specific IgE concentration of $\geq 0.7$ k U/l (RAST Class $\geq 2$)

*Adjusted for age, educational level, history of parental atopy, smoking habits, and body mass index

OR: Odds ratio, CI: confidence intervals, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids.

~ monounsaturated fatty acid

+ polyunsaturated fatty acid

**Bold fonts:** indicate significance

**Table 9. Associations Between Dietary Intake of Fatty Acids and Hay Fever in Adults**

| Men | Adjusted OR* with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 0.80(0.33 to 1.94) | 0.72(0.29 to 1.79) | 1.09(0.47 to 2.50) | 0.89 |
| SFA | 1.00 | 0.74(0.31 to 1.78) | 0.81(0.35 to 1.90) | 0.74(0.31 to 1.76) | 0.54 |
| MUFA | 1.00 | 0.82(0.34 to 1.98) | 0.79(0.33 to 1.93) | 0.98(0.42 to 2.29) | 0.95 |
| PUFA | 1.00 | 2.13(0.77 to 5.91) | 2.70(1.01 to 7.25) | 1.94(0.69 to 5.46) | 0.20 |
| Palmitoleic acid~ | 1.00 | 1.09(0.45 to 2.61) | 0.66(0.25 to 1.73) | 1.12(0.47 to 2.68) | 0.97 |
| Oleic acid~ | 1.00 | 1.16(0.48 to 2.79) | 0.90(0.37 to 2.19) | 0.88(0.35 to 2.20) | 0.66 |
| Linoleic acid+ | 1.00 | 2.10(0.75 to 5.88) | 2.33(0.85 to 6.36) | 2.14(0.76 to 5.98) | 0.17 |
| Alpha-Linolenic acid+ | 1.00 | 0.56(0.22 to 1.39) | 0.52(0.20 to 1.33) | 0.97(0.43 to 2.21) | 0.96 |
| Arachidonic acid+ | 1.00 | 0.52(0.22 to 1.24) | 0.58(0.24 to 1.37) | 0.55(0.23 to 1.32) | 0.19 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.73(0.63 to 4.70) | 1.56(0.58 to 4.23) | 2.45(0.95 to 6.34) | 0.09 |
| P/S ratio | 1.00 | 1.51(0.55 to 4.10) | 1.98(0.75 to 5.23) | 2.01(0.76 to 5.32) | 0.13 |
| Omega6/Omega3 + | 1.00 | 1.55(0.56 to 4.31) | 1.40(0.51 to 3.86) | **2.81(1.10 to 7.16)** | **0.04** |

| Women | Adjusted OR* with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 3.14 (0.95 to 10.35) | 1.28 (0.34 to 4.81) | **4.51 (1.38 to 14.75)** | **0.05** |
| SFA | 1.00 | 2.83(0.84 to 9.53) | 1.93(0.55 to 6.75) | 3.13(0.95 to 10.28) | 0.13 |
| MUFA | 1.00 | 0.94(0.29 to 3.03) | 1.62(0.54 to 4.90) | **3.04(1.07 to 8.59)** | **0.01** |
| PUFA | 1.00 | 0.90(0.33 to 2.48) | 1.10(0.40 to 3.03) | 1.58(0.60 to 4.14) | 0.31 |
| Palmitoleic acid~ | 1.00 | 1.31(0.43 to 3.93) | 1.57(0.52 to 4.71) | 2.75(0.94 to 8.00) | 0.06 |
| Oleic acid~ | 1.00 | 2.60(0.76 to 8.84) | 2.36(0.67 to 8.28) | **4.99(1.53 to 16.32)** | **0.01** |
| Linoleic acid+ | 1.00 | 1.08(0.38 to 3.08) | 1.54(0.55 to 4.30) | 1.97(0.73 to 5.35) | 0.14 |
| Alpha-Linolenic acid+ | 1.00 | 0.84(0.27 to 2.63) | 1.93(0.70 to 5.33) | 1.53(0.53 to 4.40) | 0.21 |
| Arachidonic acid+ | 1.00 | 0.99(0.37 to 2.60) | 0.94(0.34 to 2.62) | 1.22(0.46 to 3.21) | 0.72 |
| Linoleic acid/Alpha-Linolenic acid+ | 1.00 | 1.42(0.53 to 3.82) | 1.39(0.50 to 3.83) | 1.37(0.49 to 3.83) | 0.58 |
| P/S ratio | 1.00 | 1.07(0.42 to 2.74) | 0.58(0.19 to 1.72) | 1.16(0.45 to 2.94) | 0.97 |
| Omega6/Omega3+ | 1.00 | 1.79(0.62 to 5.12) | 1.53(0.51 to 4.58) | 2.38(0.83 to 6.81) | 0.15 |

[c] Intake was categorised according to nutrient quartile of daily consumption
*Adjusted for age group, educational level, history of parental atopy, smoking habits, and body mass index
OR: Odds ratio, CI: confidence intervals, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, P/S ratio: polyunsaturated to saturated ratio.
~ monounsaturated fatty acid
+ polyunsaturated fatty acid
**Bold fonts:** indicate significance

**Table 10. Associations Between Dietary Intake of Fatty Acids and Atopic Eczema in Adults**

| Men | Adjusted OR with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 1.44(0.79 to 2.63) | 1.16(0.63 to 2.16) | 0.75(0.39 to 1.44) | 0.31 |
| SFA | 1.00 | 0.76(0.41 to 1.38) | 0.82(0.45 to 1.49) | 0.54(0.28 to 1.01) | 0.08 |
| MUFA | 1.00 | 0.78(0.42 to 1.43) | 1.08(0.60 to 1.94) | 0.56(0.29 to 1.06) | 0.19 |
| PUFA | 1.00 | 1.10(0.58 to 2.09) | 1.40(0.75 to 2.61) | 1.30(0.69 to 2.43) | 0.32 |
| Palmitoleic acid~ | 1.00 | 1.48(0.80 to 2.74) | 1.28(0.68 to 2.40) | 0.81(0.41 to 1.59) | 0.50 |
| Oleic acid~ | 1.00 | 0.90(0.49 to 1.68) | 1.24(0.68 to 2.27) | 0.46(0.23 to 0.92) | 0.10 |
| Linoleic acid+ | 1.00 | 0.94(0.49 to 1.82) | 1.71(0.92 to 3.19) | 1.07(0.56 to 2.06) | 0.42 |
| Alpha-Linolenic acid+ | 1.00 | 1.20(0.64 to 2.25) | 1.10(0.58 to 2.06) | 0.90(0.47 to 1.73) | 0.71 |
| Arachidonic acid+ | 1.00 | 0.77(0.41 to 1.47) | 0.76(0.39 to 1.48) | 1.57(0.85 to 2.89) | 0.15 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.29(0.67 to 2.49) | 1.69(0.89 to 3.21) | 1.35(0.70 to 2.59) | 0.32 |
| P/S ratio | 1.00 | 1.56(0.81 to 3.01) | 1.44(0.74 to 2.81) | 1.77(0.93 to 3.38) | 0.12 |
| Omega6/Omega3 + | 1.00 | 1.45(0.75 to 2.80) | 1.58(0.82 to 3.04) | 1.49(0.78 to 2.85) | 0.23 |

| Women | Adjusted OR* with 95% CI | | | | |
|---|---|---|---|---|---|
| Intake [c] g/1000Kcal/day | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P for Trend |
| Total fat | 1.00 | 1.18(0.59 to 2.35) | 1.01 (0.50 to 2.03) | 0.98(0.49 to 1.98) | 0.85 |
| SFA | 1.00 | 1.04(0.50 to 2.14) | 1.62(0.81 to 3.24) | 1.08(0.53 to 2.21) | 0.55 |
| MUFA | 1.00 | 1.12(0.56 to 2.24) | 0.88(0.43 to 1.80) | 1.19(0.60 to 2.38) | 0.79 |
| PUFA | 1.00 | 0.88(0.44 to 1.74) | 0.84(0.42 to 1.69) | 0.82(0.41 to 1.64) | 0.57 |
| Palmitoleic acid~ | 1.00 | 1.12(0.55 to 2.30) | 1.75(0.87 to 3.50) | 1.07(0.52 to 2.21) | 0.57 |
| Oleic acid~ | 1.00 | 0.81(0.40 to 1.64) | 0.94(0.47 to 1.88) | 1.04(0.52 to 2.08) | 0.82 |
| Linoleic acid+ | 1.00 | 1.16(0.59 to 2.30) | 0.75(0.36 to 1.53) | 1.02(0.51 to 2.04) | 0.75 |
| Alpha-Linolenic acid+ | 1.00 | 0.98(0.50 to 1.91) | 0.77(0.38 to 1.54) | **0.47(0.22 to 0.98)** | **0.04** |
| Arachidonic acid+ | 1.00 | 2.01(1.01 to 4.02) | 1.10(0.53 to 2.28) | 1.19(0.57 to 2.47) | 0.91 |
| Linoleic acid/Alpha-Linolenic+ | 1.00 | 1.09(0.52 to 2.29) | 1.79(0.88 to 3.65) | 1.95(0.96 to 3.98) | **0.03** |
| P/S ratio | 1.00 | 1.57(0.78 to 3.19) | 2.19(1.08 to 4.45) | 0.80(0.37 to 1.72) | 0.82 |
| Omega6/Omega3 + | 1.00 | 1.36(0.65 to 2.85) | 1.74(0.84 to 3.59) | 2.02(0.98 to 4.15) | **0.04** |

[c] Intake was categorised according to nutrient quartile of daily consumption

*Adjusted for age group, educational level, history of parental atopy, smoking habits, and body mass index

OR: Odds ratio, CI: confidence intervals, SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, P/S ratio: polyunsaturated to saturated ratio.

~ monounsaturated fatty acid

+ polyunsaturated fatty acid

**Bold fonts:** indicate significance

**Table 11. Associations Between Dietary Intake of Antioxidants and Bronchial Hyperresponsiveness[a] in Adults**

| Men | Adjusted OR with 95% CI | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.06 | (0.44-2.54) | 1.18 | (0.51-2.76) | 1.82 | (0.82-4.06) | 0.41 |
| Carotene | 1.00 | 0.99 | (0.45-2.19) | 0.84 | (0.37-1.92) | 0.94 | (0.42-2.11) | 0.82 |
| Vitamin E | 1.00 | 0.97 | (0.44-2.11) | 0.94 | (0.42-2.09) | 0.80 | (0.35-1.85) | 0.76 |
| Vitamin C | 1.00 | 0.38 | (0.16-0.92) | 0.69 | (0.32-1.48) | 0.76 | (0.35-1.63) | 0.11 |
| Zinc | 1.00 | 0.73 | (0.35-1.55) | 0.62 | (0.29-1.35) | **0.29** | **(0.11-0.73)** | 0.05 |

| Women | Adjusted OR* with 95% CI | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 0.66 | (0.29-1.53) | 0.77 | (0.33-1.78) | 1.36 | (0.61-3.04) | 0.73 |
| Carotene | 1.00 | 2.02 | (0.89-4.57) | 1.09 | (0.43-2.74) | 1.99 | (0.86-4.59) | 0.14 |
| Vitamin E | 1.00 | 1.07 | (0.49-2.37) | 0.94 | (0.40-2.17) | 1.23 | (0.54-2.79) | 0.84 |
| Vitamin C | 1.00 | 0.98 | (0.42-2.30) | 1.71 | (0.77-3.77) | 0.88 | (0.36-2.11) | 0.64 |
| Zinc | 1.00 | 1.43 | (0.63-3.26) | 1.30 | (0.57-2.96) | 1.10 | (0.45-2.68) | 0.48 |

[c] Intake was categorised according to food quartile of daily consumption
[a] BHR: bronchial hyperresponsiveness. Defined as 20% drop in $FEV_1$ during methacholine provocation test.
*Adjusted for age, educational level, history of parental atopy, smoking habits, and body mass index
OR: Odds ratio, CI: confidence intervals
**Bold fonts:** indicate significance

**Table 12. Associations Between Dietary Intake Antioxidants and Allergic Sensitisation in Adults**

| Men | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Adjusted OR with 95% CI | | | | |
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.98 | (1.03-3.79) | 1.67 | (0.86-3.25) | 1.43 | (0.73-2.82) | 0.07 |
| Carotene | 1.00 | 0.84 | (0.45-1.56) | 0.87 | (0.47-1.64) | 0.77 | (0.41-1.45) | 0.46 |
| Vitamin E | 1.00 | 0.86 | (0.47-1.59) | 0.81 | (0.43-1.50) | 0.67 | (0.35-1.27) | 0.32 |
| Vitamin C | 1.00 | 0.60 | (0.80-0.71) | 0.32 | (0.44-0.38) | 1.14 | (1.48-1.31) | 0.16 |
| Zinc | 1.00 | 0.97 | (0.51-1.86) | 1.75 | (0.96-3.22) | 0.77 | (0.39-1.51) | 0.64 |

| Women | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Adjusted OR* with 95% CI | | | | |
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.42 | (0.65-3.13) | 1.84 | (0.82-4.10) | 2.06 | (0.94-4.56) | 0.10 |
| Carotene | 1.00 | 0.70 | (0.32-1.55) | 1.15 | (0.53-2.47) | 1.39 | (0.66-2.92) | 0.88 |
| Vitamin E | 1.00 | 1.08 | (0.53-2.22) | 0.62 | (0.29-1.34) | 0.80 | (0.37-1.72) | 0.52 |
| Vitamin C | 1.00 | 1.74 | (0.83-3.66) | 0.56 | (0.24-1.34) | 1.45 | (0.68-3.08) | 0.61 |
| Zinc | 1.00 | 0.90 | (0.43-1.88) | 1.11 | (0.54-2.29) | 0.72 | (0.32-1.62) | 0.77 |

[c] Intake was categorised according to food quartile of daily consumption
[a] Defined as at least one specific IgE concentration of $\geq 0.7$ k U/l (RAST Class$\geq 2$)
*Adjusted for age, educational level, history of parental atopy, smoking habits, and body mass index
OR: Odds ratio, CI: confidence intervals
**Bold fonts:** indicate significance

**Table 13. Associations Between Dietary Intake of Antioxidants and Hay Fever in Adults**

| Men | | | | | | | | Adjusted OR with 95% CI |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.40 | (0.56-3.48) | 0.77 | (0.28-2.16) | 1.95 | (0.82-4.65) | 0.44 |
| Carotene | 1.00 | 0.48 | (0.17-1.34) | 0.98 | (0.41-2.36) | 1.36 | (0.60-3.08) | 0.80 |
| Vitamin E | 1.00 | 2.80 | (0.97-8.16) | 4.06 | (1.44-11.42) | 1.66 | (0.53-5.25) | 0.04 |
| Vitamin C | 1.00 | 0.72 | (0.29-1.80) | 1.20 | (0.53-2.73) | 0.74 | (0.30-1.84) | 0.72 |
| Zinc | 1.00 | 1.93 | (0.81-4.59) | 1.65 | (0.68-4.01) | 0.54 | (0.17-1.66) | 0.45 |

| Women | | | | | | | | Adjusted OR with 95% CI |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.50 | (0.50-4.46) | 3.04 | (1.10-8.45) | 1.38 | (0.45-4.27) | 0.17 |
| Carotene | 1.00 | 0.77 | (0.27-2.16) | 1.33 | (0.51-3.45) | 1.03 | (0.39-2.76) | 0.95 |
| Vitamin E | 1.00 | 1.08 | (0.41-2.85) | 1.35 | (0.53-3.44) | 0.82 | (0.30-2.28) | 0.85 |
| Vitamin C | 1.00 | 1.60 | (0.64-4.03) | 0.87 | (0.31-2.43) | 0.69 | (0.24-2.00) | 0.93 |
| Zinc | 1.00 | 1.15 | (0.45-2.94) | 1.29 | (0.51-3.25) | 0.56 | (0.19-1.67) | 0.99 |

[c] Intake was categorised according to food quartile of daily consumption
[a] Defined as at least one specific IgE concentration of $\geq 0.7$ k U/l (RAST Class$\geq$2)
*Adjusted for age, educational level, history of parental atopy, smoking habits, and body mass index
OR: Odds ratio, CI: confidence intervals
**Bold fonts:** indicate significance

**Table 14. Associations Between Dietary Intake of Antioxidants and Atopic Eczema in Adults**

| Men | Adjusted OR with 95% CI | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 1.15 | (0.62-2.12) | 0.95 | (0.51-1.80) | 0.94 | (0.50-1.78) | 0.96 |
| Carotene | 1.00 | 1.34 | (0.72-2.50) | 1.02 | (0.54-1.94) | 0.89 | (0.46-1.72) | 0.78 |
| Vitamin E | 1.00 | 1.06 | (0.56-2.02) | 1.10 | (0.58-2.08) | 1.41 | (0.75-2.63) | 0.53 |
| Vitamin C | 1.00 | 1.77 | (0.89-3.52) | 2.15 | (1.10-4.22) | 2.00 | (1.02-3.91) | **0.02** |
| Zinc | 1.00 | 1.61 | (0.86-3.00) | 1.16 | (0.61-2.20) | 0.98 | (0.50-1.89) | 0.44 |

| Women | Adjusted OR with 95% CI | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intake [c] Mg/1000Kcal/day | 1st Quartile | 2nd Quartile | | 3rd Quartile | | 4th Quartile | | P for Trend |
| Vitamin A | 1.00 | 0.78 | (0.39-1.56) | 0.72 | (0.36-1.47) | 0.95 | (0.48-1.90) | 0.48 |
| Carotene | 1.00 | 0.83 | (0.41-1.71) | 1.45 | (0.72-2.88) | 0.86 | (0.42-1.77) | 0.95 |
| Vitamin E | 1.00 | 0.97 | (0.49-1.90) | 0.52 | (0.25-1.08) | 1.08 | (0.55-2.12) | 0.51 |
| Vitamin C | 1.00 | 1.29 | (0.65-2.54) | 0.82 | (0.40-1.65) | 0.57 | (0.27-1.18) | 0.60 |
| Zinc | 1.00 | 1.34 | (0.67-2.71) | 1.13 | (0.55-2.30) | 1.32 | (0.65-2.72) | 0.44 |

[c] Intake was categorised according to food quartile of daily consumption
[a] Defined as at least one specific IgE concentration of $\geq 0.7$ k U/l (RAST Class$\geq$2)
*Adjusted for age, educational level, history of parental atopy, smoking habits, and body mass index
OR: Odds ratio, CI: confidence intervals
**Bold fonts:** indicate significance

# 4 Discussion

## 4.1 Methodology

In cross-sectional studies the time frame between exposition and the disease expression is considerable, therefore causality can not be demonstrated. Nonetheless, this epidemiological design allows the postulation of hypothesis based in description of the prevalence of any given condition in a study population, delivering valuable evidence and setting the basis for further research. The instruments of data collection (ECRHS and MONICA study) as well as the methodology were validated. All data were checked for plausibility. Although three day weighed records have some limitations, as do all other dietary assessment methods, they allowed precise nutrient calculations. (Table 15/Attachments ).

## 4.2 Study Relevance

This study suggests that dietary fat intake is associated with the risk for allergic sensitisation and disease manifestation, with somewhat different findings in men and women. In both men and women, there were indications for an increased risk with a high intake of omega-6 and a low intake of omega-3 fatty acids. In women, also total fat and high monounsaturated fatty acids intake were associated with an increased risk of suffering atopic manifestations. This data adds to the limited epidemiological evidence available on associations between dietary habits and atopic disease prevalence. Most of the published studies were conducted in children, and dietary intake was assessed using simple food item lists, not always well validated, or on an aggregated level. Previous epidemiological studies in Germany used data on preferred types of bread spread as surrogate for the type of consumed fat and without specific fatty acid determination. They did not consider that the total fat intake from the diet may influence the immune response.[7-8-9-49]

## 4.3 Fat and Fatty Acids Intake

Our finding a relation of margarine consumption to hay fever prevalence in males is consistent with the findings from a cross-sectional study conducted in children.[7] Also, results from a Japanese study support the role of polyunsaturated fatty acids intake, assessed with a food frequency protocol, in the aetiology of seasonal allergic-rhinoconjunctivitis in women.[9] High levels of omega-6 fatty acids may alter the immune response favouring the synthesis of pro-inflammatory mediators, thus enhancing the response to allergens.[2] Moreover, the ratio of omega-6 to omega-3 fatty acids as well as the supply of the omega-6 metabolite arachidonic acid were reported to modulate cell membrane composition, gene expression, gut permeability and the activity of the lymphocytes and macrophages, as well as enhancing IgE production.[2-49-50-51-52]

In most published studies, the intake of total and omega-6 polyunsaturated fatty acids intake was inferred from margarine consumption.[1-2-7] Depending on the conditions of its production, margarine is usually a good source of omega-6 polyunsaturated fatty acids, but is often also rich in monounsaturated and trans-fatty acids. We did not analyse potential effects of trans fatty acids since no reliable information on trans fatty acids was available from the German Food Composition Database. Trans fatty acids appear to impair the desaturation of linoleic acid and $\alpha$-linolenic acid to their long chain metabolites.[53] Results from a European ecological study support the hypotheses that high monounsaturated fatty acids intake might promote the development of allergic sensitisation.[10] We found these similar effects in women, such as an association of specific high IgE concentration with high monounsaturated fatty acids intake, and also with high total fat and SFA consumption. Moreover, we found a positive association between the intake of the two major monounsaturated fatty acids, palmitoleic and oleic acids, in relation to allergic sensitisation. Consistently, high fat intakes, a high monounsaturated fatty acid intake—specifically a high consumption of oleic acid—were also associated with hay fever. New evidence is also consistent with these findings. A very recent paper on data of a German prospective study provided further evidence of a positive association between high intake of oleic acid with hay fever prevalence.[23] This research group speculated that the intake of oleic acid correlates with a high intake of

trans fatty acids because both are delivered by the same food sources.[23] Kompauer et al., in a publication posterior to this study, analyzed the blood samples of the ECRHS population, and as a result, corroborated the positive association between allergic sensitisation and oleic acid levels in serum phospholipids. Also consistently with the present epidemiological findings, the positive association between hay fever and seric arachidonic acid was also confirmed.[54] Our data suggests that a high consumption of alpha linolenic acid was negatively associated with the prevalence of eczema. Horrobin formulated the hypothesis that atopic eczema may be a minor inherited abnormality of EFA metabolism. Thus, atopic eczema may be linked to different pathophysiological mechanisms rather than other atopic manifestations. [55]

Due to the low fish intake of the analysed sample, this study was unable to find an inverse association between fish consumption and atopic disease, such as observed in the epidemiological study of Haby and Peat.[8] Subsequently, no associations between omega-3 fatty acids consumption and atopic disease were found.

This study was unable to determinate any association between dietary fat, asthma and BHR. The low prevalence of self-reported doctor's diagnosis of asthma in the study sample impeded the application of multiple statistical tests. Additionally, the lack of significant associations between BHR and fatty acid intake may be related to the reduced number of participants on the methacholine provocation test, thus causing a loss of statistical power.

## 4.4 Fruit, Vegetable and Antioxidants Intake

As another potential covariable, a decreased fruit and vegetable consumption with a low intake of antioxidants was suggested to be associated with recent increases in asthma prevalence.[12-15-56] According to the present data, high vegetable consumption showed an inverse association with allergic sensitisation in men. Similarly, in women, a moderate and a normal vegetable products intake was also inversely associated with allergic sensitisation. Data to compare those findings are scarce. Heinrich et al. found in an ecological study an inverse association between mean fruit intake and the prevalence of allergic sensitisation.[10] Deveraux et al. affirmed that dietary intake of fruit,

antioxidant vitamins, and selenium is increasingly being associated with a reduced prevalence of asthma and wheezing syndromes.[12] A French study conducted in women, suggested that the intake of some vegetables may decrease the prevalence of adult asthma.[16] Among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms and higher lung function. This effect was observed even at low levels of fruit consumption (one or two servings per week vs. less than one serving per week), which suggests that a small increase in the dietary intake could have a beneficial effect in this group.[57] Further studies among children and young adults have consistently shown a positive impact of fresh fruit and vegetable intake, although the type of beneficial foods varies across studies.[17] Some evidence is available for vitamin E and C; their low consumption is related to increased prevalence and incidence of asthma, wheezing, lower levels of lung function and hay fever.[1-12-20-23] A recent German study observed a negative association between high plasma carotenoids levels and the prevalence of allergic rhinitis and gamma-tocopherol concentration with allergic sensitisation.[58]

Despite the observed negative association between high vegetable intake and sensitisation, which allows to hypothesize that antioxidants constituents of vegetables and fruit may protect against atopic diseases, this study failed to demonstrate any association between vitamin A, carotene, vitamin C, and vitamin E intake and allergy outcomes variables as sensitisation and hay fever in both analyzed strata. Conversely, vitamin C has been shown in several cross-sectional and case-controlled studies to be associated with a reduced asthma risk. However, a large intervention study on vitamin C among adults failed to demonstrate any protective effect of vitamin C.[58] The lack of findings in this study could reflect some food composition data limitations.

Furthermore, other potent antioxidants and mineral constituents of vegetables and fruits, such as selenium, iron, manganese, and flavonoids, may influence the immune response and were not assessed.[60-61] Three-day records may have limitations in reflecting habitual antioxidants consumption, due to the irregular intake among the days and seasonal variations of fruit and vegetable availability. The variability of protective foods across published studies might also be linked to different dietary patterns characteristic of the studied populations.

The positive association computed for high vegetable intake, vitamin C and atopic eczema could be a proxy variable, denoting that men who are suffering skin lesions follow a healthier diet. We consider unlikely that the observed OR indicates a possible specific food allergy association.

## 4.5 Gender Differences

Most statistically significant effects in relation to fat consumption and allergic disease in our study were limited to women. Gender-specific dietary patterns might partly explain the observed differences. In our study, significantly higher consumption of? absolute butter, margarine in men were observed. In addition, the development of atopic diseases may underlie different gender-linked physiological mechanisms. Furthermore, we could not exclude that the lower participation rate in women induced bias.

We did not consider alcohol consumption as confounder, which is usually markedly higher in men and might enhance oxidative stress and modulate immune responses.[17-21]

## 4.6 Ongoing Related Research

The possible modulating role of the intestinal microflora, the dietary intake of non-digestible carbohydrates that serve as substrates for colonic bacteria, and of intestinal trophic factors has received increased attention following indications that administration of specific lactobacilli in early life may reduce the risk of atopic dermatitis.[62] Thus, the effects of dietary components other than fat and antioxidants intake on the immune response needs to be considered in further evaluations. Another promising field of research focuses on the importance of antenatal nutrition in the development of atopy later in life. Deveraux et al. recently delivered reliable evidence pinpointing that dietary modification or supplementation with vitamin E, vitamin C, and zinc during pregnancy modifies the risk of developing childhood asthma and eczema.[63-64] Emerging evidence suggests that exposures during pregnancy and the early postnatal period can modify gene expression and disease propensity, suggesting that

early exposures to dietary immunomodulatory factors, including PUFA, may shape the development of atopic disease [65-66-67-68] A prospective study concluded recently that the development of atopic diseases in early childhood is associated with prenatal exposure to n-6 vs. n-3 fatty acids, but also observed inconsistencies between different atopy manifestations. [69]

Innovative research is focusing on common genetic variations, evidencing the presence of polymorphisms in the fatty acid desaturase gene cluster, affecting the PUFA and LC-PUFA status on humans. [70-71]

Finally, based on the analysis of fatty acids in serum phospholipids from this same studied population, new findings emerged. Results were consistent with the present study showing positive associations between hay fever and arachidonic acid, and also between allergic sensitisation and oleic acid. An analysis of the association of fatty acids in serum phospholipids with lung function and bronchial hyperresponsiveness established that a high concentration of docosahexaenoic acid in serum phospholipids may have a protective effect on lung function. Moreover, no association between the n6/n3-ratio in serum-phospholipids and hay fever or allergic sensitization was observed.[72-73-74]


## 4.7 Conclusion

Given the large number of associations tested in this study, some of the founded effects may be due to chance. However, we hypothesize that consistency across outcome measurements, such as atopic sensitisation and hay fever, and independent effects observed between highly correlated fatty acids intake and atopy outcomes, reflect a valid pattern of associations.

Based on the results of this study and previously published results, we hypothesize that an excess of fat or imbalance in fat intake, particularly of monounsaturated fatty acids, could alter immune function and increase the risk of an allergic reaction. This data cannot demonstrate a causal association between fat consumption and atopy, in which case diet would be a modifiable risk factor and dietary manipulation might serve as a useful tool in public health programs oriented to prevent

and treat allergic disease. The development of dietary guidelines for the population in general and for individuals at risk of suffering atopic disease would be a challenge.

The complexity of this topic requires further scientific investigations. Prospective intervention trials would offer an opportunity to investigate these hypotheses, which hold a great potential for health prevention strategies.

# 5 Abstract

It was hypothesized that high fat consumption, specifically from polyunsaturated fatty acids, may be positively related to atopic disease prevalence. On the other hand, antioxidants constituents of the diet may exert a protective effect against disorders related to the immune system.

The aim of the present cross-sectional study was to assess the relationship between dietary intake of selected foods, fatty acids, and dietary antioxidants with atopic disease prevalence in adults.

Data from the European Community Respiratory Health Survey in Erfurt, combined with a three-day weighed records from the MONICA dietary survey, was used. Complete data was available from 469 men and 333 women aged between 20 and 64 years. Multiple logistic regression was applied comparing the highest with the lowest quartile of dietary exposures and linear trends were tested stratified by gender. In men, margarine intake and a high ratio of omega-6 to omega-3 fatty acids were positively associated with hay fever (p for trend 0.03 and 0.04 respectively). In women, a high intake of total fat, palmitoleic and oleic acids were positively associated with sensitisation (aOR 2.42, p for trend 0.11, 3.04, p for trend 0.02, 2.47, p for trend 0.03 respectively). A high total fat (aOR 4.51, p for trend 0.05), high monounsaturated fatty acids (aOR 3.04, p for trend 0.01), and high oleic acid consumption (aOR 4.99, p for trend 0.01) were positively associated with hay fever.

No clear relationships between antioxidant nutrients consumption and allergic disease were observed.

Whilst an excessive intake of fat or imbalance in fat intake, particularly of monounsaturated fatty acids, increased the risk for hay fever and allergic sensitisation in women. Mainly, no significant associations were found for men. Dietary factors were mostly not related with prevalence rates of bronchial hyperresponsiveness and atopic eczema neither in men nor in women.

# 5 Zusammenfassung

Es besteht die Hypothese, dass eine hohe Fettaufnahme, besonders von mehrfach ungesättigten Fettsäuren, positiv mit der Prävalenz von atopischen Erkrankungen korreliert. Andererseits könnte die Aufnahme von Antioxidantient aus der Nahrung gegen immunassozierte Störungen protektiv wirken.

Ziel der vorliegenden Querschnittstudie ist, den Zusammenhang zwischen der Einnahme ausgewählter Nahrungsmitteln, Fettsäuren und Antioxidantien aus der Nahrung sowie die Prävalenz von atopischen Erkrankungen bei Erwachsenen zu evaluieren.

Daten von der Europäischen Studie zur Prävalenz von Atemwegserkrankungen in Erfurt, zusammen mit von der MONICA Ernährungsuntersuchung stammenden drei Tage-Wäge-Protokolle wurden analysiert. Vollständige Daten von 469 Männern und 333 Frauen im Alter von 20 bis 64 Jahren wurden erfasst. Geschlechtstratifizierte multiple logistische Regressionmodelle inklusive lineare Trends wurden vorgenommen, um die höchste und niedrigste Einnahmequartile der diätetischen Exposition zu vergleichen.

Die Prävalenz von Heuschnupfen wurde sowohl mit der Margarinaufnahme als auch mit einem hohem Omega-6 zu Omega-3 Fettsäurenratio bei Männern positiv assoziiert (beziehungsweise, p für Trend 0,03 and 0,04).

Bei Frauen wurde eine hohe Gesamtfettaufnahme sowie ein erhöhter Palmitoleinsäure- und Ölsäureverzehr mit allergischen Sensibilisierung positiv assoziiert (bzw. aOR 2,42, p für trend 0,11; 3,04, p für trend 0,02; 2,47, p für trend 0,03). Ein hoher Verzehr von Gesamtfett-, einfach ungesättigtet Fettsäuren und Ölsäure wurde mit der Heuschnupfenprävalenz positiv verbunden.

Es wurden keine eindeutigen Zusammenhänge zwischen der Aufnahme von Antioxidantienten aus der Nahrung und allergischen Erkrankungen festgestellt.

Während bei Frauen eine überhöhte Zufuhr von Fett oder eine unausgeglichene Fettaufnahme, insbesondere der einfach ungesättigten Fettsäuren das Risiko für Heuschnupfen- und allergische Sensibilisierung inkrementieren, wurden bei Männern meistens keine signifikante Assoziationen gefunden.

Weder bei den Männern noch bei den Frauen bestand ein Zusammenhang zwischen diätetische Faktoren und der Prävalenz von bronchialen Hyperreaktivitäts- und atopischen Ekzem.

# 6 Acknowledgements

# 7 Glossary of common terms

**Allergen:** the source of an allergy-producing substance, the allergy-producing substance itself, or one or more of the specific proteins that make up the substance and provoke the immune response, including IgE antibodies. They are often common, usually harmless substances such as pollen, mold spores, animal dander, dust, foods, insect venoms, and drugs.

**Allergic diseases:** represent the clinical manifestations of adverse immune responses (including IgE responses), following repeated contact with usually harmless substances such as pollen, mold spores, animal dander, dust, foods, insect venoms, and drugs; include diseases of the atopic diathesis as well as diseases which may have an allergic component.

**Allergic sensitisation**: outcome variable defined as at least one specific immunoglobulin E concentration of ≥0.7 k UL- (radioallergosorbent test class ≥2).

**Asthma:** is a chronic inflammatory disease of the airways characterized by airway obstruction which is at least partially reversible with or without medication, and increased bronchial responsiveness to a variety of stimuli.

**Atopy:** the genetic tendency to develop the "classical" allergic diseases, namely, allergic rhinitis, asthma, and atopic dermatitis. Atopy is typically associated with a genetically determined capacity to mount IgE responses to common allergens, especially inhaled allergens and food allergens.

**Bronchial hyperresponsiveness**: increased bronchial responsiveness was defined as 20% or greater fall in baseline forced expiratory volume in one second before a maximal cumulative dose of methacholine (2 mg) was administered.

**Eczema:** is an inflammatory disease of the skin with lesions that can be erythematous, edematous, papular, crusting, lichenified, scaling, itching, or burning. Sometimes skin discoloration can occur.

**Hay fever:** is an IgE-mediated reaction of the nasal mucosa to one or more seasonal allergens, characterized by inflammation of the mucous membranes of the nose with symptoms of sneezing, itching, nasal discharge, and congestion

**Spirometry (FEV1):** pulmonary measurements made with a spirometer to evaluate airway obstruction, and if so, whether it is reversible with a bronchodilator. It is mandatory to diagnose and characterize asthma severity.

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# 9 ATTACHMENTS

**Table 15. Advantages and Disadvantages of the Prospective Three-Day Dietary Intake Records.**

| Advantages | Disadvantages |
|---|---|
| • The study subject is not required to recall food intake, thus avoiding memory deficiencies.<br><br>• Timeframe is predefined.<br><br><br>• Consumed and wasted food is accurately recorded.<br><br>• Allows precise nutrient intake calculations.<br><br><br>• Food habits could be described. | • Involves a high commitment level from the participant.<br>• Demands more financial resources as well as intensive time investment.<br>• Health-conscious subjects could be overrepresented.<br>• Out-of-home consumption is often inaccurately recorded.<br>• Unfeasible in prolonged study time or larger populations.<br>• Trained observers are requested.<br>• Food intake could be altered, especially while the subject is aware of being observed.<br>• Coding of the items for data management is work-intensive. |

**Table 16. Selected Epidemiological Studies Evidencing Relationships Between Nutrient Intakes and Atopic Diseases.**

| Authors/Country | Publication | Study Design | Study Population/Age range | Method of Data Collection | Outcome | Considered Confounders | Results |
|---|---|---|---|---|---|---|---|
| Haby, Peat. Australia | Thorax 2001 | Cross-sectional | Children (3-5 years) n=974 | Questionnaire/ Fat intake | Asthma (Diagnosed by a physician/symptomatic in the last 12 months) Atopy /Prick test (as co-variable) | Number of siblings Infections | Atopy(+) Infections(+) PUFA(+) Number of siblings(-) Breast feeding(-) |
| Wakai, Okamoto Japan | AEP 2001 | Cross-sectional | Women (nurses) (22-57 years) n=1012 | Questionnaire/ FFQ | Seasonal Allergy (Rhinoconjunctivitis) | Age, genetic predisposition, diagnosed atopy, smoking | PUFA(+) |
| Bolte, Frye Germany | Am J Respir Crit Care Med. 2001 | Cross-sectional | Children (5-14 years) n=2348 | Questionnaire/ Fat intake | Sensitisation (Rast I ) Rhinitis | Age, living conditions, educational level of the parents, number of siblings, BMI | Margarine(+) |
| Heinrich, Hölscher Germany | Eur Resp 2001 | Ecological Study | Adults n=3872 | ECRHS Dietary Surveys (records or recalls) 8 Centers | Sensitisation | Age, gender | MUFA(+) Fruits(-) |
| Barth, Weigl Switzerland | Eur J Derm 2001 | Cross-sectional | Adults n=116 | FFQ | Atopic Dermatitis (symptomatic) | ? | Nuts(+) Milk products, Fish, Eggs, Fruits (-) |

BMI: Body Mass Index, ECRHS: European Community Respiratory Health Survey, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, FFQ: Food frequency questionnaire, (+): positive association, (-): negative association.

## EUROPAISCHE KOMMISSION FÜR ATEMWEGSERKRANKUNGEN

LUNGENFUNKTIONSUNTERSUCHUNGEN ERGEBNISBOGEN

Projektnr. (Personal n.): ...................     Auswahlkriterien (Sample): ....    Area-Nr.033

Erfurt, den __ . __ . __

### BASIS SPIROMETRIE

1. Größe EL01GROE __.__ m, 2. Gewicht _____ kg, 3. Alter ____ , 4. Geschlecht EL02GEW   EL03ALT   EL04SEX   ml☐ w☐

5. Predicted FEV1 .. EL05FEV1

6. Initialer

| | FEV1 | FVC | PEF(1/s) |
|---|---|---|---|
| 1 | EL06FEV1 | EL06FVC1 | EL06PEF1 |
| 2 | EL06FEV2 | EL06FVC2 | EL06PEF2 |
| 3 | EL06FEV3 | EL06FVC3 | EL06PEF3 |
| 4 | EL06FEV4 | EL06FVC4 | EL06PEF4 |
| 5 | EL06FEV5 | EL06FVC5 | EL06PEF5 |

6.1 Anzahl der zurückgewiesenen Versuche ☐ EL067

7. Bester initialer FEV1 in % des vorhergesagten FEV1 Sollwertes   EL07FEV1

WENN DER BESTE AUSGANGS-FEV1    A) KLEINER ALS 70% DES SOLLWERTES
                                B) KLEINER ALS 1.5 LITER
MUSS EINE BRONCHODILATATION GEMACHT WERDEN, KEINE METHACHOLIN PROVOKATION.

### METHACHOLIN PROVOKATION

Hat der Teilnehmer/in die Einverständniserklärung unterschrieben?    NEIN   JA
                                   EL METHAC   ☐   ☐

Provokation mit Lösung _____ 8.   Kontroll FEV1 nach Inhalation mit Lösung:

8.1 Zwei technisch zufriedenstellende Ergebnisse: 1 EL0811   2 EL0812

8.2 Anzahl der zurückgewiesenen Versuche   ☐ EL082

9. Bester Kontroll-FEV1 (Post-diluent) in % des initialen FEV1   EL09FEV1

WENN DER BESTE KONTROLL FEV1 KLEINER ALS 90% DES BESTEN AUSGANGS-FEV1 IST, MIT METHACHOLIN PROVOKATION AUFHÖREN UND EINE BRONCHODILATATION MACHEN.

Wahl des langen oder kurzen Provokations-Protokolls

10. War einer der Fragen im Screening Fragebogen 1, 2, 3, 5 mit "JA" beantwortet?
     NEIN ☐        JA ☐   EL10

WENN "NEIN", KURZES PROTOKOLL, WENN "JA", LANGES PROTOKOLL.

11. Wird ein langes oder kurzes Protokoll durchgeführt? (1=lang 2=kurz)   ☐ EL11

Kurzes Protokoll:

WECHSLE ZUM LANGEN PROTOKOLL, wenn FEV1 unter 90% des Kontroll-FEV1 fällt,
BEENDE METHACHOLIN-PROVOKATION, wenn FEV1 unter 80% des Kontroll-FEV1 fällt.
            EL11F90 90% DES KONTROLL-FEV1 __.__

Langes Protokoll:

BEENDE METHACHOLIN-PROVOKATION, wenn FEV1 unter 80% des Kontroll-FEV1 fällt.
            EL11F80 80% DES KONTROLL-FEV1 __.__

---

## METHACHOLIN-PROVOKATION

laufende Prov.-Nr. EL11LFPN

laufende Nr. der Methacholin Lösungszubereitung EL11LOES der wievielte dieser EL11ANZ

| Dosis-Stufe | Kumul.Dosis | Verneblernr. | FEV1 | FEV1 | ungültige Vers. |
|---|---|---|---|---|---|
| 1 | 0.0078 mg | EL11NEB1 | EL11FEA1 | EL11FEB1 | EL11VER1 |
| 2 | 0.0156 | EL11NEB2 | EL11FEA2 | EL11FEB2 | EL11VER2 |
| 3 | 0.0312 | EL11NEB3 | EL11FEA3 | EL11FEB3 | EL11VER3 |
| 4 | 0.0625 | EL11NEB4 | EL11FEA4 | EL11FEB4 | EL11VER4 |
| 5 | 0.125 | EL11NEB5 | EL11FEA5 | EL11FEB5 | EL11VER5 |
| 6 | 0.25 | EL11NEB6 | EL11FEA6 | EL11FEB6 | EL11VER6 |
| 7 | 0.5 | EL11NEB7 | EL11FEA7 | EL11FEB7 | EL11VER7 |
| 8 | 1.0 | EL11NEB8 | EL11FEA8 | EL11FEB8 | EL11VER8 |
| 9 | 2.0 mg | EL11NEB9 | EL11FEA9 | EL11FEB9 | EL11VER9 |

12. Warum wurde die Methacholin-Provokation beendet?      EL12
     A) Ende vom Test mit 2 mg wurde erreicht
     B) FEV1-Abfall von 20% erreicht                    1☐
     C) 2 reproduzierbare Atemstöße nicht durchführbar    2☐
     D) Teilnehmer/in wünschte Abbruch                  3☐
     E) andere (bitte angeben)..........................................   4☐
                                               5☐

Reversibilität der Bronchokonstriktion

13. FEV1 und FVC

    13.1 Die zwei ersten technisch guten Ergebnisse      FEV1       FVC
        (bis zu 5 Versuche)                      1 EL131FEV   EL131FVC
                                        2 EL132FEV   EL132FVC

    13.2 Anzahl der ungültigen Versuche          EL132ANZ ☐

14. Bester FEV1 in % vom Ausgangs-FEV1         EL14FEV1

15. Ist der FEV1 jetzt nicht schlechter als 10% unterhalb des Ausgangs-FEV1
EL15   NEIN ☐      JA ☐      Wenn JA, okay, wenn NEIN weiter Broncholyse.

### ALLEINIGE BRONCHOLYSE

Hat der Teilnehmer/in die Einverständniserklärung unterschrieben?    NEIN   JA
                             ELBRONCH   ☐   ☐

16. FEV1 und FVC

    16.1 Die zwei ersten technisch guten Ergebnisse      FEV1       FVC
        (bis zu 9 Versuche)                      1 EL161FEV   EL161FVC
                                        2 EL162FEV   EL162FVC

    16.2 Anzahl der ungültigen Versuche
                              EL162ANZ ☐
                              Untersucher . . . . . .

12. Haben Sie Schwierigkeiten beim Gehen aus anderen Gründen als aus Herz- oder Lungenerkrankungen ?

EH12    NEIN ❏   JA ❏

WENN "JA": 12.0 WELCHE ?:_____
UND SETZE MIT FRAGE 13 FORT

WENN "NEIN":

12.1. Werden Sie kurzatmig wenn Sie schneller oder bergauf gehen ?

EH121    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 13, WENN "JA":

12.1.1. Werden Sie kurzatmig, wenn Sie mit anderen Leuten Ihres Alters im Ebenen gehen ?

EH1211    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 13, WENN "JA":

12.1.1.1. Müssen Sie zum Luftholen stehen bleiben, wenn Sie in Ihrem eigenen Tempo gehen ?

EH12111    NEIN ❏   JA ❏

## Asthma

13. Haben Sie jemals Asthma gehabt ?

EH13    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 14, WENN "JA":
13.1. Wurde dies durch einen Arzt bestätigt ?

EH131    NEIN ❏   JA ❏

13.2. Wie alt waren Sie, als Sie Ihren ersten Asthmaanfall hatten ?    Jahre ❏❏

EH132

13.3. Wie alt waren Sie, als Sie Ihren letzten Asthmaanfall hatten ?    Jahre ❏❏

EH133

13.4. In welchen Monaten haben Sie üblicherweise Asthmaanfälle ?    NEIN JA

| | | NEIN | JA |
|---|---|---|---|
| 13.4.1. | Januar / Februar    EH1341 | ❏ | ❏ |
| 13.4.2. | März / April    EH1342 | ❏ | ❏ |
| 13.4.3. | Mai / Juni    EH1343 | ❏ | ❏ |
| 13.4.4. | Juli / August    EH1344 | ❏ | ❏ |
| 13.4.5. | September / Oktober    EH1345 | ❏ | ❏ |
| 13.4.6. | November / Dezember    EH1346 | ❏ | ❏ |

13.5. Hatten Sie in den letzten 12 Monaten einen Asthmaanfall ?

EH135    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 13.6. WENN "JA":

13.5.1. Wieviele Asthmaanfälle hatten Sie in letzten 12 Monaten ?    Anzahl: ❏❏
EH1351

13.6. Nehmen Sie gegenwärtig Medikamente gegen Asthma ein (einschließlich Inhalationen, Dosieraerosolen (Sprays) oder Tabletten) ?

EH136    NEIN ❏   JA ❏

## Andere Beschwerden

14. Haben Sie allergischen Schnupfen, zum Beispiel "Heuschnupfen" ?

EH14    NEIN ❏   JA ❏

15. Haben Sie jemals Ekzeme oder irgendwelche Arten von Hautallergien gehabt ?

EH15    NEIN ❏   JA ❏

16. Sind Sie allergisch auf Insektenstiche oder Bisse (ungewöhnlich stark) ?

EH16    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 17, WENN "JA":

16.1 Welche(s) Insekt(en) ? _____ EH161COD ❏ ❏

16.2. Welche Reaktion hatten Sie ?    NEIN JA

EH1621  16.2.1. Atemschwierigkeiten, Ohnmachtsgefühl, Übelkeit oder Fieber    ❏   ❏

EH1622  16.2.2. Rötung, Juckreiz oder Schwellung an der Einstichstelle    ❏   ❏

EH1623  16.2.3. andere (bitte angeben): _____    ❏   ❏

17. Haben Sie jemals irgend ein Problem mit Ihrer Atmung nach der Einnahme von Medikamenten gehabt ?

EH17    NEIN ❏   JA ❏

WENN "NEIN", GEHEN SIE ZU FRAGE 18, WENN "JA":

17.1. Welche(s) Medikament(e)?_____ EH171ME1 _____ ❏
_____ ❏

3

4

47. Benutzen Sie einen Luftbefeuchter ? (einschließlich irgendwelcher Befeuchtersysteme
in Ihrem Heizungssystems)       NEIN JA   ?

EH47 ☐ ☐   ☐

Wenn "Nein" oder "Weiss Nicht", gehen Sie zu Frage 48, wenn "Ja":

47.1. Welchen Typ von Befeuchter benutzen Sie ?     *(eine Wahl)*

A)   Befeuchter im Heizsystem eingebaut     EH471    1 ☐

B)   tragbar, kalter Dunst (Ultraschall oder Drehscheibe)    2 ☐

C)   tragbar, heisser Verdampfer    3 ☐

D)   andere *(bitte angeben)*: _____   4 ☐

47.2. Unter welchen Umständen benutzen Sie den Befeuchter ?    *(eine Wahl)*

A)   nur wenn jemand krank ist - in dessen Zimmer   EH472   1 ☐

B)   um das Haus zu befeuchten    2 ☐

C)   anderes *(bitte angeben)*:_____   3 ☐

## Tiere, Staub und Federn

48. Halten Sie eine Katze ?     NEIN JA

EH48   ☐ ☐

Wenn "Nein", gehen Sie zu Frage 49, wenn "Ja":

48.1. Darf Ihre Katze jemals in Ihr Schlafzimmer ?     NEIN JA

EH481 ☐ ☐

48.2. Bleiben alle Ihre Katzen außerhalb des Hauses ?     NEIN JA

EH482 ☐ ☐

49. Halten Sie einen Hund ?     NEIN JA

EH49   ☐ ☐

Wenn "Nein", gehen Sie zu Frage 50, wenn "Ja":

49.1. Darf Ihr Hund jemals in Ihr Schlafzimmer ?     NEIN JA

EH491 ☐ ☐

49.2. Bleiben alle Ihre Hunde außerhalb des Hauses ?     NEIN JA

EH492 ☐ ☐

50. Halten Sie irgendwelche Vögel ?     NEIN JA

EH50   ☐ ☐

Wenn "Nein", gehen Sie zu Frage 51, wenn "Ja":

11

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50.1. Werden irgendwelche dieser Vögel im Haus gehalten ?   NEIN JA

EH501 ☐   ☐

51. Als Sie ein Kind waren, hielt jemand in Ihrem Haushalt eines der folgenden
Haustiere ?     NEIN JA

51.1.   Katzen     EH5101 ☐   ☐

51.2.   Hunde     EH5102 ☐   ☐

51.3.   Pferde     EH5103 ☐   ☐

51.4.   Vögel     EH5104 ☐   ☐

51.5.   Meerschweinchen     EH5105 ☐   ☐

51.6.   Hamster     EH5106 ☐   ☐

51.7.   Mäuse     EH5107 ☐   ☐

51.8.   Ratten     EH5108 ☐   ☐

51.9.   Hasen, Kaninchen     EH5109 ☐   ☐

51.10. Gerbils     EH5110 ☐   ☐

51.11. Frettchen (Iltis)     EH5111 ☐   ☐

51.12. andere *(bitte angeben)*: _____ EH5112 ☐   ☐

52. Haben Sie jemals, wenn Sie sich in der Nähe von Tieren (z.B. Katzen, Hunden,
Pferden), von Federn (einschließlich Kissen, Steppdecken oder Daunen) oder in
einem staubigen Teil des Hauses aufhalten,     NEIN JA

52.1. angefangen zu husten ?     EH521 ☐   ☐

52.2. ein pfeifendes oder brummendes Atemgeräusch bemerkt ? EH522 ☐   ☐

52.3. ein Engegefühl in Ihrem Brustkorb bemerkt ?   EH523 ☐   ☐

52.4. Kurzatmigkeit gespürt ?     EH524 ☐   ☐

52.5. eine laufende oder verstopfte Nase bekommen oder angefangen zu
niesen ?     EH525 ☐   ☐

52.6. juckende oder tränende Augen bekommen ?    EH526 ☐   ☐

## Bäume, Gräser, Pflanzen, Blumen oder Pollen

53. Haben Sie jemals, wenn Sie sich in der Nähe von Bäumen, Gräsern oder
Blumen aufhalten oder wenn starker Pollenflug herrscht,     NEIN JA

53.1. angefangen zu husten ?     EH531 ☐   ☐

53.2. ein pfeifendes oder brummendes Atemgeräusch bemerkt ? EH532 ☐   ☐

53.3. ein Engegefühl in Ihrem Brustkorb bemerkt ?   EH533 ☐   ☐

12

58.2.1 - 4 Wieviel rauchen Sie jetzt durchschnittlich ?      Anzahl

    58.2.1. Zigaretten pro Tag      EH5821 ☐☐

    58.2.2. Zigarillos pro Tag      EH5822 ☐☐

    58.2.3. Zigarren pro Woche      EH5823 ☐☐

    58.2.4. Pfeifentabak in Gramm pro Woche      EH5824 ☐☐☐

58.3. Haben Sie das Rauchen reduziert oder aufgegeben ?      NEIN   JA

     EH583   ☐    ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 58.4. WENN "JA":

58.3.1. Wie alt waren Sie, als Sie das Rauchen reduziert bzw. aufgegeben haben ?
     Jahre

     EH5831 ☐☐

    58.3.2.1 - 4 Wieviel rauchten Sie früher durchschnittlich, bezogen auf die ganze
    Zeit, die Sie rauchten ?      Anzahl

    58.3.2.1. Zigaretten pro Tag      EH58321 ☐☐

    58.3.2.2. Zigarillos pro Tag      EH58322 ☐☐

    58.3.2.3. Zigarren pro Woche      EH58323 ☐☐

    58.3.2.4. Pfeifentabak in Gramm pro Woche      EH58324 ☐☐☐

58.4 Haben oder hatten Sie den Rauch inhaliert ?      NEIN   JA

     EH584   ☐    ☐

59. Sind Sie regelmäßig in den letzten 12 Monaten Tabakrauch anderer ausgesetzt
gewesen ? (Regelmäßig bedeutet an den meisten Tagen oder Nächten)   NEIN   JA

     EH59   ☐    ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 60 WENN "JA":

59.1. Wieviele Personen rauchen in Ihrem Haushalt regelmäßig außer Ihnen ?
     Anzahl

     EH591 ☐☐

59.2. Wird in dem Raum, in dem Sie arbeiten, regelmäßig von anderen geraucht?
     NEIN   JA

     EH592   ☐    ☐

59.3. Wieviele Stunden pro Tag sind Sie dem Tabakrauch anderer Leute ausgesetzt ?
     Stunden

     EH593 ☐☐

15

## Medikamente und Inhalationen

60. Haben Sie in den letzten 12 Monaten irgendein inhalierbares Medikament zur
Verbesserung Ihrer Atmung benutzt ?      NEIN   JA

     EH60   ☐    ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 61 WENN "JA":

60.1 - 6 BITTE SCHAUEN SIE DIE LISTE DER ZU INHALIERENDEN MEDIKAMENTE DURCH
UND GEBEN SIE DIEJENIGEN AN, DIE SIE IN DEN LETZTEN 12 MONATEN BENUTZT
HABEN.

60.1.    Beta$_2$-Sympathomimetika      NEIN   JA

     EH601 ☐    ☐

    60.1.1. Wenn ja, welches ?_____
3☐ Berotec, 4☐ Bricanyl, 5☐ Bronchospasmin, 6☐ Etoscol, 7☐ Pirem,
8☐ Sultanol, 9☐ Berotec

60.2.    Unspezifische Beta-Sympathomimetika      NEIN   JA

     EH602 ☐    ☐

    60.2.1. Wenn ja, welches ?_____
3☐ Adrenalin Medihaler, 4☐ Aludrin, 5☐ Alupent, 6☐ Bellasthman

60.3.    Inhalierbare Vagolytika (Anticholinergika)      NEIN   JA

     EH603 ☐    ☐

    60.3.1. Wenn ja, welches ?_____
3☐ Atrovent, 4☐ Ventilat

60.4.    Inhalierbare Corticosteroide      NEIN   JA

     EH604 ☐    ☐

    60.4.1. Wenn ja, welches ?-_____
3☐ Sanasthmax, 4☐ Pulmicort, 5☐ Sanasthmyl

60.5.    Andere inhalierbare nicht steroidale Einzelwirkstoffe      NEIN   JA

     EH605 ☐    ☐

    60.3.1. Wenn ja, welches ?_____
3☐ DNCG, 4☐ Intal, 5☐ Tilade

60.6.    Kombinierte Bronchodilatatoren      NEIN   JA

     EH606 ☐    ☐

    60.3.1. Wenn ja, welches ?_____
3☐ Berodual, 4☐ Allergospasmin, 5☐ Aarane, 6☐ afdosa-N

16

65. Haben Sie in den letzten 12 Monaten irgendwelche anderen Hilfsmittel zur Verbesserung Ihrer Atmung benützt ?

NEIN  JA

EH65  ☐  ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 66, WENN "JA":

65.1.  Welche Hilfsmittel ?  _____  EH651COO _____
_____
_____

66. Nehmen Sie jeden Tag Medikamente zur Verbesserung Ihrer Atmung auch wenn Sie sich nicht kurzatmig fühlen ?

NEIN  JA

EH66  ☐  ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 67, WENN "JA":

66.1.  Welche Medikamente ?_____  EH661COO _____
_____
_____
_____
_____
_____
_____

67. Nehmen Sie irgendwelche Medikamente nur bei Anfällen von Luftnot ?  NEIN  JA

EH67  ☐  ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 68, WENN "JA":

67.1.  Welche Medikamente ?_____  EH671COO _____
_____
_____
_____
_____

67.2.  Nehmen Sie diese Medikamente  *nur eine Wahl*
A)  am Beginn von Anfällen ?  EH672  1☐
B)  nur wenn die Anfälle schwer werden ?  2☐

68. Hat Ihr Arzt Ihnen zur Verbesserung Ihrer Atmung jemals Medikamente verschrieben ?

NEIN  JA

EH68  ☐  ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 69, WENN "JA":

19

68.1.  Wenn Ihnen Medikamente für die Atemwege verschrieben wurden, nehmen Sie normalerweise  *(nur eine Wahl)*

A)  alle Medikamente ein ?  EH681  1☐
B)  die meisten Medikamente ein ?  2☐
C)  manche der Medikamente ein ?  3☐
D)  keines der Medikamente ein ?  4☐

68.2.  Wenn Sie plötzlich Atembeschwerden haben und Ihnen Medikamente zur Linderung verschrieben wurden, nehmen Sie normalerweise *(nur eine Wahl)*

A)  alle Medikamente ein ?  EH682  1☐
B)  die meisten Medikamente ein ?  2☐
C)  manche der Medikamente ein ?  3☐
D)  keines der Medikamente ein ?  4☐

68.3.  Glauben Sie, daß es Ihnen schadet, wenn Sie ständig Medikamente zur Unterstützung Ihrer Atmung nehmen ?

NEIN  JA

EH683  ☐  ☐

68.4.  Glauben Sie, daß Sie so viele Medikamente nehmen sollten, wie Sie brauchen, um vollständig beschwerdefrei zu werden ?

NEIN  JA

EH684  ☐  ☐

69. Haben Sie jemals wegen Atemproblemen die Notaufnahme eines Krankenhauses aufgesucht ?

NEIN  JA

EH69  ☐  ☐

70. Haben Sie jemals wegen Atemproblemen eine Nacht in einem Krankenhaus verbracht ?

NEIN  JA

EH70  ☐  ☐

WENN "NEIN", GEHEN SIE ZU FRAGE 71, WENN "JA":

70.1.  Wie oft in den letzten 12 Monaten ?  Anzahl

EH701  ☐☐

71. Sind Sie jemals von einem Arzt wegen Atembeschwerden oder wegen Kurzatmigkeit untersucht worden ?

NEIN  JA

EH71  ☐  ☐

20

WENN "NEIN", GEHEN SIE ZU M ENDE, WENN "JA":

71.1. Wann sind Sie das letzte Mal wegen Atembeschwerden oder Atemnot von
einem Arzt untersucht worden ?                          *(nur eine Wahl)*

    A)   in den letzten 7 Tagen          EH711     1☐

    B)   vor mehr als 7 Tagen, aber innerhalb der letzten 4 Wochen     2☐

    C)   vor mehr als 4 Wochen, aber innerhalb der letzten 12 Monate     3☐

    D)   vor mehr als einem Jahr     4☐

71.2. Wo wurden Sie zuletzt untersucht?                          *(nur eine Wahl)*

    A)   von einem praktischen Arzt zu Hause        EH712     1☐

    B)   in einer Allgemeinarztpraxis     2☐

    C)   vom Lungenfacharzt zu Hause     3☐

    D)   in der Lungenfacharztpraxis oder in der Lungen-Ambulanz eines

        Krankenhauses     4☐

    E)   in der Notaufnahme oder vom Notarzt     5☐

    F)   im Rahmen eines stationären Krankenhausaufenthaltes     6☐

ENDE

                   EHINT     Interviewer     ☐

                              Gebiet     ☒0 ☒3 ☒3

                              Personen-Id     ☐☐☐☐☐

                              Untersuchungs-Nr.     ☐

          EHUNTOAT     Datum:     ☐☐ ☐☐ ☐☐

21

## 10 Index of Figures and Tables