RESEARCH

Anu Turunen

Epidemiological studies on fish consumption and cardiovascular health

Results from the Fishermen study and the Health 2000 survey

79

Anu Turunen

Epidemiological studies on fish consumption and cardiovascular health

Results from the Fishermen study and the Health 2000 survey

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Science and Forestry of the University of Eastern Finland for public examination in Medistudia Auditorium ML1, Yliopistonranta 1A, on Friday 25th of May 2012, at 12:00.

National Institute for Health and Welfare,
Department of Environmental Health, Kuopio, Finland
and
University of Eastern Finland,
Department of Environmental Science, Kuopio, Finland

Kuopio 2012

NATIONAL INSTITUTE
FOR HEALTH AND WELFARE

Cover photo: Juha Ahvenharju, Cartina Finland Oy

Supervisors
Adjunct Professor Pia Verkasalo, MD, PhD
Kuopio University Hospital
Department of Adult Psychiatry
Kuopio, Finland

Adjunct Professor Antti Jula, MD, PhD
National Institute for Health and Welfare (THL)
Department of Chronic Disease Prevention
Turku, Finland

Professor Emerita Terttu Vartiainen, PhD
National Institute for Health and Welfare (THL)
Department of Environmental Health
Kuopio, Finland

Reviewers
Adjunct Professor Liisa Valsta, PhD
University of Helsinki, Faculty of Agriculture and Forestry
Department of Food and Environmental Sciences
Helsinki, Finland
Current position:
Senior Scientific Officer
European Food Safety Authority (EFSA)
Dietary and Chemical Monitoring Unit
Parma, Italy

Adjunct Professor Lars Rylander, MD, PhD
University of Lund, Faculty of Medicine
Department of Epidemiology and Environmental Medicine
Lund, Sweden

Opponent
Professor Mikael Fogelholm, PhD
University of Helsinki, Faculty of Agriculture and Forestry
Department of Food and Environmental Sciences
Helsinki, Finland

Abstract

Anu Turunen. Epidemiological studies on fish consumption and cardiovascular health - Results from the Fishermen study and the Health 2000 survey. National Institute for Health and Welfare (THL). Research 79. 153 pages. Helsinki, Finland 2012. ISBN 978-952-245-635-9 (printed); ISBN 978-952-245-636-6 (pdf)

The health benefits of fish and fish-derived long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) may be counteracted by concomitant exposure to fish-derived environmental contaminants such as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F, generic term dioxins), polychlorinated biphenyls (PCB), and methylmercury (MeHg). The current consensus is that the beneficial effects overrule the potential hazards but some populations might be exposed to fish-derived environmental contaminants more than is considered safe. For example, the majority of Finnish professional fishermen work in the heavily contaminated Baltic Sea area and supposedly eat fish often from their own catch. Hence, the professional Baltic Sea area fishermen and their family members represented a population with high fish consumption in the present work. The Health 2000 survey participants represented the general population of Finland consuming average amounts of fish. The calculations in the mortality study were based on national mortality rates.

The aims of the present work were to investigate 1) the ability of fish consumption biomarkers, namely fish-derived omega-3 PUFAs and environmental contaminants, and separate frequency questions to reflect fish consumption, 2) the associations of fish consumption with the consumption of other foods, 3) the associations of fish consumption and fish-derived serum omega-3 PUFAs and environmental contaminants with cardiovascular risk factors, and 4) mortality in a population with high fish consumption and presumably high exposure to environmental contaminants.

Blood concentrations of fish-derived omega-3 PUFAs, dioxins, PCBs, and MeHg functioned fairly well as biomarkers of fish consumption. Separate frequency questions were able to measure fish consumption as well as the calibrated food frequency questionnaire on the whole diet. Fish consumption was positively associated with the consumption of vegetables, fruit, berries, potatoes, vegetable oils, and wine both among the professional fishermen and their wives and in the general population. The hypothesised beneficial effects of omega-3 PUFAs on inflammatory markers, insulin resistance, and arterial stiffness were seen in the general population sub-sample but not clearly in the Fishermen study. Among the men of the Fishermen study, high concentrations of environmental contaminants seemed to be associated with high insulin resistance and arterial stiffness, but the risk of atherosclerotic plaques in the carotid artery was not elevated. During a follow-up from 1980 to 2005, mortality from many natural causes, such as

ischaemic heart disease, was lower among the fishermen and their wives than in the general population of Finland.

To conclude, fish consumption appears to be a marker for healthy dietary habits and thus, the health benefits of fish consumption may be partially explained by a generally healthy diet. This work adds to the current understanding that the beneficial effects of fish consumption and omega-3 PUFA intake outweigh the potential hazardous effects of fish-derived environmental contaminants probably even when the exposure is high. Based on the present work, however, the possibility of some harmful effects of high exposure cannot be excluded.

Keywords: fish, omega-3 polyunsaturated fatty acid, environmental contaminant, dioxin, polychlorinated biphenyl, methylmercury, cardiovascular disease, epidemiology

Tiivistelmä

Anu Turunen. Epidemiological studies on fish consumption and cardiovascular health - Results from the Fishermen study and the Health 2000 survey. [Epidemiologisia tutkimuksia kalan käytöstä ja sydän- ja verisuoniterveydestä - Tuloksia Kalastaja- ja Terveys 2000 -tutkimuksista]. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 79. 153 sivua. Helsinki, Finland 2012.
ISBN 978-952-245-635-9 (painettu); ISBN 978-952-245-636-6 (pdf)

Terveydelle hyödyllisten ravintoaineiden, kuten pitkäketjuisten moni-tyydyttymättömien omega-3-rasvahappojen lisäksi kala voi sisältää ympäristö-myrkkyjä, kuten polykloorattuja dibentso-*p*-dioksiineja ja dibentsofuraaneja (PCDD/F, yleisnimitys dioksiinit), polykloorattuja bifenyylejä (PCB) ja metyyli-elohopeaa (MeHg). Nykykäsityksen mukaan kalan käytön terveyshyödyt ovat suuremmat kuin kalasta saatavien ympäristömyrkkyjen mahdolliset haitat, mutta osa väestöstä saattaa altistua vaarallisen korkeille ympäristömyrkkypitoisuuksille. Suurin osa suomalaisista ammattikalastajista työskentelee Itämeren alueella ja he todennäköisesti syövät usein ympäristömyrkkyjä sisältävää Itämeren kalaa. Tämän vuoksi Itämeren ammattikalastajat, heidän puolisonsa ja muut perheenjäsenensä edustivat tässä tutkimuksessa runsaasti kalaa käyttävää väestöä. Terveys 2000 -tutkimuksen aineistoa käytettiin kuvaamaan tavanomaisia määriä kalaa käyttävää Suomen perusväestöä. Rekisteriaineistoon perustuvassa kuolleisuustutkimuksessa käytettiin kansallisia kuolleisuuslukuja.

Tutkimuksen tavoitteena oli tarkastella 1) kalan käytön biomarkkereiden eli kalaperäisten omega-3-rasvahappojen ja ympäristömyrkkyjen, sekä yksittäisten frekvenssikysymysten kykyä kuvata kalan käyttöä, 2) kalan käytön yhteyksiä muiden ruoka-aineiden käyttöön, 3) kalan käytön, omega-3-rasvahappojen ja ympäristömyrkkyjen yhteyksiä sydän- ja verisuonisairauksien riskitekijöihin, ja 4) kuolleisuutta väestössä, joka käyttää runsaasti kalaa ja on oletettavasti saanut sitä kautta runsaasti ympäristömyrkkyjä.

Verestä mitatut kalaperäisten omega-3-rasvahappojen, dioksiinin, PCB-yhdisteiden ja metyylielohopean pitoisuudet toimivat verrattain hyvin kalan käytön biomarkkereina. Yksittäiset frenvenssikysymykset mittasivat kalan käyttöä yhtä hyvin kuin koko ruokavaliota mittaava kalibroitu ruokavalion frekvenssikysely. Runsas kalan käyttö oli yhteydessä runsaaseen kasvisten, hedelmien, marjojen, perunan ja kasviöljyjen käyttöön sekä ammattikalastajilla ja heidän puolisoillaan että perusväestössä. Omega-3-rasvahappojen oletettu hyödyllinen vaikutus tulehdus-markkereihin, insuliiniresistenssiin ja kaulavaltimon seinämän jäykkyyteen näkyi perusväestön alaotoksessa mutta ei Kalastajatutkimuksessa. Kalastajatutkimuksen miehillä korkeat ympäristömyrkkypitoisuudet näyttivät olevan yhteydessä insuliini-resistenssiin ja kaulavaltimon seinämän jäykkyyteen, mutta ne eivät lisänneet ateroskleroottisten plakkien riskiä kaulavaltimossa. Kuolleisuus moniin luonnollisiin

kuolinsyihin, kuten iskeemisiin sydänsairauksiin oli vuosina 1980–2005 alhaisempi kalastajilla ja heidän vaimoillaan verrattuna Suomen perusväestöön.

Kalankäyttö näyttää olevan yhteydessä terveellisiin ruokailutottumuksiin, joten osa kalan edullisista terveysvaikutuksista saattaa välittyä muun ruokavalion kautta. Tämä tutkimus vahvistaa osaltaan käsitystä siitä, että vaikka ympäristömyrkky-altistus olisi suuri, kalan käytön ja omega-3-rasvahappojen saannin hyödylliset terveysvaikutukset ovat suuremmat kuin kalan sisältämien ympäristömyrkkyjen mahdolliset haitat. Ympäristömyrkyillä voi kuitenkin olla haittavaikutuksia, joita ei voi sulkea pois pelkästään tämän tutkimuksen perusteella.

Avainsanat: kala, omega-3-rasvahappo, ympäristömyrkky, dioksiini, polyklooratut bifenyyli, metyylielohopea, sydän- ja verisuonisairaus, epidemiologia

Sammandrag

Utöver nyttiga näringsämnen såsom långkedjad fleromättad omega-3-fettsyror kan fisken också innehålla miljögifter, såsom polyklorerade dibenzo-*p*-dioxiner och dibenzofuraner (PCDD/F, allmän benämning dioxiner), polyklorerade bifenyler (PCB) och metylkvicksilver (MeHg). Enligt dagens uppfattning är de hälsofördelar som fisken ger större än de eventuella nackdelar som medförs av de miljögifter som finns i fisken, men en del av befolkningen kan exponeras för skadligt höga halter av miljögift. Största delen av de finländska yrkesfiskarna är verksamma i Östersjöområdet och äter sannolikt ofta Östersjöfisk som innehåller miljögifter. Yrkesfiskare, deras makor och andra familjemedlemmar representerar därför i denna studie en sådan befolkning som äter rikligt med fisk. I undersökningen Hälsa 2000 har ett urval som representerar hela landets befolkning och ett mindre delurval tillämpats. I den dödlighetsundersökning som baserar sig på registermaterial har nationella dödlighetstal använts.

Studien hade som mål att undersöka 1) möjligheten att beskriva fiskkonsumtionen med hjälp av biomarkörer för fiskkonsumtionen, det vill säga omega-3-fettsyror och miljögifter och enskilda frekvensfrågor, 2) sambandet mellan fiskkonsumtionen och konsumtionen av andra födoämnen, 3) fiskkonsumtionens, omega-3-fettsyrornas och miljögifternas koppling till riskfaktorerna för hjärt- och kärlsjukdomar och 4) dödligheten bland den befolkning som äter rikligt med fisk och som därigenom kan antas få i sig rikligt med miljögifter.

Halterna av omega-3-fettsyror, dioxiner, PCB och metylkvicksilver i blodet utgjorde relativt goda biomarkörer för fiskkonsumtionen. Enskilda frekvensfrågor mätte fiskkonsumtionen lika bra som en kalibrerad frekvensenkät som mäter hela kosten. En riklig konsumtion av fisk var kopplad till en riklig konsumtion av grönsaker, frukt, bär, potatis och vegetabilisk olja såväl bland yrkesfiskarna och deras makor som bland hela landets befolkning. Den förväntade fördelaktiga effekten av omega-3-fettsyror på inflammationsmarkörerna, insulinresistensen och artärstyvheten framträdde i delurvalet för hela befolkningen, men inte i Fiskarundersökningen. Hos de män som deltog i Fiskarundersökningen verkar halterna av miljögifter ha ett samband med insulinresistensen och artärstyvheten, men de ökar inte risken för aterosklerotisk plack i halsartären. Dödligheten i många naturliga dödsorsaker, såsom ischemiska hjärtsjukdomar, var lägre bland fiskare och deras makor jämfört med hela landets befolkning under åren 1980–2005.

Det förefaller som om fiskkonsumtionen har ett samband med hälsosamma matvanor, och därför kan en del av de fördelaktiga hälsoeffekterna som fisken ger mycket väl komma från den övriga kosten. Denna studie bekräftar således att de fördelaktiga hälsoeffekter som erhålls av fisk och omega-3-fettsyror är större än de eventuella skadliga effekterna av miljögifterna i fisk, även i det fallet att exponeringen för miljögifter är hög. Miljögifterna kan dock ha biverkningar som inte kan uteslutas enbart med stöd av denna studie.

Nyckelord: fisk, omega-3-fettsyra, miljögift, dioxin, polyklorerade bifenyl, metylkvicksilver, hjärt- och kärlsjukdom, epidemiologi

Contents

Epidemiological studies on
fish consumption and
cardiovascular health

THL — Research 79/2012   **12**   Epidemiological studies on
fish consumption and
cardiovascular health

THL — Research 79/2012   **13**   Epidemiological studies on
fish consumption and
cardiovascular health

List of original papers

I   Turunen AW, Männistö S, Kiviranta H, Marniemi J, Jula A, Tiittanen P, Suominen-Taipale L, Vartiainen T, Verkasalo PK. Dioxins, polychlorinated biphenyls, methylmercury and omega-3 polyunsaturated fatty acids as biomarkers of fish consumption. Eur J Clin Nutr. 2010; 64(3):313-323.

II   Turunen AW, Männistö S, Suominen AL, Tiittanen P, Verkasalo PK. Fish consumption in relation to other foods in the diet. Br J Nutr. 2011; 106:1570–1580.

III   Turunen AW, Jula A, Suominen AL, Männistö S, Marniemi J, Kiviranta H, Tiittanen P, Karanko H, Moilanen L, Nieminen M, Kesäniemi YA, Kähönen M, Verkasalo PK. Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis. Submitted.

IV   Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Männistö S, Räsänen R, Marniemi J, Vartiainen T. Mortality in a cohort with high fish consumption. Int J Epidemiol. 2008; 37(5):1008-1017.

Abbreviations

ADC	Arterial diameter change
AHA	American Heart Association
ALA	Alpha-linolenic acid (18:3, n-3)
AMI	Acute myocardial infarction
BMI	Body mass index
CAC	Coronary artery compliance
CAD	Coronary artery disease
CCA	Common carotid artery
CHD	Coronary heart disease
CI	Confidence interval
CRP	Highly sensitive C-reactive protein
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid (22:6, n-3)
DPA	Docosapentaenoic acid (22:5, n-3)
EPA	Eicosapentaenoic acid (20:5, n-3)
EU	European Union
FFQ	Food frequency questionnaire
HDL	High-density lipoprotein
HOMA	Homeostasis model assessment
HOMA-%B	HOMA beta cell function index
HOMA-IR	HOMA insulin resistance index
IARC	International Agency for Research on Cancer
IHD	Ischaemic heart disease
IL-6	Interleukin 6
IMT	Intima-media thickness
MeHg	Methylmercury
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-p-dioxin
PCDF	Polychlorinated dibenzofuran
PUFA	Polyunsaturated fatty acid
RR	Risk ratio
SI	β-stiffness index (a measure of vascular compliance)
SMR	Standardised mortality ratio
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF	Toxic equivalency factor
TEq	Toxic equivalent quantity
THL	National Institute for Health and Welfare
TNF-α	Tumour necrosis factor α
TWI	Tolerable weekly intake

USA	United States of America
WHO	World Health Organisation
YEM	Young's elastic modulus (a measure of vascular compliance)

THL — Research 79/2012　　　**17**　　　Epidemiological studies on
fish consumption and
cardiovascular health

1 Introduction

Fish contains several beneficial nutritional compounds such as long-chain polyunsaturated fatty acids (omega-3 PUFAs), high-quality protein, vitamins D and B_{12}, potassium, phosphorus, iodine, calcium, and selenium. However, fish may also contain various environmental contaminants, for instance polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F, generic term dioxins), polychlorinated biphenyls (PCB), and methylmercury (MeHg) that can bioaccumulate to toxicologically relevant concentrations.

Consequently, simultaneous exposure to both beneficial and hazardous fish-derived compounds has led to speculation about the competing and overall health effects of fish consumption. Although the current consensus is that the beneficial effects overrule the potential hazards, the strength of the evidence on the actual benefits of fish consumption has been challenged and new hypotheses concerning the potential deleterious effects of environmental contaminants have been emerging. In addition, some special populations may be exposed to fish-derived contaminants more than is considered safe. The Baltic Sea area in particular is still heavily contaminated with persistent organic pollutants, although the environmental concentrations have slowly been decreasing during the last decades (Hallikainen et al. 2011).

The majority of Finnish professional fishermen live and work in the Baltic Sea area, and it has been inferred that fishermen eat more fish than the general population based on their high serum concentrations of fish-derived environmental contaminants (Kiviranta et al. 2000; Kiviranta et al. 2002). These observations became the foundation of the present work and the whole research project. The hypothesis was that the fishermen have both high intakes of omega-3 PUFAs and high exposure to environmental contaminants from the Baltic Sea because they probably often eat fish from their own catch.

For the Fishermen study, all the professional fishermen registered at least once between 1980 and 2002 were identified from the Professional Fishermen Register currently maintained by the Centre for Economic Development, Transport and the Environment, whereas the fishermen's wives and other family members were identified from the Population Information System of the Population Register Centre. The cross-sectional study consisted of a comprehensive self-administered questionnaire on health behaviour and self-perceived health, and a health examination including blood sampling, a food frequency questionnaire (FFQ) on whole diet, basic measurements, an ultrasound examination of the right common carotid artery, and an electrocardiogram. The data was collected during 2004–2005 according to a similar study protocol to the nationally representative Health 2000 health examination survey (Health 2000 survey) (Heistaro 2008). Data from the

Epidemiological studies on
fish consumption and
cardiovascular health

Health 2000 survey was used together with the Fishermen study data to see whether the studied associations were uniform in the sample of the general population of Finland consuming average amounts of fish from various sources and in the unique population with high consumption of Baltic fish. In the register-based follow-up study, the cohorts of professional fishermen and fishermen's wives were individually linked with national cause-of-death data from the Statistics Finland and followed from 1980 to 2005. The stages of the Fishermen study are presented in the Appendix.

The general objective of the present work was to assess the overall effect of fish consumption on cardiovascular health using epidemiological methods and taking into account both beneficial and hazardous compounds in fish. The Finnish fishermen and their family members formed a natural experimental population, and the reasoning was that if we could not detect harmful effects in this highly exposed population, it would appear likely that the same holds true also in populations with lower exposures.

THL — Research 79/2012   **20**   Epidemiological studies on
fish consumption and
cardiovascular health

2 Review of the literature

2.1 Professional fishing in Finland

According to the Fishing Act (756/2001) Section 6a in the current Finnish legislation, a professional fisherman is a person who is engaged in fishing and earns his living or a substantial part of it from fishing or from the processing of the catch. In order to fulfil this condition, total fishing income should be at least 30% of the overall income (Ministry of Agriculture and Forestry 2001a). In practice, fishermen are obligated to register with the Professional Fishermen Register if they own a fishing vessel or if they fish in sea areas and their total fishing income is more than 15% of their overall income. Registering is voluntary for all inland area fishermen and for those maritime fishermen whose total fishing income is less than 15% of the overall income (Ministry of Agriculture and Forestry 2001b). The Centre for Economic Development, Transport and the Environment has maintained the Professional Fishermen Register since 1995 when Finland joined the European Union (EU) and registration became obligatory. Before that, the registration was voluntary and the register was maintained by the Finnish Game and Fisheries Research Institute under the Ministry of Agriculture and Forestry. A specification for a professional fisherman was added into law in 1996 but unlike the current definition, it did not include processing of the catch.

The number of registered commercial marine fishermen has decreased in the last three decades from approximately 4500 in 1980 to 2200 at the end of 2010. According to the latest statistics from 2010, less than one third of the registered marine fishermen earned at least 30% of their income from fishing, and the total catch was 122 million kg, consisting of Baltic herring (75%), sprat (20%), cod, perch, bream, and European whitefish (Finnish Game and Fisheries Research Institute 2011a). The number of registered commercial inland fishermen has decreased from approximately 2500 in 1980 to approximately 300 at the end of 2008. According to the latest statistics from 2008, almost two thirds of inland fishermen earned at least 30% of their overall income from fishing, and the total catch was 3.9 million kg, consisting mostly of vendace (65%) (Finnish Game and Fisheries Research Institute 2010).

2.2 Nutrient composition of fish

Fish contains several beneficial nutritional compounds, especially polyunsaturated fatty acids, high-quality protein, and vitamin D. The lipid content and fatty acid profile in fish varies according to species, life-stage and diet of the fish, geographical area, season, and water temperature. Fish are typically divided into fatty/oily/blue and lean/white fish based on the fat percentage in muscle tissue. The cut-off values vary, being typically >5% for fatty and <2% for lean fish. Hence, salmon, rainbow trout, Baltic herring, tuna, sardine, and mackerel are classified as fatty, whereas pike, perch, whitefish, and cod are classified as lean. Lean fish accumulate the majority of the fat into the liver (European Food Safety Authority 2005; National Institute for Health and Welfare 2010).

Fat in fish consists predominantly of monounsaturated and polyunsaturated fatty acids, and fish is the only dietary source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA derive from the phytoplankton that fish eat. The human body has a limited capacity to synthetisate EPA and DHA through elongation and desaturation from alpha-linolenic acid (ALA) abundant in vegetable oils, especially rapeseed and flaxseed oils. It has been estimated that among healthy adults, only 5–10% of dietary ALA can be converted into EPA, and 2–5% of EPA can be further converted into DHA (Jones and Kubow 2006; He 2009). The synthesis, especially for DHA, appears to be more efficient among women than among men (Bakewell et al. 2006). ALA is also found in fish but its concentrations are much lower than for EPA and DHA (National Institute for Health and Welfare 2010). Omega-6 PUFA concentration is typically low in fish, except for farmed fish that have been fed with feed containing high amounts of omega-6 PUFAs (European Food Safety Authority 2005).

Fish protein has a high biological value and it is easily digestible because the proportion of essential amino acids is high and the amount of connective (fibrous) tissue is smaller than in terrestrial animals (European Food Safety Authority 2005).

Fatty fish is one of the very few natural dietary sources of vitamin D. Regarding other nutrients, fish is a relatively good source of selenium, vitamin B_{12}, iodine, potassium, and phosphorus. Additionally, fish eaten with fine bones are a source of calcium (Southgate 2000; Undeland et al. 2009; National Institute for Health and Welfare 2010).

2.3 Contaminants in fish

2.3.1 Dioxins and PCBs

Dioxins are unwanted by-products of industrial processes such as incineration of mixed municipal waste at too low temperatures, metal smelting and refining, and chlorine bleaching of pulp. Emissions from these sources, except for local small scale waste burning, have decreased markedly during the last decades (European Food Safety Authority 2005; Tuomisto et al. 2011). PCBs were manufactured from the 1930s to the 1980s and were used as insulating materials in electrical equipment, softening materials in plastics, and in various other industrial products owing to their stability and low flammability. They have spread to the environment through municipal waste incineration, waste landfill volatilisation, and industrial accidents (Tuomisto et al. 2011). Although the production of PCBs has been banned since 2001 and they are no longer used in most countries, they are still present in electrical equipment, plastic products, and buildings. PCBs can contain dioxins as impurities (European Food Safety Authority 2005; Tuomisto et al. 2011).

Dioxins and PCBs are found in almost all compartments of the global ecosystem and are transported over long distances in the atmosphere, waterways, and ocean currents, even to remote areas such as the Arctic (Donaldson et al. 2010). Owing to chlorination, they are highly lipophilic, resistant to biodegradation, and are therefore extremely persistent. They bioaccumulate and biomagnify along aquatic and terrestrial food chains, and their half-life varies depending on the congener from a couple of months to tens of years, the average being from five to ten years. The highest concentrations are found in predatory animals (European Food Safety Authority 2005; Tuomisto et al. 2011). The concentrations are typically higher at the top of marine food web due to higher numbers of trophic levels compared with terrestrial food web (Donaldson et al. 2010).

Approximately 95% of human background exposure to dioxins and PCBs comes from foods of animal origin (World Health Organization 1998; Tuomisto et al. 2011), especially from fatty dairy products, meat, fish, and eggs. In the United States of America (USA), for example, dairy products and meat are the most important sources (Schecter et al. 2001), whereas in Finland, approximately 95% of dioxin exposure and 80% of PCB exposure originates from fish (Kiviranta et al. 2004). Human concentrations are determined mainly by age, body size, place of residence, dietary habits, and additionally among women, by the number of children and the length of breastfeeding (Kiviranta et al. 2005).

Theoretically, a total of 210 dioxin and 209 PCB congeners can be derived from the same parent compounds. Of those, 17 dioxin congeners and 12 dioxin-like PCB congeners are the most toxic. Differences in their potency can be expressed by the toxic equivalency factor (TEF), which is the toxicity relative to the most potent dioxin congener 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TCDD is also one of

the most toxic synthetic compounds currently known. The World Health Organisation (WHO) determined TEF values in 1998 (Van den Berg et al. 1998; World Health Organization 1998) and re-evaluated them in 2005 (Van den Berg et al. 2006), and they can be summed up to a toxic equivalent quantity (TEq).

Regarding dioxins and PCBs, the Baltic Sea is still one of the most polluted areas in the world. Environmental concentrations peaked during the 1970s and have slowly decreased since, owing to improved waste incineration techniques and banning the use of PCBs in most countries (Verta et al. 2007; Tuomisto et al. 2011). Currently, the most important sources of contamination are forest industry along the coast in respect of dioxins, and long-range atmospheric transport from the Western Europe in respect of PCBs. Despite the decrease, some fish species, especially Baltic herring, salmon, and sea trout may still exceed the maximum concentrations given for dioxins and PCBs (Hallikainen et al. 2011). It has been estimated that WHO-$_{PCDD/F-PCB}$TEq concentration is currently 3.5-fold in Baltic herring when compared with herring from other sea areas and 5-fold in wild Baltic salmon when compared with farmed salmon (European Food Safety Authority 2005). The concentrations of dioxins and PCBs are typically lower in fish from inland waters than in fish from the Baltic Sea (Isosaari et al. 2006; Hallikainen et al. 2010).

2.3.2 Mercury

Inorganic mercury is innately present in the soil, sediment, coal, and minerals. It can be released directly to aquatic ecosystems and the atmosphere through natural processes such as volcanic action and leaching from soil, and human activities such as burning of coal and other fossil fuels, industrial releases, and waste incineration (European Food Safety Authority 2004). Mercury emissions have decreased in Europe and North America but increased in other parts of the world. In Finland, for example, long-range transport is currently the main source of mercury contamination (Munthe et al. 2007).

In aquatic ecosystems, micro-organisms such as algae and bacteria can metabolise inorganic mercury into organic methylmercury (MeHg), which is the most toxic form of mercury. MeHg moves up the food chain into fish and other seafood and bioaccumulates and biomagnifies especially in large predatory fish such as swordfish, shark, tuna, and pike. Fish is practically the only source of MeHg for humans. MeHg is efficiently absorbed via the digestive system and is mostly bound to proteins in muscle tissue. Half-life in the human body is approximately two months (European Food Safety Authority 2004; Hallikainen et al. 2010).

Mercury is a problem both in inland waters and coastal sea areas (Skerfving et al. 1999). There are limited data on MeHg in the Baltic Sea but the concentrations are estimated to be lower than in inland waters and slightly higher than in other sea areas (European Food Safety Authority 2005; Hallikainen et al. 2010).

2.3.3 Regulations

According to EU regulation (1881/2006), the maximum concentrations of contaminants in fish intended for placement on the market in the member states are 4.0 pg per gram of fish (fresh weight) for $WHO\text{-}_{PCDD/F}TEq$, 8.0 pg per gram of fish (fresh weight) for $WHO\text{-}_{PCDD/F\text{-}PCB}TEq$, and depending on fish species, 0.5 mg or 1.0 mg per kilogram of fish (wet weight) for mercury. Certain fish species in the Baltic Sea, such as wild salmon, herring, trout, char, and river lamprey can exceed the maximum concentrations of dioxins and PCBs and similarly, large predatory fish from the sea or inland waters such as pike, perch, pikeperch, and burbot may exceed the maximum mercury concentration. However, omitting fish from the diet is thought to have a negative overall effect on public health. Thus, Finland and Sweden have had a temporary derogation since 2002 to keep wild Baltic Sea fish on the market in their territory even if the maximum dioxin and PCB concentrations are exceeded. Since the end of 2011, the derogation has been permanent. A prerequisite for this derogation is that consumers have to be fully informed of the consumption restrictions and vulnerable groups to avoid potential health risks (Commission of the European Communities 2006). The EU has also given a tolerable weekly intake (TWI) for dioxins and PCBs that is 14 pg/kg body weight for $WHO\text{-}_{PCDD/F\text{-}PCB}TEq$ (European Commission 2001).

2.4 Fish consumption in Finland

According to the latest supply statistics of the Finnish Game and Fisheries Research Institute, the consumption of domestic fish (filleted weight) has decreased from 6 kg in 1999 to 4.5 kg per person in 2009. During the same period, the consumption of Baltic herring has halved from 0.8 to 0.4 kg per person per year. In 2009, the most consumed domestic fish species were farmed rainbow trout, pike, vendace, perch, and Baltic herring (Finnish Game and Fisheries Research Institute 2011b). In 2009, the consumption of wild-caught Baltic salmon was very low, approximately 0.6% of the total consumption of domestic fish (Vihervuori A., personal communication 23.8.2011). The consumption of imported fish (product weight) has increased from 6.5 kg in 1999 to 11 kg per person in 2009. In 2009, the most consumed imported species were farmed salmon, canned tuna, and farmed rainbow trout (Finnish Game and Fisheries Research Institute 2011b).

Based on the sales statistic of the Information Centre of the Ministry of Agriculture and Forestry, total fish consumption has slightly increased from 13 kg per person in the year 2000 to 16 kg per person in 2009, being approximately 45 g per person per day in 2009 (Matilda Agricultural Statistics 2011).

According to the national FINDIET 2007 Survey by the National Institute for Health and Welfare, the average fish consumption of a working-age Finnish person

is 40 g per day measured by 48-hour dietary recall. This corresponds to 2.5 fish meals per week if 100 g is assumed to be an average portion size. However, fish consumption is not evenly distributed within different geographical areas and age groups. More specifically, fish consumption appears to be the lowest in the southern and northern parts of Finland and among the youngest age groups, and the highest in eastern Finland and among the oldest age groups (Paturi et al. 2008).

2.5 Recommendations for fish consumption

Both Finnish (National Nutrition Council 2011) and several foreign authorities such as the American Heart Association (AHA) (Lichtenstein et al. 2006) recommend that fish should be eaten at least twice per week and fish species should be varied. The Finnish Food Safety Authority EVIRA has given exceptions to this advice regarding children, the young, and people at fertile age. According to EVIRA, large Baltic herring (the whole fish more than 17 cm in length) and wild-caught Baltic salmon should be eaten only once or twice per month due to accumulated dioxins and PCBs. Additionally, due to accumulated methylmercury, pike and other predatory fish from the sea or inland waters should be eaten only once or twice per month, and pregnant or nursing women should not eat pike at all (Finnish Food Safety Authority Evira 2010).

2.6 Historical landmarks in the research on fish consumption and cardiovascular health

Fish consumption became a topic of scientific research decades ago when the health authorities reported an unusually low incidence of cardiovascular diseases (CVD) and diabetes in Greenland in the 1950s and 1960s. In the 1970s, the Greenland Inuit were reported to have lower serum concentrations of cholesterol and triglycerides (Bang et al. 1971), a higher proportion of eicosapentaenoic acid from all serum fatty acids (Dyerberg et al. 1975), and higher adipose tissue concentrations of PCBs (Jensen and Clausen 1979) than Danes. In the 1980s, the occurrence of acute myocardial infarction (AMI), diabetes (Kromann and Green 1980), and mortality from ischaemic heart disease (IHD) (Bjerregaard and Dyerberg 1988) were reported to be lower among the Greenland Inuit when compared with Danes. These observations were hypothesised to be at least partially caused by environmental factors such as a staple traditional diet consisting mainly of whale, seal, and fish (Bang et al. 1980). It was suspected that a marine diet protected Inuit from CVD still the 1990s (Feskens and Kromhout 1993) but at present, the consumption of traditional foods has decreased (Deutch et al. 2007), and the prevalence of CVD and

its risk markers among the Inuit no longer differs from that of Western populations either in Greenland (Jorgensen et al. 2008) or in Canada (Chateau-Degat et al. 2010).

In addition to Inuit studies, other historical landmarks in the research on the association between fish consumption and cardiovascular health were the Zutphen study and the Diet And Reinfarction Trial (DART) in the 1980s, and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) - prevention trial in the 1990s. In the Zutphen study, mortality from coronary heart disease (CHD) during the 20-year follow-up between 1960 and 1980 was reported to be over 50% lower among those consuming at least 30 g of fish per day when compared with non-consumers (Kromhout et al. 1985). In the DART trial, modest fatty fish consumption (two or three portions per week) reduced two-year all-cause mortality among male AMI survivors by 29%, whereas the risk of IHD events was not affected (Burr et al. 1989). In the GISSI prevention trial, supplementation of 1 g omega-3 PUFA per day decreased 3.5-year mortality from all causes and CVD, and the risk of non-fatal AMI (GISSI-Prevenzione Investigators 1999).

2.7 Cardiovascular benefits of fish consumption and omega-3 PUFAs

Fish contains several nutritional compounds that could theoretically benefit the cardiovascular system. Although it is plausible that, for example, vitamin D may partly explain the health benefits of fish (Nadir et al. 2010; Wang et al. 2010; Elamin et al. 2011), the research has predominantly focused on the fish-derived omega-3 PUFAs, namely EPA and DHA. They are essential components of cell membranes and thought to be the key nutrients behind the established cardiovascular benefits of fish consumption.

Papers cited in the following literature review were identified through PubMed MEDLINE, and the search was restricted to human studies on adults published between 2000 and 2011 in the English language. The most relevant papers were selected based on scale, quality, and the author's interpretation of the evidence, with a slight emphasis on the most current literature. Many of the original articles published before the year 2000 have been included in meta-analyses and reviews cited in the following review of literature.

2.7.1 CVD risk factors

Fish-derived omega-3 PUFAs have been observed to beneficially modify CVD risk factors but the mechanisms behind the benefits are not completely understood (Mozaffarian 2008). The suspected intermediary effects include hypotriglyseridemic, anti-inflammatory, blood pressure lowering, endothelial cell function improving, arterial elasticity increasing, anti-thrombotic (e.g., decreased platelet aggregation), atherosclerotic plaque stabilising, and anti-arrhythmic effects (Calder 2004; Tziomalos et al. 2007; de Roos et al. 2009; He 2009; Riediger et al. 2009; Di Minno et al. 2010; De Caterina 2011; Mozaffarian and Wu 2011; Richardson et al. 2011).

The hypotriglyseridemic effect of fish-derived omega-3 PUFAs is well-documented (Hartweg et al. 2008; Jacobson 2008; Eslick et al. 2009). Although triglyceride is not directly atherogenic, its concentration in serum can be used as a marker of CVD risk (Miller et al. 2011).

Inflammation has an important role in the pathogenesis of atherosclerosis, metabolic syndrome, diabetes, and obesity. High intake of fish-derived omega-3 PUFAs has been shown to decrease the production of inflammatory eicosanoids, cytokines, reactive oxygen species, and the expression of adhesion molecules, and hence to protect from diseases involving inflammatory processes (Calder 2006; Calder 2011). Through anti-inflammatory effects, omega-3 PUFAs may, for example, decrease plaque inflammation and prevent plaque rupture (Weitz et al. 2010). Recently, a persistent inverse association between CRP and the risk of CHD, ischaemic stroke, and vascular mortality has been seen in an individual participant meta-analysis on follow-up studies (Kaptoge et al. 2010). Regarding individual intervention studies, no consistent anti-inflammatory effect of omega-3 PUFAs has been observed in intervention studies among Danes (Madsen et al. 2003), the Dutch (Pot et al. 2009), Swedish overweight men (Lindqvist et al. 2009), and Americans with moderate hypertriglyceridemia (Skulas-Ray et al. 2011), whereas the anti-inflammatory effect has been observed in an intervention study on Australians with hyperlipidemia (Micallef and Garg 2009).

In several cross-sectional studies, omega-3 PUFA intake has been observed to be inversely associated with serum concentrations of inflammatory markers such as CRP, tumour necrosis factor (TNF), interleukin 6 (IL-6), for example, among American male health professionals (Pischon et al. 2003) and female nurses (Pischon et al. 2003; Lopez-Garcia et al. 2004), Italians (Ferrucci et al. 2006), Japanese (Niu et al. 2006; Ohsawa et al. 2008), Americans (He et al. 2009), Australians (Micallef et al. 2009), Greeks (Kalogeropoulos et al. 2010), and Americans with coronary artery disease (CAD) (Farzaneh-Far et al. 2009).

Hypertension and endothelial dysfunction are contributing factors in the progression of atherosclerosis. In meta-analyses on randomised controlled trials, high-dose omega-3 PUFA supplementation has been observed to lower heart rate especially among those with high baseline heart rate (Mozaffarian et al. 2005b) and

to lower blood pressure especially among hypertensive individuals and in older populations (Geleijnse et al. 2002). In individual intervention studies, DHA supplementation has been observed to lower diastolic blood pressure among Britons (Theobald et al. 2007) but no antihypertensive effect of omega-3 PUFA has been seen among Italians, Danes, Swedes, Finns, and Australians (Rasmussen et al. 2006). During a 20-year follow-up among American young adults, non-fried fish consumption and omega-3 PUFA intake have been observed to be inversely associated with blood pressure (Xun et al. 2011). Similarly, an inverse association between omega-3 PUFAs and blood pressure has been seen in a cross-sectional study among healthy Americans (Liu et al. 2011a). Improvements in endothelial function after omega-3 PUFA supplementation have been reported in a recent review on intervention studies among overweight, dyslipidemic, and diabetic individuals but the evidence regarding healthy individuals was inconsistent (Egert and Stehle 2011). In a recent follow-up study, on the other hand, fish consumption has been observed to be positively associated with endothelial function among healthy Dutch individuals (van Bussel et al. 2011).

Arterial stiffness is both a risk factor and a surrogate end point for CVD. The effects of fish-derived omega-3 PUFAs on arterial stiffness might be mediated, for example, by serum triglycerides, blood pressure, and endothelial function. An arterial stiffness decreasing effect of omega-3 PUFAs has been observed in a recent meta-analysis on randomised controlled trials (Pase et al. 2011) and in individual intervention studies among Britons (Chong et al. 2010), elderly hypercholesterolemic Norwegian men (Hjerkinn et al. 2006), overweight hypertensive Chinese (Wang et al. 2008a), and overweight or obese Australians (Sjoberg et al. 2010). An intervention study among Britons without history of CVD, however, found no effect of omega-3 PUFAs on arterial stiffness (Senders et al. 2011) whereas an inverse association between omega-3 PUFAs and arterial stiffness has been observed in a follow-up study among Britons (Anderson et al. 2009).

Atherosclerosis is the underlying process behind CVD. Intima-media thickness (IMT), the presence of formed atherosclerotic plaques, and coronary calcification score are generally used as markers of the progression of atherosclerosis. In cross-sectional studies, fish consumption and omega-3 PUFA intake have been observed to be inversely associated with IMT among Japanese men (Nakamura et al. 2007; Sekikawa et al. 2008), Alaskan Inuit (Ebbesson et al. 2008), and Spaniards with dyslipidemia (Sala-Vila et al. 2010). Additionally, fish consumption and omega-3 PUFA intake have been observed to be inversely associated with the prevalence of subclinical atherosclerosis in a cross-sectional study on a multiethnic group free of clinical CVD and living in the USA (He et al. 2008). Similarly, an inverse association has been observed between fish consumption and both coronary artery diameter and the prevalence of atherosclerotic lesions in a follow-up study among postmenopausal women with CAD (Erkkila et al. 2004). Further, fish consumption and omega-3 PUFA intake have been observed to be inversely associated with

coronary calcification among elderly Dutch individuals (Heine-Broring et al. 2010), Japanese men (Sekikawa et al. 2008), and Japanese AMI patients (Ueeda et al. 2008).

With regard to atherosclerotic plaque stability, omega-3 PUFA supplementation has been reported to increase plaque stability among Norwegian CAD patients (Serebruany et al. 2011) and British carotid endarterectomy patients (Thies et al. 2003; Cawood et al. 2010).

Based mainly on the results of the GISSI prevention trial (GISSI- Prevenzione Investigators 1999), the decreased susceptibility to arrhythmias has been hypothesised to be a major factor behind the cardiovascular benefits of fish consumption and omega-3 PUFAs. In an individual intervention study, omega-3 PUFA supplementation has been observed to decrease susceptibility to atrial fibrillation among healthy Australians (Kumar et al. 2011). However, a recent meta-analysis on randomised controlled trials concluded that omega-3 PUFA supplementation does not have a protective effect against atrial fibrillation (Liu et al. 2011b).

Insulin resistance has been one of the candidate mechanisms for the cardiovascular benefits of fish-derived omega-3 PUFAs based on the common pathogenesis of CVD and diabetes (Carpentier et al. 2006). However, no effects of omega-3 PUFA supplementation on glucose homeostasis or insulin resistance have been observed in meta-analyses on randomised controlled trials (Balk et al. 2006; Akinkuolie et al. 2011) or in intervention studies among healthy individuals from Italy, Denmark, Sweden, Finland, Australia (Giacco et al. 2007), the United Kingdom (Lara et al. 2007), and Italy (Rizza et al. 2009). In contrast with other intervention studies, fish oil supplementation has been observed to increase insulin resistance among Norwegian diabetics (Mostad et al. 2006) and Alaskan Inuit (Ebbesson et al. 2007). A beneficial effect of omega-3 supplementation on insulin resistance have been observed among overweight and obese young adults from Iceland, Ireland and Spain (Ramel et al. 2008) as well as among Swedish diabetics (Karlstrom et al. 2011). In cross-sectional studies, omega-3 PUFA intake has been inversely associated with insulin resistance among Canadian coronary patients with metabolic syndrome (Nigam et al. 2009) but no association has been observed among Japanese civil servants (Muramatsu et al. 2010).

2.7.2 CVD incidence and mortality

In a recent randomised controlled trial among Dutch AMI patients, low-dose omega-3 PUFA supplementation did not decrease the risk of cardiovascular events (Kromhout et al. 2010). In American follow-up studies, fish consumption and omega-3 PUFA intake have been associated with decreased risk of non-fatal AMI among women (Hu et al. 2002) and decreased risk of heart failure among post-

menopausal women (Belin et al. 2011) and older adults (Mozaffarian et al. 2011a). Conversely, a protective effect has not been observed among American male health professionals (Mozaffarian et al. 2005a) or the Dutch (Dijkstra et al. 2009; de Goede et al. 2010). Among American men, a decreased CHD incidence has been observed only after combining fatal and non-fatal CHD events (Virtanen et al. 2008). Regarding case-control studies, a decreased risk of non-fatal AMI has been observed among American female nurses (Sun et al. 2008) but not among older adults (Lemaitre et al. 2003).

Omega-3 PUFAs are thought to protect against type 2 diabetes (Nettleton and Katz 2005) possibly through beneficial effects on the metabolic syndrome components although the evidence is less consistent than for CVD. In recent follow-up studies, fish consumption and omega-3 PUFA intake have been found to be associated with decreased risk of metabolic syndrome among Korean men (Baik et al. 2010), and with decreased risk of type 2 diabetes among Chinese women (Villegas et al. 2011) and Britons (Patel et al. 2009). In contrast, fish consumption and omega-3 PUFA intake have been associated with an increased risk of type 2 diabetes among Americans (Kaushik et al. 2009; Djousse et al. 2011) and the Dutch (van Woudenbergh et al. 2009).

With regard to cardiovascular mortality, several meta-analyses and systematic reviews of randomised controlled trials, cohort studies, and case-control studies have concluded that fish consumption and omega-3 PUFA supplementation is associated with decreased risk of sudden cardiac death and decreased CHD mortality (He et al. 2004; Wang et al. 2006; Leon et al. 2008; Mozaffarian 2008; Di Minno et al. 2010; Filion et al. 2010; Musa-Veloso et al. 2011; Zheng et al. 2011). Only one systematic review has concluded that omega-3 PUFAs have no clear effect on all-cause mortality or the risk of cardiovascular events (Hooper et al. 2006) but the null result was mainly attributable to one trial with a long follow-up. Regarding the magnitude of the protective effect, modest fish consumption has been suggested to reduce the risk of CHD death by 36% (Mozaffarian 2008).

2.8 Cardiovascular hazards of dioxins, PCBs, and MeHg

The main contributors to the risk of CVD and diabetes are genetic predisposition and lifestyle factors such as obesity, low physical activity, and smoking. However, environmental contaminants such as dioxins, PCBs, and MeHg are also hypothesised to have a role in the pathogenesis of CVD and diabetes (Hennig et al. 2007; Carpenter 2008; Jones et al. 2008; Alonso-Magdalena et al. 2011).

2.8.1 CVD risk factors

It has been suspected that dioxins and PCBs increase the risk of CVD and diabetes by altering gene expression patterns, and hence inducing oxidative stress, inflammatory responses (Hennig et al. 2005; Hennig et al. 2007), glucose intolerance, and insulin resistance (Carpenter 2008). In a cross-sectional setting, high serum PCB concentration has been associated with high serum triglyceride concentration among Americans (Goncharov et al. 2008). Further, high exposure to dioxins and PCBs has been observed to be associated with elevated blood pressure among Americans in general (Ha et al. 2009) and those living near a closed PCB plant (Goncharov et al. 2011). Regarding atherosclerosis, it has been observed that high serum concentration of PCBs is associated with high IMT and increased prevalence of plaques in the carotid artery of elderly Swedish individuals (Lind et al. 2012).

Mercury is able to increase oxidative stress and inflammation, reduce oxidative defence, increase platelet aggregation, and cause vascular smooth muscle and endothelial cell dysfunction and dyslipidemia (Mozaffarian 2009; Houston 2011). In a cross-sectional setting, it has been observed that high mercury exposure is associated with elevated blood pressure among fish consumers in the Amazonian Brazil (Fillion et al. 2006), among Faroese whaling men (Choi et al. 2009), and among the Canadian Inuit (Valera et al. 2009). It has also been observed that high mercury exposure is associated with high serum concentrations of some pro-inflammatory cytokines among fish consumers in the Amazonian Brazil (Nyland et al. 2011), and high IMT among middle-aged eastern Finnish men (Salonen et al. 2000) and Faroese whaling men (Choi et al. 2009).

2.8.2 CVD events

In a cross-sectional setting, the rates of hospital discharges related to CHD, AMI, and metabolic syndrome have been higher in areas contaminated with dioxins and PCBs when compared with non-contaminated areas in the US (Sergeev and Carpenter 2005; Sergeev and Carpenter 2011). Further, serum PCBs have been observed to be associated with increased prevalence of self-reported CVD among American women (Ha et al. 2007). An increased mortality from CVD has been observed among the residents of the highest TCDD exposure zone 5–9 years after the industrial accident in Seveso Italy (Consonni et al. 2008).

It has been observed that high mercury exposure is associated with an increased risk of acute coronary events in a follow-up study on middle-aged eastern Finnish men (Virtanen et al. 2005) and with an increased risk of AMI in a case-control study among men from eight European countries and Israel (Guallar et al. 2002). On the other hand, no adverse cardiovascular effects have been observed in large case-control studies among Americans (Mozaffarian et al. 2011b) and American male

health professionals (Yoshizawa et al. 2002). The totality of the evidence has been evaluated in several reviews, and although some uncertainty remains (Mozaffarian 2009), MeHg is generally regarded as a risk factor for CVD (Stern 2005; Virtanen et al. 2007; Houston 2011).

2.8.3 Metabolic syndrome and diabetes

In a cross-sectional setting, high exposure to PCBs has been found to be associated with high plasma glucose and low plasma insulin among the elderly residents of the Faroese Islands exposed to PCB compounds by eating pilot whale blubber (Grandjean et al. 2011). Further, high exposure to dioxins and PCBs has been observed to be associated with an increased prevalence of insulin resistance among Americans (Lee et al. 2007), Japanese (Uemura et al. 2009), and Taiwanese living near a closed pentachlorophenol plant (Chang et al. 2010). Simultaneous exposure to mercury and dioxins is suspected to have a synergistic harmful effect on insulin sensitivity (Chang et al. 2011).

High serum PCB concentration has been associated with an increased risk of type 2 diabetes in cross-sectional studies among Americans (Everett et al. 2007), Swedish fishermen's wives (Rignell-Hydbom et al. 2007), and Finnish adults (Airaksinen et al. 2011). In case-control studies, an increased risk of type 2 diabetes has been observed among women after high accidental exposure to PCDFs and PCBs in Yucheng Taiwan (Wang et al. 2008b) and among young American adults environmentally exposed to PCBs (Lee et al. 2010).

THL — Research 79/2012　　　　　　　**33**　　　　　　　Epidemiological studies on
fish consumption and
cardiovascular health

2.9 The current consensus on the net health effect of fish consumption

Based on a large body of epidemiological evidence and some risk-benefit analyses, the current consensus is that the benefits of moderate fish consumption outweigh the potential risks (Mozaffarian and Rimm 2006; Park and Mozaffarian 2010). WHO has also concluded that cardiovascular benefits of fish consumption are significantly greater than the potential hazards (FAO/WHO 2011). Moderate consumption needed for the benefits is assessed to correspond to one or two fish servings per week or 250 mg of EPA+DHA per day (Mozaffarian and Rimm 2006; Park and Mozaffarian 2010). The current worldwide recommendation is to consume fatty fish at least twice per week (Mozaffarian and Wu 2011), and additionally, the AHA recommends 1 g of fish-derived omega-3 PUFAs per day for AMI patients, which corresponds to almost one fatty fish meal per day (Saravanan et al. 2010).

The public health impact of decreasing fish consumption in the fear of environmental contaminants is thought to be negative (Mozaffarian and Rimm 2006). For instance, a quantitative risk-benefit analysis on the trade-off between fish-derived omega-3 PUFAs and MeHg estimated that if the entire US population would reduce fish consumption by 17%, approximately 40,000 quality-adjusted life years (QALYs) would be lost due to the increase in CHD mortality. The risks caused by persistent organic pollutants (600 QALYs per year) were considered to be very small compared with the benefits of omega-3 PUFAs (net of 120,000 QALYs per year) (Cohen et al. 2005). The choice of farmed versus wild-caught fish has caused some debate in the field of risk-benefit assessment. For example, it has been reported that globally, the concentrations of organochlorine contaminants have been higher in farmed salmon than in wild salmon, and thus, the consumption of farmed salmon may be a health risk (Hites et al. 2004). However, another risk-benefit analysis concluded that the consumption of farmed salmon fed with contaminated feed would cause 210 excess cancer deaths per year among 387 million inhabitants in the European Economic Area. However, the restriction of salmon consumption based on contamination would prevent 40 cancer deaths per year but the net health effect would be worsened by 5200 CVD and cancer deaths yearly (Tuomisto et al. 2004).

Although the epidemiological evidence regarding the beneficial net effect is strong, it is almost exclusively based on studies among populations with relatively low exposures to fish-derived contaminants.

3 Aims of the study

The general objective of the present work was to assess the overall effect of fish consumption on cardiovascular health using epidemiological methods and taking into account both beneficial and hazardous compounds in fish. The specific aims were:

I   To evaluate whether serum concentrations of fish-derived omega-3 PUFAs and environmental contaminants reflect fish consumption measured by a food frequency questionnaire, and whether separate frequency questions measure fish consumption equally well when compared with an FFQ on whole diet (Chapter 4).

II To investigate whether fish consumption is associated with the consumption of some other foods, especially those that are considered healthy (Chapter 5).

III To elucidate the association of fish consumption, serum fish-derived omega-3 PUFAs, and fish-derived environmental contaminants with cardiovascular risk factors, especially low-grade inflammation and early signs of atherosclerosis (Chapter 6).

IV To assess mortality among Finnish professional fishermen and their wives who typically have high consumption of contaminated Baltic Sea fish (Chapter 7).

Epidemiological studies on
fish consumption and
cardiovascular health

4 Dioxins, polychlorinated biphenyls, methylmercury and omega-3 polyunsaturated fatty acids as biomarkers of fish consumption

Turunen AW,[1] Männistö S,[2] Kiviranta H,[1] Marniemi J,[3] Jula A,[3] Tiittanen P,[1] Suominen-Taipale L,[1] Vartiainen T[1], Verkasalo PK[1]

[1]   National Institute for Health and Welfare, Department of Environmental Health, Kuopio, Finland
[2]   National Institute for Health and Welfare, Department of Chronic Disease Prevention, Helsinki, Finland
[3]   National Institute for Health and Welfare, Department of Chronic Disease Prevention, Turku, Finland

Abstract

Objective: To assess biomarkers and frequency questions as measures of fish consumption.

Subjects and methods: Participants numbered 125 men and 139 women (aged 22–74) in the Fishermen sub-study, and 577 men and 712 women (aged 45–74) in the Health 2000 sub-study. Fish consumption was measured by the same validated food frequency questionnaire (FFQ) in both of the studies with a further two separate frequency questions used only in the Fishermen sub-study. Dioxins, polychlorinated biphenyls (PCBs), and methylmercury (MeHg) (in the Fishermen sub-study alone), and omega-3 polyunsaturated fatty acids (omega-3 PUFAs) (in both studies) were analysed from fasting serum/blood samples.

Results: The Spearman's correlation coefficients between FFQ fish consumption and dioxins, PCBs, MeHg, and omega-3 PUFAs were respectively 0.46, 0.48, 0.43, and 0.38 among the Fishermen sub-study men, and 0.28, 0.36, 0.45, and 0.31 among the women. Similar correlation coefficients were observed between FFQ fish consumption and serum omega-3 PUFAs in the Health 2000 sub-study, and also between FFQ fish consumption and the frequency questions on fish consumption in the Fishermen sub-study. According to multiple regression modelling and LMG metrics, the most important fish consumption biomarkers were dioxins and PCBs among the men and MeHg among the women.

Conclusions: Environmental contaminants seemed to be slightly better fish consumption biomarkers than omega-3 PUFAs in the Baltic Sea area. The separate frequency questions measured fish consumption equally well when compared with the FFQ.

4.1 Introduction

Fish consumption is beneficial especially to cardiovascular health (Mozaffarian 2008; Calder and Yaqoob 2009). Conversely, fish may also be an important source of various toxic environmental contaminants, such as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs, called dioxins in this work), polychlorinated biphenyls (PCBs) (Kiviranta et al. 2004; Isosaari et al. 2006) and methylmercury (MeHg) (EFSA 2004).

Long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) are traditional fish consumption biomarkers (Hunter 1998). The relationship between habitual fish consumption measured by a food frequency questionnaire (FFQ) and blood concentration of omega-3 PUFAs has been assessed in several studies, for instance among Norwegians (Andersen et al. 1996), Englishmen (Welch et al. 2006), Americans (Sun et al. 2007), Canadians (Philibert et al. 2006), and Australians (Mina et al. 2007). In these studies, the correlation coefficients have ranged from 0.17 to 0.50 when total fish consumption was used. The correlation coefficients have been slightly higher for fatty fish, ranging from 0.19 to 0.50 (Philibert et al. 2006; Welch et al. 2006; Mina et al. 2007), and lower for lean fish, ranging from 0.01 to 0.12 (Welch et al. 2006; Mina et al. 2007).

Many environmental contaminants are fat-soluble and therefore originate mainly from fatty fish like omega-3 PUFAs. Serum concentrations of omega-3 PUFAs are affected by several dietary and non-dietary factors such as metabolism, genetics, and lifestyle (Hunter 1998), and they reflect intake only for the last few days (Arab 2003). The concentrations of environmental contaminants are known to vary according to region, fish species, and the age and size of the fish (Kiviranta et al. 2003; Isosaari et al. 2006; Domingo and Bocio 2007) but contaminants have very slow elimination in the human body and they accumulate even at low exposures (Tuomisto et al. 1999). Owing to accumulation, environmental contaminants may reflect long-term fish intake at least in those areas where fish is an important source of exposure. To the best of our knowledge, there are no studies where the relationship between habitual fish consumption measured by an FFQ on whole diet and tissue concentrations of environmental contaminants has been assessed. Overall, studies on the relationship between fish consumption and environmental contaminants are scarce (Svensson et al. 1991; Asplund et al. 1994; Svensson et al. 1995; Bergdahl et al. 1998; Arisawa et al. 2003; Björnberg et al. 2005).

The aim of this study was to compare the ability of environmental contaminants and omega-3 PUFAs to reflect fish consumption and primarily to investigate the usefulness of environmental contaminants as biomarkers of fish consumption. Another aim was to assess whether separate frequency questions measure fish consumption equally well when compared with an FFQ on whole diet. The

associations were studied in a population with high fish consumption, and when possible, the analyses were repeated in a larger general population sub-sample.

4.2 Materials and methods

4.2.1 Study populations

In the Nutrition, Environment and Health study, 1427 professional fishermen, their wives, and other family members answered a self-administered health questionnaire (Turunen et al. 2008). This study looked at the overall health effect of fish consumption in a high fish consumption population, that is, professional fishermen and their families. A total of 309 volunteers, aged 22–74 years, and living near the Helsinki and Turku study centres participated in a health examination study (the Fishermen sub-study). Of those, 125 men and 139 women reported fish consumption through the FFQ and separate frequency questions, and had data on blood concentrations of environmental contaminants and fatty acids.

Analyses regarding FFQ fish consumption and serum fatty acids were repeated using data from the population-based Health 2000 health examination survey, which looked at major public health problems and their determinants in a nationally representative population sample in Finland (n=7977) (Aromaa and Koskinen 2004). A total of 1526 volunteers, aged 45–74 years, and living near the study locations in the five university hospital districts of Finland (Helsinki, Turku, Tampere, Kuopio and Oulu) participated in an in-depth health examination study on cardiovascular disease and diabetes (the Health 2000 sub-study). Of these, 577 men and 712 women reported fish consumption through the FFQ and had data on blood concentrations of fatty acids.

Both the Fishermen sub-study and the Health 2000 sub-study were coordinated by the National Institute for Health and Welfare in Finland (THL–which includes the former National Public Health Institute, KTL). The studies were independent of each other, and had different study populations and time frames, although they had similar study protocols, which enables comparisons. The key features of the Fishermen sub-study were high fish consumption and analysed serum concentrations of environmental contaminants, whereas the key feature of the Health 2000 sub-study was a relatively large sample with fish consumption close to that of the general population.

4.2.2 Data collection

Fish consumption and other dietary variables

In both sub-studies, diet was assessed by the same validated self-administered FFQ designed to cover the whole diet during the preceding year (Männistö et al. 1996; Paalanen et al. 2006). The FFQ consisted of 128 food items and mixed dishes with specified serving sizes, including 10 fish dishes. The nine response options ranged from "never or seldom" to "six or more times per day" (see Appendix). Dietary data were processed in the Fineli Finnish Food Composition Database (National Institute for Health and Welfare 2008), and daily fish consumption (g/day), energy (MJ/day), alcohol (ethanol, g/day) and fatty acid (g/day) intakes, and the prevalence of fish oil supplement users were calculated. In the previous validation study, the same participants completed the FFQ twice, and reproducibility between the first and the second FFQ measurement was 0.63 for fish consumption. Validity between the first FFQ measurement and the 14-day food record measurement was 0.46 for fish consumption (Männistö et al. 1996).

Additionally in the Fishermen study, the health questionnaire contained two separate frequency questions to obtain information on fish consumption from a larger population (n=1427). The participants were asked about the frequency of use of 12 fish dishes and 12 fish species (see Appendix). For both frequency questions, the six response options ranged from "never" to "almost every day" and the frequencies were summed to four variables: fish dishes, fish species, fatty fish species, and lean fish species (times/month). Species containing fat more than 3.5% according to the Fineli Finnish Food Composition Database were included in fatty fish (see Appendix).

Serum/blood concentrations of environmental contaminants and fatty acids

In both studies, the blood samples were collected after 10–12 h of fasting and analysed using the same method. Blood samples were not available for environmental contaminant analyses in the Health 2000 sub-study.

Serum concentrations (pg/g or ng/g fat) of 17 dioxin and 37 PCB congeners were analysed using a high-resolution mass spectrometer equipped with a gas chromatograph (Kiviranta et al. 2002). Toxic equivalents (TEqs) for dioxins (WHO$_{PCDD/F}$-TEq) and PCBs (WHO$_{PCB}$-TEq) were calculated with the set of toxic equivalency factors (TEF) recommended by the WHO in 1998 (Van den Berg et al. 1998). In addition, four individual congeners were included in the analyses. Based on our previous studies, pentachlorodibenzofuran (2,3,4,7,8-PeCDF), PCB 126, and PCB 153 are likely to be correlated with fish consumption, whereas octachlorodibenzo-*p*-dioxin (OCDD) is likely to be uncorrelated with fish consumption (Kiviranta et al. 2002; Kiviranta et al. 2003). Blood MeHg concentration (ng/ml) was analysed from whole blood using an isotope dilution-gas chromatograph/mass spectrometer (Yang et al. 2003; Baxter et al. 2007). The

interassay coefficients of variation were 5.3% for $WHO_{PCDD/F}$-TEq, 9.6% for WHO_{PCB}-TEq, 6.7% for 2,3,4,7,8-PeCDF, 6.8% for OCDD, 12% for PCB 126, 7.3% for PCB 153, and 4.2% for MeHg.

Serum fatty acids (proportion from all serum fatty acids, % FAs) were analysed using a gas chromatograph and flame ionisation detector (Jula et al. 2005). Omega-3 PUFAs were defined here as the sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). α-Linolenic (ALA), palmitic, and stearic acids are known to be uncorrelated with fish consumption. Interassay coefficients of variation were 12% for EPA, 12% for DPA, 19% for DHA, 4.8% for ALA, 4.9% for palmitic acid, and 7.5% for stearic acid.

Other variables

Weight (kg, using a typical scales), height (cm, using a wall-mounted stadiometer), and waist and hip girth (cm, using a flexible measuring tape) were measured during the health examination, and body mass index (kg/m^2), waist-hip ratio and age at the time of the examination (years) were calculated. Data on smoking was obtained from a self-administered health questionnaire in the Fishermen sub-study, and from a structured interview in the Health 2000 sub-study. The following questions were asked both in the questionnaire and the interview: "Have you ever smoked?", "Have you smoked at least 100 times?", "Have you ever smoked regularly (that is, daily for at least one year)?", and "When did you last smoke?". The final smoking variable had five classes: "daily smoker", "occasional smoker", "ex-smoker, cessation 1–12 months ago", "ex-smoker, cessation over a year ago", and "never-smoker". In this study, the prevalence of daily or occasional smoking (current smoking) was reported. Daily or occasional smoker was defined as a participant who reported having smoked most recently on the current date, the previous day or from 2 to 30 days previously.

4.2.3 Statistical analyses

Cross-classification was used to assess agreement between the FFQ fish consumption and the fish consumption measured by the two separate frequency questions, that is, the ability of these dietary methods to classify individuals into the same fish consumption category. The participants were categorised into quartiles by FFQ fish, fish dishes, and fish species. The percentages of participants in the same quartile, in the same or adjacent quartile, and in the extreme quartile were calculated.

Non-parametric Spearman's correlation coefficients were calculated to assess the relationships between the FFQ fish, fish dishes, fish species, and serum/blood concentrations of environmental contaminants and fatty acids.

Epidemiological studies on
fish consumption and
cardiovascular health

For multiple linear regression analyses, all dietary and biochemical variables were log-transformed according to log(x+1). FFQ fish and fish dishes were considered as dependent variables and the biomarkers were considered as regressors. Dioxins and PCBs were not simultaneously included in the models due to high correlation (r=0.9). Age and total energy intake were included in all models. Additional adjusting for body mass index and the use of fish oil supplements did not change the results of the linear regression analyses and therefore age- and energy-adjusted results are shown. LMG metrics was used to assess the regressors' relative contributions to the model's total explanatory value, that is, the relative importance of the biomarkers. This method was chosen because regressors are typically correlated and model R^2 cannot be broken down into shares from the individual regressors. In the procedure, the sequential sums of squares were averaged over all orderings of the regressors (Lindeman et al. 1980; Kruskal 1987). The partial R^2 by LMG metrics and 95% bootstrap CI was calculated by using the relaimpo package in the R statistical software (R Development Core Team 2009; Grömping 2006) (Table 5).

4.3 Results

The Fishermen sub-study participants were, on average, 5 years younger, and had slightly higher alcohol intake and prevalence of fish oil supplement use, and a smaller waist-hip ratio than the Health 2000 sub-study participants. On the basis of the FFQ on whole diet, all the participants of the Fishermen sub-study reported eating fish, whereas three men and seven women of the Health 2000 sub-study reported not eating fish (Table 1). FFQ fish consumption and serum concentrations of omega-3 PUFAs were approximately 1.5-fold among the Fishermen sub-study participants when compared with the Health 2000 sub-study participants (Table 2). The Fishermen sub-study participants were professional fishermen, fishermen's wives, and other family members, who are known to eat a lot of fish possibly due to easy availability.

FFQ fish and fish dishes were able to classify 47% of the Fishermen sub-study men into the same quartile and 87% into the same or adjacent quartile (data not shown). The corresponding proportions for fish species were 51% and 85%. Among the women, FFQ fish and fish dishes were able to classify 51% of the women into the same quartile and 88% into the same or adjacent quartile. The corresponding proportions for fish species were 37% and 78%. The proportion of grossly misclassified (classified into extreme quartiles) participants was approximately 2% among the men and 6% among the women, the same for fish dishes and fish species. The age-adjusted correlation coefficients between FFQ fish and separate frequency questions on fish consumption were 0.62 for fish dishes, 0.64 for fish species, 0.55

for fatty fish species, and 0.32 for lean fish species among the men (data not shown). The corresponding coefficients were 0.61, 0.44, 0.39, and 0.21 among the women.

The age-adjusted correlation coefficients between FFQ fish and serum/blood environmental contaminants were 0.46 for dioxins, 0.48 for PCBs, and 0.43 for MeHg among the Fishermen sub-study men (Table 3). Among the women, the corresponding correlation coefficients were 0.28 for dioxins, 0.36 for PCBs, and 0.45 for MeHg. When compared with FFQ fish, fish dishes yielded approximately 10–15% lower correlation coefficients with environmental contaminants among the men, and approximately 10–35% higher correlation coefficients among the women. Fish species yielded less than 10% lower correlation coefficients with environmental contaminants when compared with FFQ fish in both sexes.

When compared with $WHO_{PCDD/F}$-TEq, dioxin congener 2,3,4,7,8-PeCDF yielded equal correlation coefficients with all fish consumption variables among the men, and approximately 20% higher correlation coefficients among the women. PCB congener 126 yielded equal correlation coefficients with all fish consumption variables when compared with WHO_{PCB}-TEq in both sexes. As expected, dioxin congener OCDD had a weak correlation with fish consumption.

The age-adjusted correlation coefficients between FFQ fish and serum omega-3 PUFAs were 0.38 among the men and 0.31 among the women of the Fishermen sub-study. The corresponding coefficients were approximately 10% lower among the Health 2000 sub-study participants (Table 4). When compared with FFQ fish, fish dishes yielded less than 10% lower correlation coefficient and fish species a 16% lower correlation coefficient with serum omega-3 PUFAs among the Fishermen sub-study men. Among the women, fish dishes yielded 10% higher correlation coefficient and fish species a 35% lower correlation coefficient with serum omega-3 PUFAs when compared with FFQ fish. As expected, the correlation coefficients between FFQ fish and serum concentrations of ALA and the sum of palmitic and stearic acid were close to zero.

In the multiple regression modelling, all four fish consumption biomarkers were statistically significantly associated with FFQ fish, when considered in separate models (Table 5). In model 5 (dioxins, MeHg, and omega-3 PUFAs as regressors) and 6 (PCBs, MeHg, and omega-3 PUFAs as regressors), all three environmental contaminants, though not omega-3 PUFAs, were statistically significantly associated with FFQ fish among the Fishermen sub-study men. Among the women, only MeHg was statistically significantly associated with FFQ fish. Using LMG metrics to assess the relative importance of the regressors, we found that dioxins (partial R^2 13%, 95% bootstrap CI 6.9–21) and PCBs (15%, 7.8–23) had the largest relative contribution to the model's total explanatory value among the men, although the contribution of MeHg was not notably lower (8.6%, 3.6–16 in model 5; 8.1%, 3.2–15 in model 6). In contrast, MeHg (16%, 8.9–25 in model 5; 16%, 8.5–24 in model 6) was clearly the most important biomarker among the women. When fish dishes was considered as the dependent variable, the differences between the relative

contributions of the biomarkers almost disappeared among the men, while MeHg remained the most important biomarker among the women (Table 5).

4.4 Discussion

In this study, serum/blood environmental contaminants seemed to be slightly better fish consumption biomarkers than serum omega-3 PUFAs. Dioxins and PCBs were the most important biomarkers among the men, whereas MeHg was the most important among the women. There was a satisfactory agreement between fish consumption from the FFQ on whole diet and the separate frequency questions.

This is one of the rare studies using data on both a validated FFQ on whole diet (Männistö et al. 1996; Paalanen et al. 2006) and serum/blood concentrations of environmental contaminants. To the best of our knowledge, this is also the first study to assess the relative importance of different fish consumption biomarkers. LMG metrics has only been used rarely but remains, to our knowledge, the best method to quantify the relative contributions of the regressors to the model's total explanatory value (Grömping 2006).

As to the limitations of this study, FFQ measures the usual long-term diet, for example, over the past year, whereas serum fatty acid concentration reflects intake over the past few days. Adipose tissue would have been the most preferable media for fatty acid analyses as it reflects long-term dietary intake under homeostatic conditions (Arab 2003). In addition, FFQ is designed to rank individuals according to their dietary intake and not to measure absolute intake. Thus, there can be some measurement error in FFQ estimates due to under- and over reporting (Willett 1998). Our FFQ has been reported to somewhat overestimate fish consumption (Männistö et al. 1996). In addition, the use of a total fish consumption variable including both fatty (oily) and lean (white) fish may also have attenuated the studied associations as lean fish typically has lower correlations with serum omega-3 PUFAs than fatty fish. In general, concentration biomarkers are not always affordable or even eligible for validation purposes or as a surrogate source of dietary data (Jenab et al. 2009). They are affected by many non-dietary factors such as metabolism, genetics and life style (for example, smoking, obesity, and physical activity) (Hunter 1998).

The correlation coefficients between FFQ fish consumption and serum omega-3 PUFAs were almost of the same magnitude in the Fishermen sub-study and in the Health 2000 sub-study. This indicates that the results of the Fishermen sub-study are probably generalisable at least to the Finnish general population.

The validated FFQ on whole diet (Männistö et al. 1996; Paalanen et al. 2006) and separate frequency questions on fish consumption were independent and unrelated sources of fish consumption data. However, they seemed to classify the majority of the participants into the same or adjacent fish consumption quartile, and their

THL — Research 79/2012   **44**   Epidemiological studies on
fish consumption and
cardiovascular health

agreement can be considered good as less than 10% of the participants were grossly misclassified (Masson et al. 2003). Thus, the non-validated frequency questions may be used as measures of fish consumption in further epidemiological studies.

In the Fishermen sub-study, fish consumption yielded higher correlation coefficients with environmental contaminants than with omega-3 PUFAs. This is probably due to the fact that dioxins and PCBs accumulate, and their serum concentrations are fairly stable and slowly rising (Tuomisto et al. 1999).

The men in the study had higher correlation coefficients between fish consumption variables and serum/blood biomarkers when compared with the women, and the importance of the biomarkers differed by sex. This may be explained partly by the higher variation in fish consumption and lower volume of distribution (lower proportion of body fat) for fat-soluble compounds among men. Furthermore, lower concentrations of dioxins and PCBs among the women may have increased the relative importance of MeHg as a fish consumption biomarker.

Among the women, fish dishes yielded approximately 10–35% higher correlation coefficients with biomarkers than FFQ fish and approximately 15–40% higher correlation coefficients than fish species. Question on fish dishes had more indications of food preparation methods (for example, cooked, baked, fried, and smoked fish) than the FFQ (for example, frozen fish, salmon dishes, Baltic herring dishes, and whitefish/perch/vendace/pike), and therefore that question may have suited the women better. Conversely, the men may be better in reporting fish species than the women, possibly due to practical experience in fishing.

Regarding those few studies using environmental contaminants as fish consumption biomarkers, a Japanese study reported correlation coefficients ranging from 0.09 to 0.32 (depending on the investigated fish type) between fish consumption frequency (from a frequency questionnaire) and serum dioxins or PCBs in both sexes combined (Arisawa et al. 2003). Lower correlation coefficients when compared with this study may be due to lower exposure to dioxins and PCBs as well as the lack of a measure for total fish consumption. In Sweden, the correlation coefficient between total fish consumption (from a dietary interview) and plasma 2,3,7,8-TCDD was 0.84 (Svensson et al. 1991), and the correlation coefficient between total fish consumption (from a frequency questionnaire) and different serum PCB congeners ranged from 0.63 to 0.87 (Asplund et al. 1994). The higher correlation coefficients when compared with those seen in this study are probably due to higher exposure to dioxins and PCBs and a small study group (n=34) consisting of men from extreme fish consumption groups.

In this study, MeHg was analysed from whole blood as it was available for all the study participants. Although concentrations in hair are most commonly used in epidemiological studies, whole-blood concentrations correlate well with hair concentrations (Björnberg et al. 2005). Two Swedish studies have reported correlation coefficients around 0.50 between total fish consumption (from dietary

interviews) and blood MeHg (Svensson et al. 1995; Bergdahl et al. 1998), which is only marginally higher than in this study.

In this study, fatty acids were analysed from total serum including all three lipid fractions (cholesterol esters, phospholipids and triglycerides), which reflects intake over the last few days only (Arab 2003) but has been shown to be a feasible biomarker (Hodson et al. 2008) and more affordable than sub-fraction analysis (Baylin et al. 2005). Only three of the previous studies (Andersen et al. 1999; Philibert et al. 2006; Sun et al. 2007) using an FFQ have used total serum or plasma to analyse fatty acids. Two of them reported correlation coefficients around 0.50 between FFQ fish consumption (total fish) or FFQ omega-3 PUFA intake and serum omega-3 PUFAs (Andersen et al. 1999; Philibert et al. 2006). Reasons for the slightly higher correlation coefficients when compared with this study may be the use of a selected occupational group as a study population (Andersen et al. 1999), and using an FFQ with a special emphasis on fish consumption (Philibert et al. 2006). In the previous studies, phospholipids have been the most common choice for fatty acid analyses. The correlation coefficients between FFQ fish consumption (total fish) or FFQ omega-3 PUFA intake and serum omega-3 PUFAs have been slightly lower than in this study, ranging from 0.09 to 0.36 and being typically around 0.20 and 0.30 (Ma et al. 1995; Andersen et al. 1996; Hjårtaker et al. 1997; Li et al. 2001; Woods et al. 2002; Kobayashi et al. 2003; Welch et al. 2006). One study using erythrocytes reported similar correlation coefficients (Mina et al. 2007) to this study. In the previous studies, the correlation coefficients between FFQ fish and serum omega-3 PUFAs have been somewhat higher when fatty fish was used. In our study, only total fish consumption was available from the FFQ.

To conclude, self-reported fish consumption was reflected reasonably well in serum/blood concentrations of dioxins, PCBs, MeHg, and omega-3 PUFAs. The associations were approximately at the same level as those reported in earlier studies. The results of our study indicate that serum/blood concentrations of dioxins, PCBs, and MeHg may be better fish consumption biomarkers than serum concentrations of omega-3 PUFAs. However, this may be generalisable only to those populations where fish is an important source of these environmental contaminants like in the Baltic Sea area. The relative importance of the biomarkers seemed to differ between the sexes. Dioxins and PCBs were the most important biomarkers among the men, whereas MeHg was the most important biomarker among the women. The separate frequency questions appeared to yield equally good estimates of habitual fish consumption as the FFQ on whole diet, and they may be used in further epidemiological studies.

Table 1. Characteristics of the Fishermen sub-study and Health 2000 sub-study participants

| | Fishermen sub-study | | | | Health 2000 sub-study[a] | | | |
| | Men (n=125) | | Women (n=139) | | Men (n=577) | | Women (n=712) | |
	Mean	SE[b]	Mean	SE[b]	Mean	SE[b]	Mean	SE[b]
Age (years)	53	0.93	50	1.0	58	0.33	58	0.31
Height (cm)	178	0.59	165	0.49	176	0.29	162	0.24
Weight (kg)	88	1.3	74	1.4	85	0.57	71	0.49
Body mass index (kg/m^2)	28	0.38	27	0.50	27	0.16	27	0.18
Waist-hip ratio	0.95	0.0052	0.82	0.0054	0.98	0.0025	0.86	0.0023
Energy intake (MJ/day)	9.9	0.28	8.7	0.20	9.5	0.14	8.9	0.12
Alcohol intake, ethanol (g/day)	12	1.5	4.0	0.44	8.1	0.48	3.5	0.25
Fish consumer (%)	100	-	100	-	99	-	99	-
Fish oil supplement user (%)	5.6	-	7.9	-	1.6	-	3.2	-
Current smoker (%)	26	-	19	-	27	-	19	-

[a] a sub-population of the population-based Health 2000 health examination survey
[b] standard error of the mean

Epidemiological studies on
fish consumption and
cardiovascular health

Table 2. Age-adjusted means for the variables from the FFQ on whole diet, the frequency questions on fish consumption, and blood sample analyses among the Fishermen sub-study and Health 2000 sub-study participants

	Fishermen sub-study				Health 2000 sub-study[a]			
	Men (n=125)		Women (n=139)		Men (n=577)		Women (n=712)	
	Mean	SE[b]	Mean	SE[b]	Mean	SE[b]	Mean	SE[b]
FFQ on whole diet								
FFQ fish (g/day)	80	4.7	61	4.4	48	1.6	46	1.4
Omega-3 PUFAs (g/day)[c]	1.3	0.079	0.97	0.075	0.85	0.028	0.81	0.026
Frequency questions on fish consumption								
Fish dishes (times/month)	14	0.83	12	0.79	-	-	-	-
Fish species (times/month)	14	0.89	12	0.85	-	-	-	-
Fatty fish species (times/month)	7.3	0.44	5.9	0.42	-	-	-	-
Lean fish species (times/month)	4.8	0.51	5.0	0.48	-	-	-	-
Serum/blood contaminants								
WHO$_{PCDD/F}$-TEq (pg/g fat)[d]	75	4.0	46	3.8	-	-	-	-
2,3,4,7,8-PeCDF (pg/g fat)	85	4.9	46	4.7	-	-	-	-
OCDD (pg/g fat)	320	19	410	18	-	-	-	-
WHO$_{PCB}$-TEq (pg/g fat)[e]	55	3.3	31	3.1	-	-	-	-
PCB 126 (pg/g fat)	190	13	120	12	-	-	-	-
PCB 153 (ng/g fat)	410	26	200	24	-	-	-	-
MeHg (ng/ml)	5.2	0.47	2.9	0.45	-	-	-	-
Serum fatty acids								
Omega-3 PUFAs (% FAs)[f,g]	6.8	0.26	6.8	0.24	3.9	0.067	4.0	0.060
EPA (% FAs)[g]	2.2	0.14	1.8	0.14	1.2	0.031	1.2	0.028
DHA (% FAs)[g]	3.9	0.16	4.4	0.15	2.2	0.036	2.2	0.032
DPA (% FAs)[g]	0.68	0.016	0.62	0.015	0.50	0.0055	0.49	0.0049
ALA (% FAs)[g]	0.90	0.023	0.89	0.021	0.81	0.0098	0.81	0.0088
Palmitic and stearic acids (% FAs)[g]	30	0.30	31	0.28	32	0.088	32	0.079

Abbreviations: ALA, a-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FFQ, food frequency questionnaire; MeHg, methylmercury; OCDD, octachlorodibenzo-*p*-dioxin; PCB, polychlorinated biphenyl; PeCDF, pentachlorodibenzofuran; PUFA, polyunsaturated fatty acid; TEq, toxic equivalent; WHO, World Health Organization

[a] a sub-population of the population-based Health 2000 health examination survey
[b] standard error of the mean
[c] the sum of EPA, DHA, and DPA, as well as eicosatrienoic, eicosatetraenoic, heneicosapentaenoic, and docosatetraenoic acid
[d] World Health Organization's toxic equivalent quantity for dioxins
[e] World Health Organization's toxic equivalent quantity for polychlorinated biphenyls
[f] the sum of EPA, DHA and DPA
[g] proportion from all serum fatty acids

Table 3. Age-adjusted Spearman's correlation coefficients between serum/blood environmental contaminants and fish consumption variables from the FFQ on whole diet and the frequency questions on fish consumption among the Fishermen sub-study participants

	Serum/blood contaminants						
	"WHO$_{PCDD/F}$-TEq (pg/g fat)[a]	2,3,4,7,8-PeCDF (pg/g fat)	OCDD (pg/g fat)	WHO$_{PCB}$-TEq (pg/g fat)[b]	PCB 126 (pg/g fat)	PCB 153 (ng/g fat)	MeHg (ng/ml)
Fishermen sub-study men (n=125)							
FFQ on whole diet							
FFQ fish (g/day)	0.46	0.47	0.19	0.48	0.50	0.41	0.43
Omega-3 PUFAs (g/day)[c]	0.44	0.45	0.16	0.42	0.48	0.35	0.36
Frequency questions on fish consumption							
Fish dishes (times/month)	0.40	0.42	0.08	0.40	0.41	0.40	0.39
Fish species (times/month)	0.44	0.45	0.07	0.45	0.44	0.42	0.40
Fatty fish species (times/month)	0.41	0.42	0.08	0.33	0.39	0.33	0.22
Lean fish species (times/month)	0.12	0.13	0.03	0.20	0.21	0.19	0.21
Serum/blood contaminants							
2,3,4,7,8-PeCDF (pg/g fat)	0.99	1	-	-	-	-	-
OCDD (pg/g fat)	0.21	0.18	1	-	-	-	-
WHO$_{PCB}$-TEq (pg/g fat)[b]	0.90	0.90	0.23	1	-	-	-
PCB 126 (pg/g fat)	0.90	0.89	0.26	0.91	1	-	-
PCB 153 (ng/g fat)	0.84	0.84	0.21	0.96	0.80	1	-
MeHg (ng/ml)	0.58	0.56	0.19	0.62	0.60	0.53	1
Serum fatty acids							
Omega-3 PUFAs (% FAs)[d,e]	0.60	0.58	0.23	0.52	0.59	0.46	0.49
EPA (% FAs)[e]	0.54	0.54	0.18	0.48	0.53	0.42	0.44
DHA (% FAs)[e]	0.57	0.56	0.20	0.51	0.58	0.45	0.48
ALA (% FAs)[e]	-0.18	-0.16	-0.12	-0.11	-0.17	-0.07	-0.02
Palmitic and stearic acid (% FAs)[e]	0.03	0.03	0.08	-0.07	0.03	-0.12	-0.07

(Table 3. Continued)

	Fishermen sub-study women (n=139)						
FFQ on whole diet							
FFQ fish (g/day)	0.28	0.34	-0.11	0.36	0.32	0.31	0.45
Omega-3 PUFAs (g/day)[c]	0.20	0.26	-0.09	0.26	0.23	0.23	0.31
Frequency questions on fish consumption							
Fish dishes (times/month)	0.38	0.44	0.08	0.46	0.45	0.40	0.50
Fish species (times/month)	0.27	0.32	0.02	0.34	0.35	0.27	0.42
Fatty fish species (times/month)	0.26	0.32	-0.14	0.27	0.29	0.23	0.27
Lean fish species (times/month)	0.15	0.18	0.10	0.21	0.21	0.20	0.29
Serum/blood contaminants							
2,3,4,7,8-PeCDF (pg/g fat)	0.97	1	-	-	-	-	-
OCDD (pg/g fat)	0.23	0.15	1	-	-	-	-
WHO_{PCB}-TEq (pg/g fat)[b]	0.90	0.90	0.16	1	-	-	-
PCB 126 (pg/g fat)	0.81	0.82	0.19	0.91	1	-	-
PCB 153 (ng/g fat)	0.86	0.86	0.13	0.91	0.72	1	-
MeHg (ng/ml)	0.55	0.58	0.11	0.62	0.61	0.53	1
Serum fatty acids							
Omega-3 PUFAs (% FAs)[d,e]	0.20	0.25	-0.03	0.26	0.29	0.20	0.26
EPA (% FAs)[e]	0.29	0.31	-0.05	0.30	0.33	0.25	0.34
DHA (% FAs)[e]	0.16	0.21	0.00	0.24	0.26	0.18	0.23
ALA (% FAs)[e]	0.16	0.14	-0.04	0.13	0.07	0.12	0.08
Palmitic and stearic acid (% FAs)[e]	-0.14	-0.10	-0.13	-0.08	-0.02	-0.10	-0.12

Abbreviations: ALA, α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FFQ, food frequency questionnaire; MeHg, methylmercury; OCDD, octachlorodibenzo-*p*-dioxin; PCB, polychlorinated biphenyl; PeCDF, pentachlorodibenzofuran; PUFA, polyunsaturated fatty acid; TEq, toxic equivalent; WHO, World Health Organization

[a] World Health Organization's toxic equivalent quantity for dioxins
[b] World Health Organization's toxic equivalent quantity for polychlorinated biphenyls
[c] the sum of EPA, DHA, and DPA, as well as eicosatrienoic, eicosatetraenoic, heneicosapentaenoic, and docosatetraenoic acid
[d] the sum of EPA, DHA, and DPA
[e] proportion from all serum fatty acids

Table 4. Age-adjusted Spearman's correlation coefficients between serum fatty acids and fish consumption variables from the FFQ on whole diet and the frequency questions on fish consumption among the Fishermen sub-study and Health 2000 sub-study participants

	Serum fatty acids				
	Omega-3 PUFAs (% FAs)[a,b]	EPA (% FAs)[b]	DHA (% FAs)[b]	ALA (% FAs)[b]	Palmitic and stearic acid (% FAs)[b]
Fishermen sub-study men (n=125)					
FFQ on whole diet					
FFQ fish (g/day)	0.38	0.36	0.37	-0.00	-0.05
Omega-3 PUFAs (g/day)[c]	0.43	0.42	0.40	-0.01	-0.03
Frequency questions on fish consumption					
Fish dishes (times/month)	0.35	0.34	0.35	-0.06	-0.04
Fish species (times/month)	0.32	0.33	0.33	-0.01	-0.10
Fatty fish species (times/month)	0.36	0.35	0.36	-0.09	0.04
Lean fish species (times/month)	0.09	0.14	0.10	0.08	-0.19
Fishermen sub-study women (n=139)					
FFQ on whole diet					
FFQ fish (g/day)	0.31	0.19	0.29	0.01	0.02
Omega-3 PUFAs (g/day)[c]	0.32	0.27	0.27	-0.01	0.00
Frequency questions on fish consumption					
Fish dishes (times/month)	0.34	0.34	0.27	0.04	-0.05
Fish species (times/month)	0.20	0.24	0.16	-0.02	-0.03
Fatty fish species (times/month)	0.25	0.38	0.18	0.12	-0.08
Lean fish species (times/month)	0.04	0.07	0.01	-0.11	0.03
Health 2000 sub-study[d] men (n=577)					
FFQ on whole diet					
FFQ fish (g/day)	0.35	0.29	0.37	0.02	0.03
Omega-3 PUFAs (g/day)[c]	0.35	0.29	0.38	0.02	0.02
Health 2000 sub-study[d] women (n=712)					
FFQ on whole diet					
FFQ fish (g/day)	0.27	0.26	0.26	0.02	-0.06
Omega-3 PUFAs (g/day)[c]	0.29	0.27	0.28	0.01	-0.04

Abbreviations: ALA, a-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FFQ, food frequency questionnaire; PUFA, polyunsaturated fatty acid

[a] the sum of EPA, DHA, and DPA
[b] proportion from all serum fatty acids
[c] the sum of EPA, DHA, and DPA, as well as eicosatrienoic, eicosatetraenoic, heneicosapentaenoic, and docosatetraenoic acid
[d] a sub-population of the population-based Health 2000 health examination survey

Table 5. Results of multiple linear regression analyses between each of the two fish consumption variables (FFQ fish and fish dishes) and fish consumption biomarkers among the Fishermen sub-study participants

Fishermen sub-study men (n=125)

		β	SE[b]	p value	Adjusted model R² %	Partial R² by LMG metrics[a] %	95% CI
FFQ fish (g/day)							
Model 1	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.43	0.075	<0.01	32	23	13–34
Model 2	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.42	0.069	<0.01	34	25	15–36
Model 3	Blood MeHg (ng/ml)	0.39	0.079	<0.01	28	17	6.8–28
Model 4	Serum omega-3 PUFAs (% FAs)[e,f]	0.68	0.16	<0.01	25	14	5.9–26
Model 5	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.28	0.096	<0.01	25	13	6.9–21
	Blood MeHg (ng/ml)	0.20	0.091	0.03		8.6	3.6–16
	Serum omega-3 PUFAs (% FAs)[e,f]	0.17	0.18	0.35		6.2	2.2–13
Model 6	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.29	0.087	<0.01	35	15	7.8–23
	Blood MeHg (ng/ml)	0.16	0.093	0.08		8.1	3.2–15
	Serum omega-3 PUFAs (% FAs)[e,f]	0.21	0.17	0.23		6.3	2.3–14
Fish dishes (times/month)							
Model 1	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.38	0.074	<0.01	21	19	8.4–30
Model 2	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.34	0.070	<0.01	20	18	7.8–32
Model 3	Blood MeHg (ng/ml)	0.37	0.077	<0.01	20	17	4.2–30
Model 4	Serum omega-3 PUFAs (% FAs)[e,f]	0.68	0.15	<0.01	18	16	6.7–28
Model 5	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.20	0.095	0.03	26	10	4.1–17
	Blood MeHg (ng/ml)	0.19	0.090	0.03		8.5	2.7–17
	Serum omega-3 PUFAs (% FAs)[e,f]	0.26	0.18	0.15		7.1	2.3–14
Model 6	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.17	0.087	0.05	25	9.4	3.6–18
	Blood MeHg (ng/ml)	0.18	0.093	0.05		8.3	2.2–17
	Serum omega-3 PUFAs (% FAs)[e,f]	0.32	0.17	0.07		7.6	2.6–15

Fishermen sub-study women (n=139)

		β	SE[b]	p value	Adjusted model R² %	Partial R² by LMG metrics[a] %	95% CI
FFQ fish (g/day)							
Model 1	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.37	0.096	<0.01	14	10	4.0–18
Model 2	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.37	0.086	<0.01	16	13	5.2–21
Model 3	Blood MeHg (ng/ml)	0.62	0.097	<0.01	27	23	13–32
Model 4	Serum omega-3 PUFAs (% FAs)[e,f]	0.61	0.18	<0.01	12	8.3	2.0–18
Model 5	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.045	0.11	0.68	28	4.6	2.0–9.2
	Blood MeHg (ng/ml)	0.54	0.12	<0.01		16	8.8–25
	Serum omega-3 PUFAs (% FAs)[e,f]	0.33	0.17	0.06		4.6	1.0–11
Model 6	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.065	0.10	0.52	28	5.7	2.4–11
	Blood MeHg (ng/ml)	0.52	0.12	<0.01		16	8.3–25
	Serum omega-3 PUFAs (% FAs)[e,f]	0.32	0.18	0.07		4.4	0.9–11
Fish dishes (times/month)							
Model 1	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.48	0.092	<0.01	18	17	8.1–27
Model 2	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.47	0.082	<0.01	21	19	9.8–30
Model 3	Blood MeHg (ng/ml)	0.67	0.095	<0.01	28	27	15–40
Model 4	Serum omega-3 PUFAs (% FAs)[e,f]	0.75	0.18	<0.01	14	13	4.6–24
Model 5	Serum WHO$_{PCDD/F}$-TEq (pg/g fat)[c]	0.16	0.10	0.12	33	8.0	3.6–14
	Blood MeHg (ng/ml)	0.49	0.12	<0.01		18	8.9–27
	Serum omega-3 PUFAs (% FAs)[e,f]	0.45	0.17	0.01		7.4	2.1–15
Model 6	Serum WHO$_{PCB}$-TEq (pg/g fat)[d]	0.17	0.097	0.09	33	9.3	4.3–16
	Blood MeHg (ng/ml)	0.47	0.12	<0.01		17	9.4–26
	Serum omega-3 PUFAs (% FAs)[e,f]	0.43	0.17	0.012		7.0	2.6–14

Abbreviations: DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FFQ, food frequency questionnaire; PUFA, polyunsaturated fatty acid; TEq, toxic equivalent; WHO, World Health Organization

Fish consumption and biomarker variables are log transformed, adjusted for age and total energy intake.

[a] regressors' relative contribution to the model's total explanatory value with 95% bootstrap confidence interval, i.e., the relative importance of the biomarker
[b] standard error of the beta coefficient
[c] World Health Organization's toxic equivalent quantity for dioxins
[d] World Health Organization's toxic equivalent quantity for polychlorinated biphenyls
[e] the sum of EPA, DHA, and DPA
[f] proportion from all serum fatty acids

Appendix

Details of the original fish consumption questions

FFQ on whole diet (available for the Fishermen sub-study and the Health 2000 sub-study)

FFQ fish (g/day):
How often have you eaten the following foods during the past 12 months?

Food list	Frequency response options
fish soup, plateful	never or seldom
frozen fish or fish sticks, 1 portion	1–3 times per month
salmon or rainbow trout dishes, 1 portion	once per week
Baltic herring dishes, 1 portion	2–4 times per week
whitefish, perch, vendace or pike, 1 portion	5–6 times per week
spiced or salted fish, 1 portion	once per day
tuna or other canned fish, 0.5 dl	2–3 times per day
fish in rye crust (a traditional Finnish dish), 150 g	4–5 times per day
	6+ times per day

Frequency questions on fish consumption in a health questionnaire (available only for the Fishermen sub-study)

Fish dishes (times/month):
How often do you eat the following fish dishes with your meals?

Food list	Frequency response options
cooked fish (e.g., in fish soup)	never
oven-baked fish	less frequently than once per month
pan-fried fish	1–2 times per month
smoked fish (cold or warm smoked)	once per week
salted fish (e.g., rawpickled)	a couple of times per week
spiced fish (e.g., pickled herring)	almost every day
fish balls or fish loaf	
fish sticks	
fish in rye crust	
domestic canned fish	
foreign canned fish	
roe	

Fish species (times/month):
How often do you eat the following fish species?

Food list	Frequency response options
frozen fish (coalfish, cod, redfish, fish sticks)[a]	never
canned ocean fish (tuna, sardine, herring, mackerel)[b]	less frequently than once per month
rainbow trout (e.g., fresh, frozen, canned)[b]	1–2 times per month
Baltic herring (e.g., fresh, frozen, canned)[b]	once per week
predatory fish from inland waters (pike, perch, burbot, pike-perch)[a]	a couple of times per week
vendace[a]	almost every day
other fish from inland waters (whitefish, bream, roach)[a]	
Baltic salmon and trout[b]	
other Baltic fish[a]	
other ocean fish (e.g., smoked mackerel, Norwegian salmon)[b]	

[a] included in lean fish species
[b] included in fatty fish species

Acknowledgements

References

Andersen LF, Solvoll K, Drevon CA. Very-long-chain n-3 fatty acids as biomarkers for intake of fish and n-3 fatty acid concentrates. Am J Clin Nutr. 1996; 64(3):305-311.

Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol. 1999; 150(1):75-87.

Arab L. Biomarkers of fat and fatty acid intake. J Nutr. 2003; 133 Suppl 3(925S-932S.

Arisawa K, Matsumura T, Tohyama C, Saito H, Satoh H, Nagai M, et al. Fish intake, plasma omega-3 polyunsaturated fatty acids, and polychlorinated dibenzo-p-dioxins/polychlorinated dibenzo-furans and co-planar polychlorinated biphenyls in the blood of the Japanese population. Int Arch Occup Environ Health. 2003; 76(3):205-215.

Aromaa A, Koskinen S. Health and functional capacity in Finland. Baseline Results of the Health 2000 Health Examination Survey. National Public Health Institute. Report No.: B12/2004. Available at: http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2004b12.pdf

Asplund L, Svensson BG, Nilsson A, Eriksson U, Jansson B, Jensen S, et al. Polychlorinated biphenyls, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT) and 1,1-dichloro-2,2-bis(p-chlorophenyl)-ethylene (p,p'-DDE) in human plasma related to fish consumption. ArchEnvironHealth. 1994; 49(6):477-486.

Baxter DC, Rodushkin I, Engstrom E, Klockare D, Waara H. Methylmercury measurement in whole blood by isotope-dilution GC-ICPMS with 2 sample preparation methods. Clin Chem. 2007; 53(1):111-116.

Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, et al. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol. 2005; 162(4):373-381.

Bergdahl IA, Schutz A, Ahlqwist M, Bengtsson C, Lapidus L, Lissner L, et al. Methylmercury and inorganic mercury in serum--correlation to fish consumption and dental amalgam in a cohort of women born in 1922. Environ Res. 1998; 77(1):20-24.

Björnberg KA, Vahter M, Grawe KP, Berglund M. Methyl mercury exposure in Swedish women with high fish consumption. Sci Total Environ. 2005; 341(1-3):45-52.

Calder PC, Yaqoob P. Omega-3 polyunsaturated fatty acids and human health outcomes. Biofactors. 2009; 35(3):266-272.

Domingo JL, Bocio A. Levels of PCDD/PCDFs and PCBs in edible marine species and human intake: A literature review. Environ Int. 2007; 33(3):397-405.

European Food Safety Authority. Opinion of the scientific panel on contaminants in the food chain on a request from the Commission related to mercury and methylmercury in food. EFSA Journal. 2004; (34):1-14.

Grömping U. Relative importance for linear regression in R: The package relaimpo

Journal of Statistical Software. 2006; 17(1):1-27.

Hjårtaker A, Lund E, Bjerve KS. Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. Eur J Clin Nutr. 1997; 51(11):736-742.

Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Prog Lipid Res. 2008; 47(5):348-380.

Hunter DJ. Biochemical indicators of dietary intake. In: Willett W, editor. Nutritional Epidemiology. New York: Oxford University Press; 1998.

Isosaari P, Hallikainen A, Kiviranta H, Vuorinen PJ, Parmanne R, Koistinen J, et al. Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls, naphthalenes and polybrominated diphenyl ethers in the edible fish caught from the Baltic Sea and lakes in Finland. Environ Pollut. 2006; 141(2):213-225.

Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet. 2009; 125(5-6):507-525.

Jula A, Marniemi J, Ronnemaa T, Virtanen A, Huupponen R. Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: a randomized controlled trial. Arterioscler Thromb Vasc Biol. 2005; 25(9):1952-1959.

Kiviranta H, Ovaskainen ML, Vartiainen T. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environ Int. 2004; 30(7):923-932.

Kiviranta H, Vartiainen T, Parmanne R, Hallikainen A, Koistinen J. PCDD/Fs and PCBs in Baltic herring during the 1990s. Chemosphere. 2003; 50(9):1201-1216.

Kiviranta H, Vartiainen T, Tuomisto J. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 2002; 110(4):355-361.

Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Tsugane S. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess fatty acid intake: comparison with dietary records and serum phospholipid level. J Epidemiol. 2003; 13(1 Suppl):S64-81.

Kruskal W. Relative importance by averaging over orderings. The American Statistician. 1987; 41(1):6-10.

Li D, Zhang H, Hsu-Hage BH, Wahlqvist ML, Sinclair AJ. The influence of fish, meat and polyunsaturated fat intakes on platelet phospholipid polyunsaturated fatty acids in male Melbourne Chinese and Caucasian. Eur J Clin Nutr. 2001; 55(12):1036-1042.

Lindeman RH, Merenda PF, Gold RZ. Introduction to Bivariate and Multivariate Analysis. Scott Foresman & Co; 1980.

Ma J, Folsom AR, Shahar E, Eckfeldt JH. Plasma fatty acid composition as an indicator of habitual dietary fat intake in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Am J Clin Nutr. 1995; 62(3):564-571.

Masson LF, McNeill G, Tomany JO, Simpson JA, Peace HS, Wei L, et al. Statistical approaches for assessing the relative validity of a food-frequency questionnaire: use of correlation coefficients and the kappa statistic. Public Health Nutr. 2003; 6(3):313-321.

Mina K, Fritschi L, Knuiman M. A valid semiquantitative food frequency questionnaire to measure fish consumption. Eur J Clin Nutr. 2007; 61(8):1023-1031.

Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. Am J Clin Nutr. 2008; 87(6):1991S-1996S.

Männistö S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. J Clin Epidemiol. 1996; 49(4):401-409.

National Institute for Health and Welfare. Fineli Finnish Food Composition Database. [cited 3.9.2008]. Available at: http://www.fineli.fi/

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, et al. Validity of

57

a food frequency questionnaire varied by age and body mass index. J Clin Epidemiol. 2006; 59(9):994-1001.

Philibert A, Vanier C, Abdelouahab N, Chan HM, Mergler D. Fish intake and serum fatty acid profiles from freshwater fish. Am J Clin Nutr. 2006; 84(6):1299-1307.

R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2009.

Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. Am J Clin Nutr. 2007; 86(1):74-81.

Svensson BG, Nilsson A, Hansson M, Rappe C, Akesson B, Skerfving S. Exposure to dioxins and dibenzofurans through the consumption of fish. N Engl J Med. 1991; 324(1):8-12.

Svensson BG, Nilsson A, Jonsson E, Schutz A, Akesson B, Hagmar L. Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. ScandJWork EnvironHealth. 1995; 21(2):96-105.

Tuomisto J, Vartiainen T, Tuomisto J. Synopsis on dioxins and PCBs. National Public health Institute. Report No.: B17/1999.

Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Mannisto S, et al.

Mortality in a cohort with high fish consumption. Int J Epidemiol. 2008; 37(5):1008-1017.

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect. 1998; 106(12):775-792.

Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, et al. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. Am J Clin Nutr. 2006; 84(6):1330-1339.

Willett WC. Food frequency methods. In: Willett WC, editor. Nutritional Epidemiology. 2 ed. New York: Oxford University Press; 1998.

Woods RK, Stoney RM, Ireland PD, Bailey MJ, Raven JM, Thien FC, et al. A valid food frequency questionnaire for measuring dietary fish intake. Asia Pac J Clin Nutr. 2002; 11(1):56-61.

Yang L, Colombini V, Maxwell P, Mester Z, Sturgeon RE. Application of isotope dilution to the determination of methylmercury in fish tissue by solid-phase microextraction gas chromatography-mass spectrometry. J Chromatogr A. 2003; 1011(1-2):135-142.

5 Fish consumption in relation to other foods in the diet

Turunen AW,[1] Männistö S,[2] Suominen AL,[1,3] Tiittanen P[1], Verkasalo PK[1]

[1] National Institute for Health and Welfare, Department of Environmental Health, Kuopio, Finland
[2] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Helsinki, Finland
[3] University of Turku, Institute of Dentistry, Turku, Finland

Abstract

Our aim was to investigate whether fish consumption is associated with the consumption of other healthy foods. The study population consisted of 2605 men and 3199 women from the nationally representative Health 2000 survey and 114 professional fishermen and 114 fishermen's wives (the Fishermen sub-study) in Finland. Dietary data were collected using a calibrated (i.e., determined to have relative validity) FFQ. Model-adjusted means for food consumption and p values for linear trend were calculated across fish consumption tertiles. Those with the highest fish consumption had the highest consumption of vegetables, fruit and berries, potato, oil, and wine even after adjusting for other food groups. The consumption of red meat and sausages had a tendency to decrease across fish consumption tertiles but the associations were inconsistent in the study populations. In conclusion, fish consumption had a positive linear association with the consumption of some other healthy foods such as vegetables, fruit, berries, and oil both in the general population of Finland and in a population with high fish consumption. Additional adjustment for other food groups had a clear effect on some of the studied associations. Therefore, when evaluating the health effects of fish consumption, confounding by other foods characterising a healthy diet needs to be considered.

5.1 Introduction

According to official nutrition recommendations, it is advisable to eat fish at least twice per week (National Nutrition Council 1998; Lichtenstein et al. 2006). Fish consumption and long-chain polyunsaturated fatty acid (omega-3 PUFA) intake are thought to be important for human health (Sidhu 2003; Calder and Yaqoob 2009; Riediger et al. 2009), and to protect especially from CVD (Mozaffarian 2008; He 2009), diabetes (Nettleton and Katz 2005; Patel et al. 2009; Djousse et al. 2010), and possibly some cancers (Wolk 2005; Gonzalez and Riboli 2006) although the conclusions seem partly contradictory (Hooper et al. 2006; Kaushik et al. 2009). Despite the large body of evidence, it has been hypothesised that at least a part of the observed beneficial effects of fish consumption could be explained by an overall healthy diet, and fish consumption may even be a surrogate for healthy lifestyle in general (He 2009; Suominen-Taipale et al. 2010). This implies that the postulated health benefits of fish consumption would not be achieved by eating fish alone.

Many epidemiological studies on the associations between fish consumption and chronic diseases such as CVD (Ascherio et al. 1995; Mozaffarian et al. 2003; Iso et al. 2006; Anderson et al. 2010) including cerebrovascular diseases (Iso et al. 2001; He et al. 2002; Mozaffarian et al. 2005; Montonen et al. 2009) and cardiovascular mortality (Albert et al. 1998; Oomen et al. 2000; Hu et al. 2003; Yamagishi et al. 2008), diabetes (Patel et al. 2009) and cancer (Kobayashi et al. 2004; Wolk et al. 2006; Engeset et al. 2007; Chavarro et al. 2008; Sugawara et al. 2009) have reported associations between fish and other foods as baseline characteristics to describe their study populations. These studies have provided descriptive data on, for example, the association between the consumption of fish and vegetables but have mostly not accounted for the effects of confounding factors such as lifestyle and other foods in diet. To the best of our knowledge, the specific association between fish consumption and the overall diet has not been the main research question in previous studies, and has thus not gained the attention it deserves to provide strong evidence for dietary recommendations.

In the present study, we wanted to investigate whether fish consumption is associated with the consumption of some other foods, especially those that are considered healthy based on official nutrition recommendations. In other words, we wanted to explore if there are some common features in the diets of those who eat a lot of fish. The analyses were conducted in a unique population with high fish consumption where the effects of fish could be most easily seen. In addition, the analyses were repeated in a large sample of the general population of Finland.

5.2 Methods

5.2.1 Study populations

The nationally representative Health 2000 health examination survey (the Health 2000 survey) was conducted during 2001–2002 (Aromaa and Koskinen 2002) and coordinated by the National Institute for Health and Welfare in Finland (THL, merged from the former National Public Health Institute (KTL) and the National Research and Development Centre for Welfare and Health (STAKES)). The main study was carried out in a population aged 30 years or over, and it included an interview, several questionnaires and a health examination. A total of 5998 participants completed an FFQ (Heistaro 2008), and 2605 men and 3199 women had all the required data for the present study.

The Nutrition, Environment and Health study (the Fishermen study) was conducted during 2004–2005 and coordinated by THL. A total of 1427 professional fishermen, their wives, and other family members answered a self-administered health questionnaire. Of those, 309 volunteers, aged 22–74 years, and living near Helsinki and Turku study centres participated in a health examination study (the Fishermen sub-study) including, for example, blood sampling, basic measurements, and an FFQ (Turunen et al. 2008). Of those, 114 professional fishermen and 114 fishermen's wives had all the required data for the present study. In our previous study, we showed that fish consumption among the fishermen and their wives was approximately 1.5-fold when compared with that of the general population (Turunen et al. 2008), which attests our hypothesis of a population with high fish consumption.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and the protocols of the Health 2000 survey and the Fishermen study were approved by the ethical committee of the Hospital District of Helsinki and Uusimaa. A written informed consent was obtained from all participants.

5.2.2 Dietary data

In both studies, diet was assessed by the same calibrated (i.e., determined to have relative validity), self-administered FFQ designed to cover the whole diet over the past 12 months (Männistö et al. 1996; Paalanen et al. 2006). The FFQ consisted of 128 commonly used and/or nutritionally important food items, mixed dishes, and alcoholic beverages based on the national FINDIET study (Paturi et al. 2008). Serving sizes were specified by natural units (for example, serving, slice, glass, cup) or weight/volume measures, and the nine response options ranged from "never or seldom" to "six or more times per day" (for more information, see Appendix in our earlier publication) (Turunen et al. 2010). Daily consumption of foods (g/day) and the intake of energy (MJ/day) and nutrients were calculated by the national Fineli

Finnish Food Composition Database (Reinivuo et al. 2010). For the purpose of the present study, food items and mixed dishes were combined into twenty food groups based on culinary use, nutrient profile, and nutritional relevance (see Appendix).

5.2.3 Other covariates

Age (years) was calculated at the time of sampling in the Health 2000 survey and at the time of the health examination in the Fishermen sub-study.

Data on education, marital status, and smoking were obtained from a structured interview in the Health 2000 survey and from the self-administered health questionnaire in the Fishermen sub-study. With regard to education, two questions were used in the Health 2000 survey: "What is your basic education?" with eight response options from "less than elementary school" to "high school" and "What is your highest education after basic education?" with 11 response options from "no vocational education" to "doctoral degree". In the Fishermen sub-study, education level was determined by question "What is your education?" with eight response options from "less than elementary school" to "academic degree". The final education variable was constructed similarly in both studies, and it consisted of three classes: basic, intermediate, and high education. The final marital status consisted of three classes: married or cohabiting, unmarried, and divorced/separated or widowed. Regarding smoking, the following questions were asked: "Have you ever smoked?", "Have you smoked at least 100 times?", "Have you ever smoked regularly (i.e., daily for at least one year)?", and "When did you last smoke?". The final smoking variable consisted of three classes: never, occasional or ex-, and daily smoker.

Data on physical activity was obtained from the self-administered health questionnaire both in the Health 2000 survey and in the Fishermen sub-study. Free time physical activity was determined by question "How often do you exercise in your free time so that the duration is at least half an hour and you get at least mildly out of breath?" with response options ranging from "daily" to "a couple of times per year or less often". Physical activity while commuting was determined by question "How many minutes do you walk or cycle while going to work?" with response options ranging from "not at all" to "2 hours per day or more". The final physical activity variable consisted of three classes: sufficient, intermediate, and sedentary.

Weight (kg) and height (cm) were measured during the health examination by trained research personnel. Weight in light clothing was measured to an accuracy of 0.1 kg using a bioimpedance device or digital scales in the Health 2000 survey, and digital scales in the Fishermen sub-study. Height was recorded using a wall-mounted stadiometer to an accuracy of 0.5 cm.

5.2.4 Statistical analyses

Statistical analyses to produce Tables 1–3 were performed by using the SAS statistical software package version 9.2. SAS survey procedures were used to account for the sampling design of the Health 2000 survey data. In addition, a post-stratification weight was used to adjust for the oversampling of the 80-year-old and older individuals, and for the non-response to the FFQ (Djerf et al. 2008). For the Fishermen sub-study, basic SAS procedures were used. For the categorical variables in Table 1, however, SAS SURVEYFREQ procedure was used also for the Fishermen sub-study since the basic SAS FREQ procedure does not yield 95% CI for the multinomial proportions.

SAS GLM procedure was used to produce model-adjusted consumption of different food groups by fish consumption tertiles for Tables 2 and 3. We used three different adjustments: age and total energy intake (model 1); age, total energy intake, and lifestyle factors (BMI, education, marital status, smoking, and physical activity) (data not shown); and age, lifestyle factors, and the consumption of eighteen other food groups (model 2). Total energy intake was omitted from model 2 due to multicollinearity caused by simultaneous inclusion of energy and all food groups. Energy and continuous food group variables were transformed according to natural logarithm $\log(x+1)$, which clearly improved normality of the variable distributions and fulfilled the model assumptions. Antilogarithms were taken from the arithmetic means of the log-transformed variables, and the resulting geometric means and their 95% CIs were reported. In addition, p values for linear trends across fish consumption tertiles were calculated. The coefficients for linear contrasts needed for the calculation of these p values were produced by SAS/IML software (SAS Institute Inc. 2008) because geometric means for the fish consumption tertiles were not equally spaced. All the results were reported separately for the sexes and the two studies. To check for multicollinearity, pairwise Pearson correlation coefficients and collinearity diagnostics, namely tolerance, variance inflation factor, and condition index, were calculated.

As sensitivity analyses, we applied an additive model with thin-plate regression spline in the multiple generalised cross-validation package (mgcv) for R Statistical Software version 2.9.1 (Wood 2006; R Development Core Team 2009). An additive model is a non-parametric extension of a linear model for Gaussian response and allows the data to "speak for themselves" because a smoothing function does not assume a rigid form for the dependence. It can be used to explore the relationships between the dependent variable and the independent variables, for example, to visually assess linearity of the studied associations. In the sensitivity analyses of the present study, each food group was treated as a response variable (at a time), continuous fish consumption as a smoothed predictor, and all other covariates (as in model 2) as parametric predictors. As a result of sensitivity analyses, scatter plots with regression curves and approximate 95% CIs were drawn, and the most

important observed associations were visualised in Figures 1 and 2. In the figures, the plotted points are partial residuals, the solid curve is the additive model fit, and the dashed curves represent the approximate 95% confidence interval. The fit is named as s(log_fish, edf), where edf is the estimated degrees of freedom describing the wiggliness of the fit. When edf for the smooth is close to one, the curve fits to a straight line. However, the CI typically becomes wider (and the uncertainty increases) towards the ends of the curve due to decreasing number of observations, and therefore, only the central part of the curve is usually reliable.

5.3 Results

The fishermen were, on average, 4 years older and had a higher proportion of individuals having only basic education when compared with the general population men in the Health 2000 survey (Table 1). The proportion of daily smokers was lower among the fishermen and their wives than in the general population. The geometric mean for fish consumption was over twofold among the fishermen when compared with the general population men, and 1.6-fold among the fishermen's wives when compared with the general population women.

Both in the general population and among the fishermen and their wives, those with the highest fish consumption had the highest consumption of vegetables, fruit and berries, potato, oil, and wine (Tables 2 and 3). All these associations were relatively consistent regardless of adjustments. Red meat and sausage consumption had a tendency to decrease across fish consumption tertiles. The inverse association between fish and red meat was more evident among the fishermen and their wives, whereas the inverse association between fish and sausages was more evident among the women in both studies. In general, adjustment for lifestyle factors in addition to age and total energy intake (data not shown) had only a minor effect on the results, whereas an additional adjustment for other food groups attenuated the observed associations. For example, when adjusted only for age, total energy intake, and lifestyle factors, those with the highest fish consumption also had the highest consumption of poultry and the lowest consumption of liquid milk products, and sugar and confectionery, but these associations practically disappeared after adjusting for other food groups.

The regression curves produced by the additive model gave reassurance that a linear trend test could be applied for the studied associations. In addition, the shapes of the curves supported the conclusions made based on the model-adjusted means. For example, the regression curves showed a clear positive association between smoothed fish consumption and the consumption fruit and berries (Figure 1), and a clear negative association between smoothed fish consumption and the consumption sausages (Figure 2). On the other hand, the regression curves showing the association

between smoothed fish consumption and red meat consumption (Figure 2) were relatively flat, and the 95% CI appeared to include zero. The regression curves for the fishermen and their wives are not shown due to small number of observations.

5.4 Discussion

In the present study, those with the highest fish consumption had the highest consumption of vegetables, fruit and berries, potato, oil, and wine. These trends were essentially the same regardless of adjustments and study population. Red meat consumption had a tendency to decrease across fish consumption tertiles especially among the fishermen and their wives whereas sausage consumption decreased across fish consumption tertiles especially among the women in the general population and the fishermen's wives. When adjusted for lifestyle, those with the highest fish consumption had the lowest consumption of liquid milk products and sugar and confectionery in both studies but these associations practically disappeared after adjusting for other food groups.

We used a calibrated FFQ (Männistö et al. 1996; Paalanen et al. 2006) on whole diet, which is a primary method to measure usual long-term food consumption (Willett 1998). Although absolute food consumption was reported in the present study, it should be noted that an FFQ is designed only to rank participants according to their dietary intake. With regard to multivariate modelling, a high number of covariates in a regression model may cause instability in the estimates. In the present study, however, the correlations between the covariates were relatively low, and collinearity seemed not to be a problem. To increase the validity of the results, the analyses were performed in two study populations: in a large nationally representative population with an exceptionally high response rate and in a unique population with high fish consumption.

In the present study, fish consumption seemed to have a strong positive linear association with vegetable, fruit, and berry consumption even after adjusting for other food groups. This association was seen also among the fishermen, despite the fact that among them, high fish consumption has been thought to be an occupational characteristic and derive from tradition and easy availability of fish. Similar positive linear associations have also been seen in all the previous studies that have reported age-adjusted or unadjusted means as baseline characteristics (Ascherio et al. 1995; Albert et al. 1998; Oomen et al. 2000; Iso et al. 2001; Hu et al. 2003; Mozaffarian et al. 2003; Kobayashi et al. 2004; Mozaffarian et al. 2005; Iso et al. 2006; Wolk et al. 2006; Engeset et al. 2007; Chavarro et al. 2008; Yamagishi et al. 2008; Montonen et al. 2009; Patel et al. 2009; Sugawara et al. 2009; Anderson et al. 2010). Additionally, fish typically loads to a prudent dietary pattern together with vegetables and fruit in

dietary pattern analyses (van Dam et al. 2002; Pala et al. 2006; Heidemann et al. 2008).

Consuming more of one protein source usually means consuming less of some other source of protein. In the majority of previous studies, those with the highest fish consumption had the lowest meat consumption (Ascherio et al. 1995; Iso et al. 2001; Hu et al. 2003; Mozaffarian et al. 2003; Mozaffarian et al. 2005; Chavarro et al. 2008), but in some studies the direction of the association was the opposite (Kobayashi et al. 2004; Iso et al. 2006; Wolk et al. 2006; Engeset et al. 2007; Sugawara et al. 2009), possibly due to combining all types of meat (red and white) in one variable. In the present study, an inverse association between fish and red meat consumption was observed but it was more distinguishable among the fishermen and their wives than in the general population. The explanation for this might be that fishermen and their wives have fish consumption high enough to replace other sources of protein in their diet. Further, there was an inverse association between fish and sausage consumption in the general population and among the fishermen's wives. Overall, this association was more distinctive among the women than among the men, which may be due to the fact that women are typically more health conscious than men and they may prefer fish over sausages. In addition, energy intake and the total amount of food consumed are usually smaller among women and therefore fish may be able to partially replace other types of meats in their diet. With regard to poultry consumption in previous studies, those who had the highest fish consumption had the highest consumption of poultry (Albert et al. 1998; Iso et al. 2001; Albert et al. 2002; Iso et al. 2006; Engeset et al. 2007). In the present study, this association was seen only in the general population, although the positive linear association practically disappeared especially among the women after adjusting for other food groups.

In some previous studies, those with the highest fish consumption had the lowest consumption of dairy products (Ascherio et al. 1995; Albert et al. 1998; Chavarro et al. 2008), but in some studies, the direction of the association was the opposite (Iso et al. 2001; Iso et al. 2006). In only one previous study, the consumption of sweets was reported by fish consumption groups, and the association seemed to be inverse (Ascherio et al. 1995). In the present study, there was an inverse linear association between fish consumption and the consumption of liquid milk products and sugar and confectionery when adjusted only for lifestyle factors but the association practically disappeared after adjusting for other food groups.

Alcohol consumption was typically the highest among those who had the highest fish consumption in some (Oomen et al. 2000; Wolk et al. 2006; Chavarro et al. 2008; Patel et al. 2009) but not all (Mozaffarian et al. 2003; Anderson et al. 2010) previous studies. The positive linear association was especially evident among the Italian men (Oomen et al. 2000). Similarly, in the present study, the more the general population consumed fish, the higher was their wine and spirit consumption. A positive linear association between fish and wine consumption was also seen

among the fishermen and their wives. This may be seen, together with the increasing trend in vegetable and fruit consumption, as an indication of the Mediterranean-style diet (Willett et al. 1995) also among the Finnish fish consumers. Additionally, oil consumption was positively associated with fish consumption, which is also concordant with the Mediterranean-style diet.

The above referenced epidemiological studies have reported associations between fish and other foods as either age-adjusted (Ascherio et al. 1995; Albert et al. 1998; Hu et al. 2003; Mozaffarian et al. 2005; Wolk et al. 2006; Yamagishi et al. 2008) or crude (Oomen et al. 2000; Iso et al. 2001; Mozaffarian et al. 2003; Kobayashi et al. 2004; Iso et al. 2006; Engeset et al. 2007; Chavarro et al. 2008; Montonen et al. 2009; Patel et al. 2009; Sugawara et al. 2009; Anderson et al. 2010). This is understandable since they reported food consumption means across fish consumption groups as baseline characteristics of their study populations. The aim of the present study was specifically to study the associations between fish and other foods, and, therefore, adjustments were essential. Adjusting for total energy intake is needed since, at least for some food groups, the more an individual eats one food, the more he or she tends to eat other foods too. Adjusting for lifestyle and all other food groups enables to see the independent remaining effect after the confounding effect of lifestyle and the other food groups has been removed. In the present study, adjusting for other food groups attenuated the observed associations but the majority of them remained distinguishable even after the diet adjustment. This persistence can be seen as an indication of relatively strong and consistent associations. For the most part, our observations were parallel with the observations of the above referenced studies, suggesting that the present results are generalisable to other populations. Overall, diet associated with fish consumption appears to be relatively universal across populations regardless of differences in social and cultural circumstances (Balder et al. 2003) and dietary habits.

In summary, fish consumption seemed to have a positive linear association with the consumption of some other healthy foods such as vegetables, fruit, berries, and oil both in the general population of Finland and in the population with high fish consumption. Additional adjustment for other food groups had a clear effect on some of the studied associations. Therefore, when evaluating the health effects of fish consumption, confounding by other foods characterising a healthy diet needs to be considered.

Appendix

Food groupings[a] used in the present study

Food group	Food items
Fish	fish and fish products
Vegetables	root vegetables, leaf vegetables, fruit vegetables, cabbage, onion-family vegetables, canned vegetables, legumes, nuts, and mushrooms
Fruit and berries	fruit and berries
Potato	potato and potato products
Wheat	wheat, pasta, and biscuits
Rye	rye and crisp bread
Oil	vegetable oils (e.g., rapeseed, sunflower seed, olive, soybean, corn, palm)
Margarine	margarines and fat spreads
Butter	butter and butter spreads
Poultry meat	chicken and turkey meat
Red meat	beef, pork, cold cuts, game meat, and offal
Sausages	sausages
Liquid milk products	milks and fermented milk products (e.g., soured milks, yoghurts, and sour whole milks)
Cheese	cheeses
Sugar and confectionery	sugar, confectionery, and chocolate
Coffee	coffee
Soft drinks and juices	soft drinks, juice drinks , and juices
Beer	beers
Wine	wines
Spirits	spirits

[a] Food consumption (g/day) is derived from a 128-item FFQ.

Table 1. Background data of the Health 2000 survey and the Fishermen sub-study participants (Mean values or percentages with 95% confidence intervals)

	Health 2000 survey men (n=2605)		Health 2000 survey women (n=3199)		Fishermen (n=114)		Fishermen's wives (n=114)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age (years)	51	51–52	54	53–54	55	53–56	54	52–56
Energy intake (MJ/day)	10	9.9–10	9.1	9.0–9.3	9.8	9.3–10	8.8	8.3–9.3
Fish consumption (g/day)								
Arithmetic mean	46	44–48	45	43–46	86	74–99	64	57–72
Geometric mean	34	33–36	33	32–34	70	62–79	53	47–61
BMI (kg/m^2)	27	27–27	27	27–27	28	27–29	28	27–29
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Education level								
Basic	37	35–39	40	38–42	54	44–63	33	25–42
Intermediate	38	36–40	27	26–29	37	28–46	27	19–35
High	25	24–27	33	31–35	9.6	4.1–15	39	30–49
Marital status								
Married or cohabiting	77	75–78	65	63–67	78	70–86	90	85–96
Unmarried	13	12–14	9.9	8.8–11	9.6	4.1–15	0	-
Divorced/separated or widowed	10	9.4–12	25	23–27	12	6.1–18	9.6	4.1–15
Smoking								
Never smoker	37	35–38	65	63–67	44	35–53	64	55–73
Occasional or ex-smoker	36	35–38	18	16–19	37	28–46	25	17–33
Daily smoker	27	25–29	17	16–19	19	12–27	11	5.5–17
Physical activity								
Sufficient	30	28–31	34	32–36	33	25–42	30	21–38
Intermediate	30	28–32	29	27–31	19	12–27	31	22–39
Sedentary	40	38–42	37	35–38	47	38–57	39	30–49

Fish consumption in relation to other foods in the diet

Table 2. Model-adjusted food consumption (g/day) by fish consumption tertiles (g/day) among the Health 2000 survey men and women (Geometric means and 95% confidence intervals)

Fish consumption tertiles	Health 2000 survey men (n=2605)							Health 2000 survey women (n=3199)						
	1st tertile[a]		2nd tertile[b]		3rd tertile[c]		p for linear trend	1st tertile[d]		2nd tertile[e]		3rd tertile[f]		p for linear trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI		Mean	95% CI	Mean	95% CI	Mean	95% CI	
Vegetables														
Model 1[g]	156	149–163	198	190–206	232	223–241	<0.01	218	210–227	254	245–263	296	285–306	<0.01
Model 2[h]	184	176–192	197	190–204	198	190–206	0.01	248	240–257	253	245–262	261	252–270	0.03
Fruit and berries														
Model 1	91	84–99	109	102–117	128	121–136	<0.01	156	147–165	171	162–180	191	180–202	<0.01
Model 2	99	91–107	105	99–112	124	116–132	<0.01	163	154–173	170	161–178	183	173–195	<0.01
Potato														
Model 1	147	142–153	157	151–163	158	151–165	0.04	139	134–145	147	142–152	148	143–153	<0.01
Model 2	147	141–153	156	150–162	159	152–167	0.02	139	133–144	145	141–150	151	146–156	<0.01
Wheat														
Model 1	83	80–86	79	76–81	74	71–76	<0.01	72	70–74	70	68–72	65	63–67	<0.01
Model 2	82	79–85	78	75–81	75	72–78	<0.01	70	68–73	70	68–72	67	65–69	0.01
Rye														
Model 1	42	40–45	43	41–46	41	38–43	0.31	39	37–42	41	39–44	42	40–44	0.09
Model 2	40	37–43	43	41–46	43	41–46	0.11	38	36–40	41	39–43	44	42–47	<0.01
Oil														
Model 1	7.1	6.9–7.3	8.2	8.0–8.4	9.5	9.2–9.7	<0.01	6.6	6.5–6.8	7.7	7.6–7.9	8.8	8.6–9.0	<0.01
Model 2	7.5	7.3–7.7	8.1	7.9–8.3	9.1	8.9–9.3	<0.01	6.9	6.7–7.1	7.6	7.5–7.8	8.6	8.4–8.8	<0.01
Margarine														
Model 1	4.6	4.1–5.2	4.3	3.8–4.8	4.4	3.9–5.0	0.67	4.5	4.1–4.9	4.6	4.2–5.0	4.0	3.6–4.4	0.13
Model 2	4.4	4.0–4.9	4.3	3.8–4.7	4.6	4.1–5.1	0.60	4.1	3.8–4.5	4.4	4.0–4.8	4.6	4.2–5.0	0.14
Butter														
Model 1	9.7	9.2–10	9.7	9.3–10	9.2	8.8–9.6	0.11	8.4	8.0–8.8	8.3	8.0–8.6	8.6	8.2–8.9	0.35
Model 2	9.3	8.8–9.7	9.5	9.2–9.9	9.8	9.4–10	0.07	8.2	7.8–8.5	8.3	8.0–8.6	8.8	8.5–9.2	<0.01
Poultry meat														
Model 1	10	9.2–11	15	14–16	19	18–21	<0.01	13	12–15	19	17–20	22	20–24	<0.01
Model 2	13	11–14	15	14–16	16	14–17	<0.01	17	15–18	18	17–20	18	16–19	0.42
Red meat														
Model 1	92	89–96	100	97–103	105	101–109	<0.01	76	73–79	82	79–85	76	73–80	0.70
Model 2	100	97–103	99	96–102	98	95–102	0.53	79	76–82	81	78–84	74	71–77	0.01
Sausages														
Model 1	36	34–38	32	30–34	28	26–30	<0.01	21	20–23	19	17–20	15	14–16	<0.01
Model 2	33	31–35	32	30–34	30	28–33	0.07	19	18–21	18	17–19	17	16–18	0.02

(Table 2. Continued)

	Men			Á	Women			Á
Liquid milk products								
Model 1	427 (401–454)	377 (356–396)	343 (324–363)	<0.01	438 (418–460)	403 (385–422)	346 (330–363)	<0.01
Model 2	387 (363–412)	373 (351–395)	382 (360–406)	0.87	400 (379–422)	402 (385–420)	380 (361–399)	0.12
Cheese								
Model 1	27 (25–29)	26 (25–28)	28 (26–30)	0.24	28 (27–30)	31 (29–33)	33 (31–35)	<0.01
Model 2	28 (26–30)	26 (24–27)	27 (25–29)	0.61	29 (28–31)	30 (29–32)	32 (30–34)	0.03
Sugar and confectionery								
Model 1	31 (30–33)	31 (29–32)	27 (25–28)	<0.01	24 (22–25)	25 (24–27)	28 (27–29)	<0.01
Model 2	30 (29–31)	30 (29–31)	29 (27–30)	0.11	26 (25–28)	26 (25–27)	25 (24–26)	0.06
Coffee								
Model 1	257 (227–290)	283 (256–314)	263 (235–293)	0.90	218 (197–241)	256 (235–278)	221 (199–246)	0.92
Model 2	243 (214–277)	284 (257–314)	277 (246–311)	0.23	215 (194–239)	249 (230–270)	230 (206–256)	0.55
Soft drinks and juices								
Model 1	124 (112–136)	160 (149–173)	155 (142–170)	<0.01	120 (109–131)	114 (104–124)	125 (115–135)	0.41
Model 2	126 (113–140)	158 (146–172)	155 (140–171)	0.02	117 (106–128)	113 (103–124)	129 (118–142)	0.13
Beer								
Model 1	25 (21–30)	29 (25–33)	31 (27–36)	0.05	3.5 (3.0–4.1)	4.8 (4.2–5.6)	4.6 (4.0–5.2)	0.03
Model 2	30 (26–35)	28 (24–32)	27 (24–31)	0.31	4.2 (3.7–4.7)	4.6 (4.0–5.2)	4.1 (3.5–4.7)	0.61
Wine								
Model 1	2.0 (1.7–2.4)	3.6 (3.2–4.1)	4.7 (4.0–5.4)	<0.01	1.6 (1.3–1.8)	2.9 (2.5–3.3)	3.6 (3.2–4.1)	<0.01
Model 2	2.7 (2.4–3.1)	3.5 (3.1–4.0)	3.7 (3.2–4.2)	<0.01	2.1 (1.9–2.4)	2.7 (2.4–3.1)	2.9 (2.6–3.3)	<0.01
Spirits								
Model 1	2.0 (1.8–2.3)	2.3 (2.0–2.5)	2.7 (2.4–3.0)	<0.01	0.44 (0.37–0.51)	0.56 (0.49–0.63)	0.65 (0.57–0.73)	<0.01
Model 2	2.1 (1.9–2.3)	2.2 (2.1–2.4)	2.6 (2.3–2.9)	<0.01	0.49 (0.42–0.56)	0.53 (0.47–0.59)	0.62 (0.54–0.70)	0.02

[a] n=868, geometric mean=14 g/day, range 0–29 g/day
[b] n=868, geometric mean=38 g/day, range 30–48 g/day
[c] n=869, geometric mean=75 g/day, range 49–557 g/day
[d] n=1065, geometric mean=13 g/day, range 0–29 g/day
[e] n=1068, geometric mean=37 g/day, range 30–46 g/day
[f] n=1066, geometric mean=72 g/day, range 46–561 g/day
[g] adjusted for age and total energy intake
[h] adjusted for age, BMI, education, marital status, smoking, physical activity, and other food groups

Table 3. Model-adjusted food consumption (g/day) by fish consumption tertiles (g/day) among the fishermen and the fishermen's wives (Geometric means and 95% confidence intervals)

Fish consumption tertiles	Fishermen (n=114)								Fishermen's wives (n=114)							
	1st tertile[a]		2nd tertile[b]		3rd tertile[c]		p for linear trend		1st tertile[d]		2nd tertile[e]		3rd tertile[f]		p for linear trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI			Mean	95% CI	Mean	95% CI	Mean	95% CI	
Vegetables															
Model 1[g]	184	155–219	183	154–218	187	157–223	0.89		232	196–274	279	236–329	286	241–340	0.12
Model 2[h]	185	156–220	171	146–201	199	168–237	0.45		261	221–309	260	223–302	272	231–320	0.74
Fruit and berries															
Model 1	118	85–163	134	96–185	115	82–160	0.81		147	111–194	193	146–254	215	161–286	0.09
Model 2	104	75–145	140	103–192	123	88–172	0.67		143	103–197	188	140–253	227	166–311	0.07
Potato															
Model 1	154	131–180	188	160–221	190	161–223	0.11		155	135–179	144	126–166	166	144–192	0.42
Model 2	159	131–194	193	161–232	178	146–218	0.60		148	124–176	147	126–172	172	146–203	0.22
Wheat															
Model 1	75	66–85	78	69–89	76	67–87	0.92		71	62–83	59	51–68	63	55–74	0.38
Model 2	78	67–91	73	63–85	78	67–91	0.89		64	54–75	58	50–67	72	61–83	0.26
Rye															
Model 1	49	38–62	43	34–55	40	31–51	0.29		30	24–38	41	33–51	49	38–62	0.01
Model 2	44	33–58	43	33–56	44	33–59	0.95		32	24–43	44	34–57	42	32–55	0.27
Oil															
Model 1	7.0	6.3–7.7	8.2	7.5–9.1	9.1	8.2–10	<0.01		7.0	6.4–7.7	8.2	7.5–9.0	7.9	7.2–8.7	0.13
Model 2	7.2	6.5–7.9	8.0	7.3–8.8	9.0	8.2–9.9	<0.01		6.9	6.2–7.7	7.9	7.2–8.7	8.3	7.5–9.2	0.03
Margarine															
Model 1	6.2	3.6–10	3.4	1.8–6.0	5.2	2.9–8.8	0.86		7.4	4.6–11	4.2	2.5–6.7	2.0	0.99–3.5	<0.01
Model 2	5.1	3.0–8.2	4.3	2.6–6.8	5.2	3.1–8.5	0.86		4.6	2.6–7.5	5.3	3.3–8.2	2.7	1.5–4.6	0.17
Butter															
Model 1	6.3	5.0–8.0	7.4	5.8–9.3	7.7	6.0–9.7	0.31		5.6	4.4–7.1	6.6	5.2–8.3	7.5	5.9–9.5	0.12
Model 2	7.2	5.7–9.0	6.8	5.5–8.4	7.3	5.8–9.2	0.85		5.9	4.6–7.5	6.9	5.5–8.6	6.9	5.4–8.6	0.46
Poultry meat															
Model 1	18	12–26	17	11–25	11	7.5–17	0.09		18	12–25	21	15–30	19	13–27	0.89
Model 2	18	12–27	17	12–25	11	7.1–16	0.05		19	12–28	17	12–25	21	14–31	0.63

(Table 3. Continued)

Food group	Mean[a]	Range	Mean[b]	Range	Mean[c]	Range	p[g]	Mean[d]	Range	Mean[e]	Range	Mean[f]	Range	p[h]
Red meat														
Model 1	94	81–109	91	79–106	83	71–96	0.21	90	77–104	78	67–90	72	62–84	0.07
Model 2	99	85–116	92	79–107	78	66–91	0.04	86	73–101	75	65–87	78	67–92	0.55
Sausages														
Model 1	31	23–41	26	19–35	30	22–40	0.98	23	16–31	17	12–23	11	7.5–15	<0.01
Model 2	29	21–40	26	19–35	31	22–43	0.74	20	15–28	16	12–21	12	8.9–16	0.03
Liquid milk products														
Model 1	429	331–555	304	234–395	298	229–387	0.09	417	321–541	313	242–404	278	212–364	0.05
Model 2	432	315–593	289	214–390	311	225–430	0.29	394	286–542	306	229–408	301	221–409	0.31
Cheese														
Model 1	24	18–34	23	16–32	17	12–23	0.09	27	21–36	35	27–45	32	25–42	0.50
Model 2	27	19–38	21	15–29	16	11–23	0.07	32	23–44	34	25–45	29	21–40	0.65
Sugar and confectionery														
Model 1	28	23–35	28	23–35	22	18–28	0.11	28	23–35	24	19–29	18	15–23	0.01
Model 2	28	22–36	27	21–35	23	18–30	0.31	23	18–30	25	20–31	21	17–27	0.63
Coffee														
Model 1	317	195–517	343	210–561	247	150–405	0.41	347	200–600	197	115–339	210	119–369	0.28
Model 2	289	163–513	330	193–565	281	158–501	0.89	363	194–681	180	102–316	220	119–404	0.38
Soft drinks and juices														
Model 1	78	50–122	104	66–163	80	51–125	0.90	61	39–96	107	69–166	77	48–122	0.65
Model 2	74	43–126	88	53–146	99	57–169	0.51	48	28–82	114	70–185	93	54–157	0.18
Beer														
Model 1	55	30–98	69	38–123	58	32–105	0.97	3.0	1.2–6.5	12	5.8–22	5.9	2.6–12	0.41
Model 2	44	25–78	74	43–126	67	37–118	0.46	2.7	0.97–6,1	11	5.8–20	6.7	3.1–14	0.25
Wine														
Model 1	4.1	2.0–7.7	7.2	3.8–13	9.4	5.1–17	0.08	3.2	1.6–5.8	8.7	5.0–15	6.4	3.5–11	0.20
Model 2	4.9	2.4–9.2	6.2	3.2–11	9.3	4.9–17	0.18	4.5	2.1–8.7	7.6	4.2–13	5.3	2.7–10	0.85
Spirits														
Model 1	6.1	4.0–9.2	3.7	2.3–5.8	4.4	2.8–6.8	0.43	0.94	0.43–1.6	1.3	0.69–2.1	1.1	0.57–1.9	0.72
Model 2	6.3	4.0–9.7	3.5	2.2–5.5	4.4	2.7–7.0	0.46	1.4	0.69–2.3	0.79	0.32–1.4	1.2	0.61–2.1	0.94

[a] n=38, geometric mean=36 g/day, range 10–49 g/day
[b] n=38, geometric mean=69 g/day, range 50–93 g/day
[c] n=38, geometric mean=137 g/day, range 94–463 g/day
[d] n=38, geometric mean=27 g/day, range 0–42 g/day
[e] n=38, geometric mean=55 g/day, range 43–72 g/day
[f] n=38, geometric mean=102 g/day, range 74–282 g/day
[g] adjusted for age and total energy intake
[h] adjusted for age, BMI, education, marital status, smoking, physical activity, and other food groups
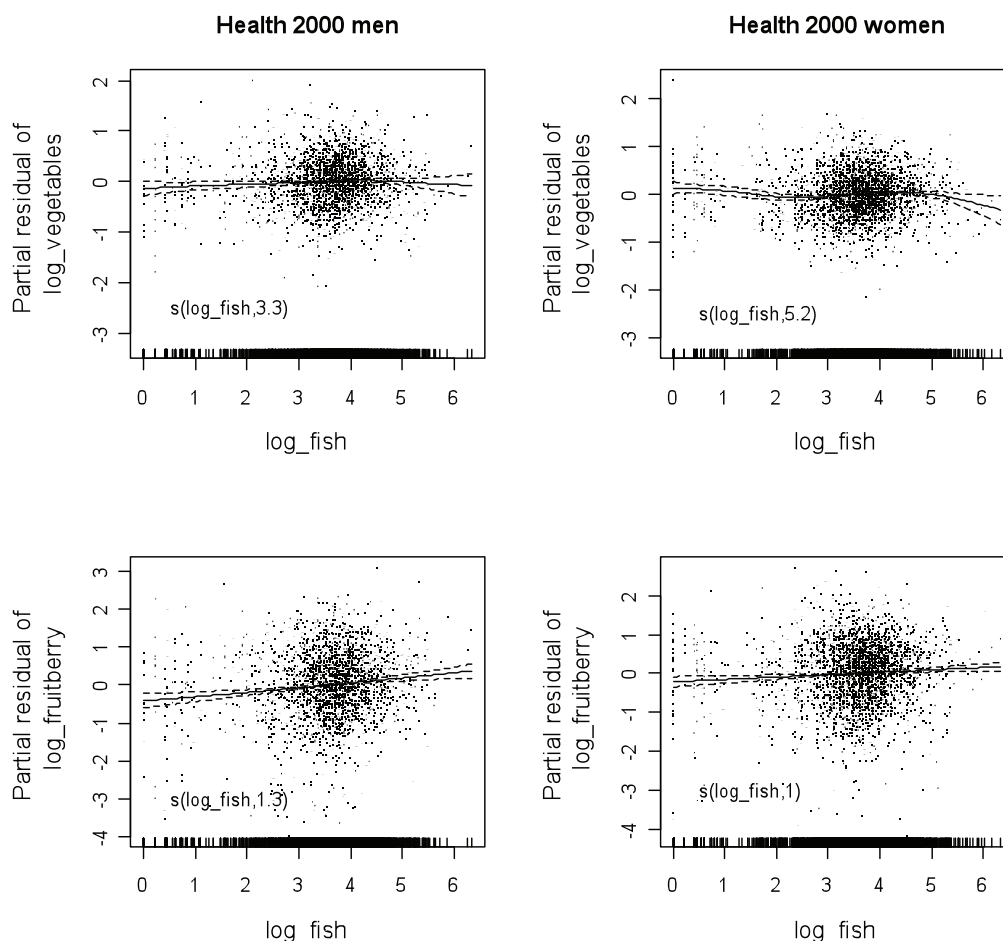
Figure 1. Adjusted smoothed associations between fish consumption and the consumption of selected foods (vegetables, (a) and (b); fruit and berries, (c) and (d)) among the Health 2000 survey men (n=2605; (a) and (c)) and women (n=3199; (b) and (d)). Associations were adjusted for age, BMI, education, marital status, smoking, physical activity and other food groups, and were produced by an additive model with a thin-plate regression spline. All the FFQ variables were transformed according to log(x+1). The solid curve is the additive model fit and the dashed curves represent the approximate 95% CI. The fit is named as s(log_fish, edf), where edf is the estimated degrees of freedom describing the wiggliness of the fit. The plotted points are partial residuals.
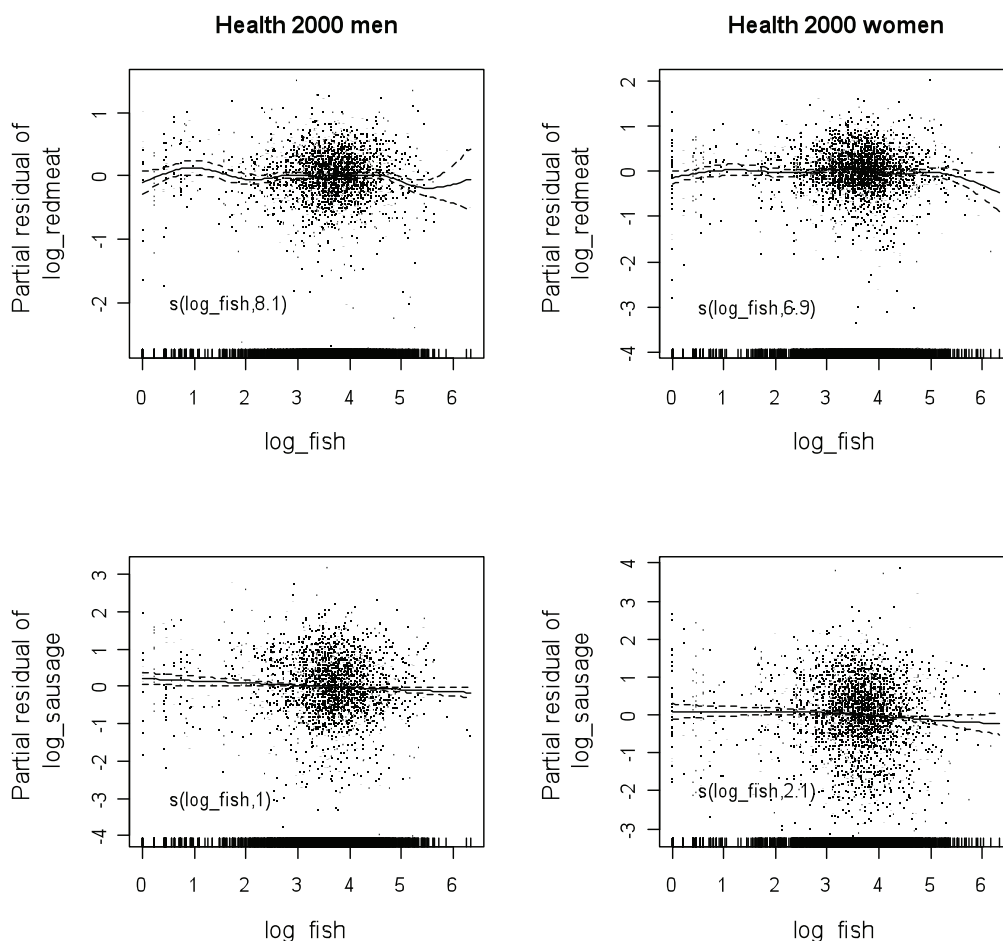
Figure 2. Adjusted smoothed associations between fish consumption and the consumption of selected foods (red meat, (a) and (b); sausages, (c) and (d)) among the Health 2000 survey men (n=2605; (a) and (c)) and women (n=3199; (b) and (d)). Associations were adjusted for age, BMI, education, marital status, smoking, physical activity and other food groups, and were produced by an additive model with a thin-plate regression spline. All the FFQ variables were transformed according to log(x+1). The solid curve is the additive model fit and the dashed curves represent the approximate 95% CI. The fit is named as s(log_fish, edf), where edf is the estimated degrees of freedom describing the wiggliness of the fit. The plotted points are partial residuals.

Acknowledgements

References

Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med. 2002; 346(15):1113-1118.

Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. JAMA. 1998; 279(1):23-28.

Anderson JS, Nettleton JA, Herrington DM, Johnson WC, Tsai MY, Siscovick D. Relation of omega-3 fatty acid and dietary fish intake with brachial artery flow-mediated vasodilation in the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr. 2010; 92(5):1204-1213.

Aromaa A, Koskinen S. Health and functional capacity in Finland. Baseline Results of the Health 2000 Health Examination Survey (in Finnish). National Public Health Institute. Report No.: B3/2002. Available at: http://www.terveys2000.fi/perusraportti/index.html

Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med. 1995; 332(15):977-982.

Balder HF, Virtanen M, Brants HA, Krogh V, Dixon LB, Tan F, et al. Common and country-specific dietary patterns in four European cohort studies. J Nutr. 2003; 133(12):4246-4251.

Calder PC, Yaqoob P. Omega-3 polyunsaturated fatty acids and human health outcomes. Biofactors. 2009; 35(3):266-272.

Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. Am J Clin Nutr. 2008; 88(5):1297-1303.

Djerf K, Laiho J, Kehtonen R, Härkänen T, Knekt P. Weighting and statistical analysis. In: Heistaro S. Methodology report. Health 2000 Survey. National Public Health Institute. Report No.: B26/2008. Available at: http://www.terveys2000.fi/doc/methodologyrep.pdf

Djousse L, Gaziano JM, Buring JE, Lee IM. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. Am J Clin Nutr. 2010.

Engeset D, Andersen V, Hjartaker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. Br J Nutr. 2007; 98(3):576-582.

Gonzalez CA, Riboli E. Diet and cancer prevention: where we are, where we are going. Nutr Cancer. 2006; 56(2):225-231.

He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease--eat fish or take fish oil supplement? Prog Cardiovasc Dis. 2009; 52(2):95-114.

He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, et al. Fish consumption and risk of stroke in men. JAMA. 2002; 288(24):3130-3136.

Heidemann C, Schulze MB, Franco OH, van Dam RM, Mantzoros CS, Hu FB. Dietary patterns and risk of mortality from

cardiovascular disease, cancer, and all causes in a prospective cohort of women. Circulation. 2008; 118(3):230-237.

Heistaro S. Methodology report. Health 2000 Survey. National Public Health Institute. Report No.: B26/2008. Available at: http://www.terveys2000.fi/doc/methodologyrep.pdf

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006; 332(7544):752-760.

Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. Circulation. 2003; 107(14):1852-1857.

Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation. 2006; 113(2):195-202.

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA. 2001; 285(3):304-312.

Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willett WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. Am J Clin Nutr. 2009; 90(3):613-620.

Kobayashi M, Tsubono Y, Otani T, Hanaoka T, Sobue T, Tsugane S. Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. Nutr Cancer. 2004; 49(1):32-40.

Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006; 114(1):82-96.

Montonen J, Jarvinen R, Reunanen A, Knekt P. Fish consumption and the incidence of cerebrovascular disease. Br J Nutr. 2009; 102(5):750-756.

Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. Am J Clin Nutr. 2008; 87(6):1991S-1996S.

Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. Circulation. 2003; 107(10):1372-1377.

Mozaffarian D, Longstreth WT, Jr., Lemaitre RN, Manolio TA, Kuller LH, Burke GL, et al. Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. Arch Intern Med. 2005; 165(2):200-206.

Männistö S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. J Clin Epidemiol. 1996; 49(4):401-409.

National Nutrition Council. Finnish Nutrition Recommendations. Ministry of Agriculture and Forestry. Report No.: 1998:7.

Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005; 105(3):428-440.

Oomen CM, Feskens EJ, Rasanen L, Fidanza F, Nissinen AM, Menotti A, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. Am J Epidemiol. 2000; 151(10):999-1006.

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, et al. Validity of a food frequency questionnaire varied by age and body mass index. J Clin Epidemiol. 2006; 59(9):994-1001.

Pala V, Sieri S, Masala G, Palli D, Panico S, Vineis P, et al. Associations between dietary pattern and lifestyle, anthropometry and other health indicators in the elderly participants of the EPIC-Italy cohort. Nutr Metab Cardiovasc Dis. 2006; 16(3):186-201.

Patel PS, Sharp SJ, Luben RN, Khaw KT, Bingham SA, Wareham NJ, et al. Association between type of dietary fish and seafood intake and the risk of incident type 2 diabetes: the European prospective investigation of cancer (EPIC)-Norfolk

cohort study. Diabetes Care. 2009; 32(10):1857-1863.

Paturi M, Tapanainen H, Reinivuo H, Pietinen P. The National FINDIET 2007 Survey. National Public Health Institute. Report No.: B23/2008. Available at: http://www.ktl.fi/attachments/suomi/julkais ut/julkaisusarja_b/2008/2008b23.pdf

R Development Core Team. R: A language and environment for statistical computing, version 2.9.1. R Foundation for Statistical Computing; 2009. Available at: http://www.R-project.org

Reinivuo H, Hirvonen T, Ovaskainen ML, Korhonen T, Valsta LM. Dietary survey methodology of FINDIET 2007 with a risk assessment perspective. Public Health Nutr. 2010; 13(6A):915-919.

Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the roles of n-3 fatty acids in health and disease. J Am Diet Assoc. 2009; 109(4):668-679.

SAS Institute Inc. SAS/IML® 9.2 User's Guide. Cary, NC: SAS Institute Inc.; 2008.

Sidhu KS. Health benefits and potential risks related to consumption of fish or fish oil. Regul Toxicol Pharmacol. 2003; 38(3):336-344.

Sugawara Y, Kuriyama S, Kakizaki M, Nagai M, Ohmori-Matsuda K, Sone T, et al. Fish consumption and the risk of colorectal cancer: the Ohsaki Cohort Study. Br J Cancer. 2009; 101(5):849-854.

Suominen-Taipale AL, Partonen T, Turunen AW, Mannisto S, Jula A, Verkasalo PK. Fish consumption and omega-3 polyunsaturated Fatty acids in relation to depressive episodes: a cross-sectional analysis. PLoS One. 2010; 5(5):e10530.

Turunen AW, Männistö S, Kiviranta H, Marniemi J, Jula A, Tiittanen P, et al.

Dioxins, polychlorinated biphenyls, methylmercury and omega-3 polyunsaturated fatty acids as biomarkers of fish consumption. Eur J Clin Nutr. 2010; 64(3):313-323.

Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Mannisto S, et al. Mortality in a cohort with high fish consumption. Int J Epidemiol. 2008; 37(5):1008-1017.

van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med. 2002; 136(3):201-209.

Willett WC. Food frequency methods. In: Willett WC, editor. Nutritional Epidemiology. 2 ed. New York: Oxford University Press; 1998.

Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995; 61(6 Suppl):1402S-1406S.

Wolk A. Diet, lifestyle and risk of prostate cancer. Acta Oncol. 2005; 44(3):277-281.

Wolk A, Larsson SC, Johansson JE, Ekman P. Long-term fatty fish consumption and renal cell carcinoma incidence in women. JAMA. 2006; 296(11):1371-1376.

Wood SN. Generalized additive models: An introduction with R. Chapman and Hall; 2006.

Yamagishi K, Iso H, Date C, Fukui M, Wakai K, Kikuchi S, et al. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. J Am Coll Cardiol. 2008; 52(12):988-996.

6 Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis

Turunen AW,[1] Jula A,[2] Suominen AL,[1,4] Männistö S,[3] Marniemi J,[2] Kiviranta H,[1] Tiittanen P,[1] Karanko H,[2] Moilanen L,[5] Nieminen MS,[6] Kesäniemi YA,[7] Kähönen M,[8] Verkasalo PK[9]

[1] National Institute for Health and Welfare, Department of Environmental Health, Kuopio, Finland
[2] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Turku, Finland
[3] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Helsinki, Finland
[4] University of Eastern Finland, Institute of Dentistry, Kuopio, Finland
[5] Kuopio University Hospital, Department of Medicine, Kuopio, Finland
[6] Helsinki University Hospital, Department of Medicine, Helsinki, Finland
[7] University of Oulu and Clinical Research Center, Department of Internal Medicine, Institute of Clinical Medicine and Oulu University Hospital, Biocenter Oulu, Oulu, Finland
[8] Tampere University Hospital, Department of Clinical Physiology and University of Tampere, Tampere, Finland
[9] Kuopio University Hospital, Department of Adult Psychiatry, Kuopio, Finland

Submitted.

Abstract

Background: Fish consumption and omega-3 polyunsaturated fatty acid (PUFA) intake are shown to protect from cardiovascular diseases (CVD). However, most fish contain environmental contaminants such as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and methylmercury (MeHg) that may have adverse effects on cardiovascular health.

Aims: Our aim was to elucidate the associations of fish consumption, omega-3 PUFAs, and environmental contaminants with low-grade inflammation, early atherosclerosis, and traditional CVD risk factors.

Methods: The Health 2000 survey participants (n=1173) represented the general Finnish population and the Fishermen study participants (n=255) represented a population with high fish consumption and high exposure to environmental contaminants. Model-adjusted geometric means and tests for linear trend were calculated for CVD risk factors by tertiles of fish consumption and serum omega-3 PUFAs, and additionally in the Fishermen study only, by tertiles of serum PCDD/F+PCB, and blood MeHg.

Results: Serum triglyceride decreased across omega-3 PUFA tertiles in both sexes and studies. Insulin resistance, C-reactive protein, tumour necrosis factor α, and interleukin 6 decreased across omega-3 PUFA tertiles among the Health 2000 survey participants. Among the Fishermen study men, insulin resistance and arterial stiffness indicated by β-stiffness index tended to increase and the RR estimate for carotid artery plaque tended to decrease across tertiles of environmental contaminants.

Conclusion: Omega-3 PUFAs seemed to have a clear hypotriglyceridemic and anti-inflammatory effect. The favourable effect on insulin sensitivity and arterial elasticity was suggested to be counteracted by high exposure to environmental contaminants, but the effect on plaque prevalence appeared not to be harmful.

6.1 Introduction

Many of the traditional risk factors for cardiovascular diseases (CVD) and diabetes, such as hypertension, dyslipidemia, and insulin resistance, are suspected to be favourably affected by high fish consumption and high intake of fish-derived long-chain omega-3 polyunsaturated fatty acids (PUFAs) (Carpentier et al. 2006; Calder and Yaqoob 2009; Riediger et al. 2009). Further, omega-3 PUFAs have been observed to decrease the production of pro-inflammatory eicosanoids and cytokines and thus, fish consumption is believed to protect from diseases involving inflammatory processes (Calder 2006; Wall et al. 2010). Fish consumption and omega-3 PUFA intake have also been suggested to slow the progression of atherosclerosis (Massaro et al. 2008) and to reduce arterial stiffness (Hall 2009).

In contrast, most fish contain bioaccumulative environmental contaminants that have endocrine-disrupting potency and may have an adverse effect on cardiovascular health (Bushkin-Bedient and Carpenter 2010). For example, high exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic congener of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), is hypothesised to increase the risk of circulatory diseases and diabetes (Consonni et al. 2008). In addition, PCDD/Fs, polychlorinated biphenyls (PCBs), and methylmercury (MeHg) are suspected to have a capacity to increase both blood pressure and oxidative stress, alter lipid, glucose and insulin metabolism, and promote inflammatory processes (Hennig et al. 2007; Mozaffarian 2009; Everett et al. 2011). Exposure especially to PCBs has lately been linked with obesity, dyslipidemia, insulin resistance (Lee et al. 2011), and the risk of diabetes (Airaksinen et al. 2011).

Although the benefits of fish consumption and omega-3 PUFAs have been extensively studied, some controversy still remains (Hooper et al. 2006; Salas-Salvado et al. 2011), and one explanation for conflicting findings might be competing effects of environmental contaminants in fish (He 2009). More importantly, the benefits of fish consumption and omega-3 PUFA intake have rarely been studied in populations with high exposure to environmental contaminants. Our aim was to study the associations of habitual fish consumption and serum concentrations of fish-derived omega-3 PUFAs and environmental contaminants with chronic low-grade systemic inflammation, early signs of atherosclerosis, and traditional CVD risk factors taking into account the overall effect of beneficial and hazardous compounds in fish. We conducted the analyses in a sub-sample of the general Finnish population and among professional Baltic Sea area fishermen and their family members. The latter is a unique population with high fish consumption and high exposure to environmental contaminants.

6.2 Methods

6.2.1 Study populations

The nationally representative Health 2000 health examination survey (the Health 2000 survey) was conducted in 2001–2002 (Heistaro 2008). A total of 1526 volunteers aged 45–74 years, and living near the five university hospitals (Helsinki, Turku, Tampere, Kuopio, and Oulu) participated in a cardiovascular and diabetes sub-study and of those, 532 men and 641 women had complete dietary, health interview, and basic health examination data for the present work. Further, of those, 406 men and 499 women had ultrasound data for the analyses of vascular structure and function.

The Nutrition, environment and health study (the Fishermen study) on professional Baltic Sea area fishermen, their wives, and other family members was conducted in 2004–2005 (Turunen et al. 2008). A total of 309 volunteers aged 22–74 years and living near Helsinki and Turku study centres participated in a health examination study and of those, 123 men and 132 women had complete dietary, health questionnaire, and basic health examination data for the present work. Further, of those, 84 men and 90 women had also ultrasound data for the analyses of vascular structure and function.

Both studies were coordinated by the National Institute for Health and Welfare (THL) in Finland. The studies were conducted according to similar study protocols and the guidelines laid down in the Declaration of Helsinki and the protocols were approved by the ethical committee of the Hospital District of Helsinki and Uusimaa. A written informed consent was obtained from all participants.

6.2.2 Dietary data

In both studies, diet was assessed by the same calibrated (i.e., determined to have relative validity), self-administered 128-item food frequency questionnaire (FFQ) designed to cover the whole diet and the use of dietary supplements (such as fish oil capsules) over the past 12 months (Männistö et al. 1996; Paalanen et al. 2006). Consumption of fish and other foods and the intakes of alcohol and salt (g/day) were calculated with the national Fineli Finnish Food Composition Database. Dietary data has been described in more detail elsewhere (Turunen et al. 2010).

6.2.3 Laboratory analyses

Blood samples were drawn from antecubital vein after 10–12 hours of fasting. Serum concentrations of fatty acids were analysed using a gas chromatograph and flame ionisation detector (Jula et al. 2005). The sum of eicosapentaenoic acid

(EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) (omega-3 PUFAs) as a proportion from all serum fatty acids (% FAs) was calculated.

In the Fishermen study only, serum concentrations of 17 PCDD/F and 37 PCB congeners were analysed gravimetrically from serum fat using a high resolution mass spectrometer equipped with a gas chromatograph. The method has been described in detail elsewhere (Kiviranta et al. 2002). PCDD/Fs and PCBs were expressed as toxic equivalent quantity (TEq) recommended by the World Health Organization (WHO). The sum of PCDD/F-TEq and PCB-TEq (PCDD/F+PCB-TEq, pg/g fat) was calculated. Blood MeHg concentration (ng/ml) was analysed from whole blood using an isotope dilution-gas chromatograph/mass spectrometer (Airaksinen et al. 2010). Blood samples to analyse environmental contaminants were not available in the Health 2000 survey.

Serum total cholesterol and triglyceride concentrations were analysed by spectrophotometric enzymatic method, high-density lipoprotein (HDL, mmol/l) cholesterol by a direct method, glucose (mmol/l) by hexokinase method, and insulin (mU/l) by microparticle enzyme immunoassay. Homeostasis model assessment (HOMA) indexes, namely insulin resistance index (HOMA-IR) and pancreatic beta cell function (HOMA-%B), were calculated using formulas listed in Appendix.

Serum concentrations of highly sensitive C-reactive protein (CRP, mg/l), tumour necrosis factor α (TNF-α, ng/l), and interleukin 6 (IL-6, ng/l) were analysed using a solid-phase enzyme-labelled chemiluminescent immunometric assay in the Health 2000 survey. In the Fishermen study, CRP was analysed immunoturbidimetrically. Participants with CRP<10 mg/l were included in the study.

6.2.4 Vascular measurements

Intima-media thickness (IMT, mm) and arterial diameter change according to pulse pressure (ADC, mm) were measured from the right common carotid artery (CCA) at the level of the carotid bifurcation by high-resolution B-mode ultrasound. The method has been described in detail elsewhere (Niiranen et al. 2007; Sipila et al. 2011). The presence of formed atherosclerotic plaques in the carotid artery, defined as a focal raised lesion of >1.5 mm in size in at least one of the images of the carotid bulb, was determined. Measures for arterial stiffness, namely carotid artery compliance (CAC, %/10 mmHg), Young's elastic modulus (YEM, kPa), and β-stiffness index (SI), were calculated based on ADC using formulas listed in Appendix. Participants with all six arterial diameter measurements were included in the analyses concerning ultrasonographic variables.

6.2.5 Body composition, blood pressure and other basic health characteristics

Body mass index (BMI) was calculated using measured weight and height. Blood pressure was measured three times from the right brachial artery by an electronic sphygmomanometer in sitting position after a 10 minute rest and. For the calculations of the vascular markers, blood pressure was measured again three times in supine position directly before the ultrasound examination. Data on smoking, physical activity, and the use of insulin, oral glucose lowering drugs, lipid modifying drugs (such as statins), and blood pressure lowering drugs were obtained from a structured interview and self-administered health questionnaire in the Health 2000 survey and from a self-administered health questionnaire in the Fishermen study.

6.2.6 Statistical analyses

For the primary analyses (Tables 2–5), the participants were categorised into tertiles according to their non-transformed total fish consumption and serum omega-3 PUFAs, and additionally in the Fishermen study only, according to their serum PCDD/F+PCB-TEq and blood MeHg. Due to skewed variable distributions, all continuous variables except for age and blood pressure were transformed according to natural logarithm. Each log-transformed risk factor or marker was treated as a response variable at a time, and their model-adjusted geometric means were calculated by the above mentioned tertiles using GLM procedure in the Statistical Analysis Systems (SAS) and tested for linear trend. Since the geometric means for the tertiles were not equally spaced, the coefficients for linear contrasts were produced by SAS/IML software. Adjusted risk ratio (RR) for the presence of atherosclerotic plaque in the carotid artery wall was calculated by the above mentioned tertiles using a Poisson regression model with robust error variance and GENMOD procedure in SAS, and tested for linear trend.

To assess the shape of the studied associations and to evaluate the reliability of the results especially in the Fishermen study, an additive model with thin-plate regression spline was applied in the multiple generalised cross-validation package (mgcv) for R Statistical Software (Wood 2006). The additive model is a non-parametric extension of a linear model for Gaussian response, and it allows the data to "speak for themselves" because a smoothing function does not assume a rigid form for the dependence. Continuous (instead of categorised) fish consumption, serum omega-3 PUFAs, serum PCDD/F+PCB-TEq, and blood MeHg were treated as a smoothed predictors. Scatter plots with regression curves and approximate 95% CIs for selected associations are presented in Figure 1.

The geometric means, RRs, and regression splines were adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and

THL — Research 79/2012　　　　　　　84　　　　　　Epidemiological studies on
fish consumption and
cardiovascular health

alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives. In addition, the means and RRs were adjusted for traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, and systolic blood pressure). Vascular markers were additionally adjusted for inflammatory markers. Potential negative confounding was controlled for by adjusting the means and RRs across omega-3 PUFA tertiles for environmental contaminants and geometric means and RRs across tertiles of environmental contaminants for omega-3 PUFAs. The covariates were chosen based on common knowledge on cardiovascular risk factors. Vegetable, fruit, berry, and oil consumption were included in the models since they were positively associated with fish consumption based on our previous study (Turunen et al. 2011).

6.3 Results

Compared with the Health 2000 survey men and women, the geometric means for fish consumption and serum omega-3 PUFAs were approximately 80% higher among the Fishermen study men and, respectively, 40% and 70% higher among the Fishermen study women (Table 1).

In the Health 2000 survey, serum HDL cholesterol increased and serum triglyceride decreased in both sexes, and serum insulin and insulin resistance measured by HOMA-IR index decreased among the women across serum omega-3 PUFA tertiles (Table 2). Additionally among the women, BMI, waist circumference, and pancreatic beta cell function measured by HOMA-%B index decreased across omega-3 PUFA tertiles. Regarding markers of inflammation and early atherosclerosis, serum TNF-α and IL-6 decreased across omega-3 PUFA tertiles in both sexes whereas serum CRP decreased across omega-3 PUFA tertiles only among the women. Arterial stiffness measured by β-stiffness index decreased across omega-3 PUFA tertiles only among the men (Table 3). Overall, similar but weaker trends were seen across fish consumption tertiles.

In the Fishermen study, many of the observed linear trends were statistically non-significant, and thus, they are referred here to as tendencies towards a linear trend. Serum triglyceride decreased across serum omega-3 PUFA tertiles among the men, and there was a tendency towards a decreasing trend among the women (Table 2). Among the men, serum CRP had a tendency to decrease across fish consumption tertiles (Table 2), and the RR estimate for atherosclerotic plaque in the carotid artery decreased across blood MeHg tertiles and had a tendency to decrease across tertiles of serum PCDD/F+PCB-TEq (Table 5).

Some unhealthy trends were also observed in the Fishermen study. Among the men, serum glucose, serum insulin, and HOMA-IR index had a tendency to increase especially across fish consumption, serum PCDD/F+PCB-TEq, and blood MeHg

tertiles (Tables 2 and 4). Additionally, carotid artery compliance decreased and β-stiffness index increased across omega-3 PUFA, PCDD/F+PCB-TEq, and MeHg tertiles among the men (Tables 3 and 5). Among the women, serum glucose concentration increased across MeHg tertiles, HOMA-%B tended to decrease across PCDD/F+PCB-TEq tertiles, and serum CRP tended to increase across MeHg tertiles (Table 4).

In both studies, all the above mentioned results stayed essentially the same after additional adjusting for traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, systolic blood pressure) and the use of fish oil supplements, and regarding vascular markers, also after additional adjusting for inflammatory markers (data not shown). The only detectable change was seen when the linear trends in serum insulin and insulin resistance slightly attenuated after adjusting for BMI. Furthermore, the observed trends especially in inflammatory markers among the Health 2000 survey men and in the RR estimate for carotid artery plaque among the Fishermen study men were attenuated when obese (BMI$\geq$30) individuals were excluded. To control for negative confounding in the Fishermen study, means across omega-3 PUFA tertiles were additionally adjusted for environmental contaminants and vice versa, but the results remained unchanged.

The regression curves produced by the additive model gave reassurance that a linear trend test could be applied for the studied associations. In addition, the shapes of the curves supported the conclusions made based on the model-adjusted means. Increasing trends in insulin resistance and β-stiffness index and a decreasing trend in the risk of carotid artery plaque across tertiles of environmental contaminants among the Fishermen study men are visualised in Figure 1.

6.4 Discussion

In the Health 2000 survey, a beneficial decreasing trend along with increasing serum fish-derived omega-3 PUFA concentration was observed in serum triglyceride, inflammatory markers, insulin resistance measured by HOMA-IR index (only among the women), and arterial stiffness measured by β-stiffness index (only among the men). Except for the hypotriglyceridemic effect, these beneficial trends were not clearly seen in the Fishermen study. On the contrary, an increasing trend in insulin resistance and arterial stiffness was observed along with increasing serum omega-3 PUFAs and environmental contaminants among the men. However, the risk of atherosclerotic plaque in the carotid artery tended to decrease along with increasing contaminant concentrations. The results stayed essentially the same regardless of adjustments.

6.4.1 Strengths and limitations

We utilised two separate study populations of which the larger was a sub-sample of the general population of Finland with an exceptionally high response rate. The smaller was a unique population of professional Baltic Sea area fishermen and their family members. Among the men in this high-exposure population, fish consumption and serum concentrations omega-3 PUFAs and environmental contaminants were almost twofold when compared with the males representing the general population of Finland (Turunen et al. 2008; Turunen et al. 2011). Furthermore, the fishermen's serum TCDD concentration was comparable to that measured among the residents in the second highest exposure zone B in Seveso Italy after the industrial accident (Pesatori et al. 2009). The multidisciplinary data included several exposures and risk factors, and both omega-3 PUFAs and environmental contaminants were simultaneously included into the models to control for potential negative confounding. In addition to testing for linear trend, we decided to present model-adjusted means by tertiles to enable one to explore also possible non-linear associations.

Due to cross-sectional setting, causality could not be established in the present work. Another limitation was the small size of the Fishermen study population, which could, at least partially, explain why some of the hypothesised associations were not detectable or some of the apparent linear tendencies across tertiles did not reach statistical significance. However, the regression curves produced by the additive model supported the conclusions made based on the model-adjusted means suggesting that the results of the primary analyses were reliable. In addition, the triglyceride lowering effect of omega-3 PUFAs was observed also in the Fishermen study, which gave reassurance that at least strong associations could be detectable. Another limitation is the lack of blood samples to analyse environmental contaminants from the general population. Additionally, data on cooking method was not available but it may not be a problem since according to unpublished data from the Fishermen study, the only heavily processed fish dish commonly used in Finland, fish fingers, consisted only 1% of the total fish consumption. Pan-frying was the most common (25%) single cooking method for fish but healthier methods, namely cooking and oven-baking combined, were as common as pan-frying.

6.4.2 Methodology

The analyses were performed separately for men and women due to potential metabolic and other differences between the sexes. Further, tertiles were considered the most appropriate due to the small size of the Fishermen study. Total fish consumption was preferred since the analyses conducted separately for fatty and lean fish consumption yielded similar results (data not shown). Similarly, total serum fish-derived omega-3 PUFA concentration was preferred since there were

only subtle differences in the results when EPA and DHA were considered separately (data not shown). More specifically, trends in HDL cholesterol and IMT were more evident across EPA tertiles, and trends in blood pressure, serum glucose, and the risk of carotid artery plaque were more evident across DHA tertiles in the general population sub-sample (data not shown). Many of the trends observed across omega-3 PUFA tertiles were weaker or even non-existent across fish consumption tertiles, which is expected since the FFQ measures long-term diet whereas serum concentrations are markers of short-term dietary intake.

The studied associations were adjusted for various combinations of covariates, for example traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, and systolic blood pressure). Additionally in the Fishermen study, potential negative confounding (Choi et al. 2008) was controlled for by adjusting means across omega-3 PUFA tertiles for environmental contaminants and vice versa. However, the adjustments did not essentially change the results.

In multiple regression modelling, over-adjustment and multicollinearity are potential problems. For example, BMI is probably an intermediate variable in the causal pathway of many of the studied associations in the present work. Regarding multicollinearity, energy intake caused multicollinearity with food consumption variables and thus, it was not included in the models. Otherwise, multicollinearity was not a problem based on pairwise Pearson correlation coefficients between the covariates (commonly around 0.2 and, at the highest, 0.6–0.7 between oil and salt intake) and the collinearity diagnostics (e.g., condition index).

6.4.3 Insulin sensitivity

Intervention studies among healthy individuals (Giacco et al. 2007; Lara et al. 2007; Damsgaard et al. 2008; Rizza et al. 2009) and many cohort studies (Dewailly et al. 2002; Nogi et al. 2007; Lee et al. 2008) have seen no effect of fish consumption or omega-3 PUFA intake on glucose and insulin metabolism. Intervention studies among high-risk individuals have yielded inconsistent results. For example, among diabetics, both a decrease (Mostad et al. 2006) and an increase (Karlstrom et al. 2011) in insulin sensitivity have been observed along with increasing omega-3 PUFA intake. In addition, an increase has also been observed among obese individuals (Ramel et al. 2008), which implies that the beneficial effect of fish consumption or omega-3 PUFA intake might be best observable among individuals with metabolic syndrome (Nigam et al. 2009). The fact that metabolic syndrome and diabetes are common in Finland could explain why beneficial inverse association between fish consumption or serum omega-3 PUFAs and insulin resistance measured by HOMA-IR was observed among women in the Health 2000 survey.

With regard to unhealthy effects, serum insulin concentrations and insulin resistance tended to increase along with increasing serum PCDD/F+PCB-TEq and blood MeHg concentrations among the men in the Fishermen study. This contradictory result could be, at least partly explained by environmental contaminants since a similar adverse trend has been observed previously among the Inuit (Ebbesson et al. 2007) who are known to eat a lot of potentially contaminated marine mammals and fish. Regarding non-dietary exposure, an increasing insulin resistance has been observed among residents near a closed pentachlorophenol and chlor-alkali factory along with increasing serum PCDD/F and blood mercury concentrations (Chang et al. 2010) and among Vietnam veterans (Kern et al. 2004) along with increasing serum TCDD concentration.

Additionally in the present work, a tendency towards a decreasing pancreatic beta cell function measured by HOMA-%B was observed along with increasing fish consumption and serum omega-3 PUFAs among the women in the Health 2000 survey and along with increasing serum PCDD/F+PCB-TEq among the women in the Fishermen study. A similar inverse association between beta cell function and dioxin-like and non-dioxin-like PCBs has been observed among the Greenland Inuit (Jorgensen et al. 2008) who have even higher serum concentrations of omega-3 PUFAs (Thorseng et al. 2009) and environmental contaminants (Bjerregaard et al. 2001; Jorgensen et al. 2008) than in the present work. Regarding the women in the Fishermen study, a weak decreasing trend could be explained by relatively high exposure to environmental contaminants. In contrast, exposure to environmental contaminants was presumably lower among the women in the Health 2000 survey. This was inferred from their low fish consumption when compared with the Fishermen study women and the fact that in Finland, approximately 95% of dioxin exposure and 80% of PCB exposure originates from fish (Kiviranta et al. 2004). A decrease in their beta cell function could be compensation after a decrease in serum insulin and an increase in insulin sensitivity along with increasing fish consumption and omega-3 PUFA intake.

6.4.4 Low-grade systemic inflammation

An inverse association between fish consumption or omega-3 PUFA intake and inflammatory markers has been observed in the majority of the previous studies on the topic (Ferrucci et al. 2006; Ohsawa et al. 2008; Farzaneh-Far et al. 2009; He et al. 2009; Kalogeropoulos et al. 2010). In the present work, the inverse association was strong in the Health 2000 survey especially regarding TNF-α and IL-6. An absence of a clear beneficial association in the Fishermen study could be due to chance, or possibly the exposure to environmental contaminants was high enough to attenuate or even cancel out the anti-inflammatory effect. On the other hand, since fish consumption and serum omega-3 PUFA concentrations were relatively high

among the Fishermen study participants and assuming there is a threshold level for an anti-inflammatory effect, a beneficial effect might have reached a plateau and would no longer be detectable. Furthermore, the anti-inflammatory effect of omega-3 PUFAs might be best observable among high-risk individuals (Ohsawa et al. 2008).

6.4.5 Early signs of atherosclerosis

In some of the previous intervention studies, omega-3 PUFA supplementation has increased arterial elasticity (Nestel et al. 2002; Wang et al. 2008; Sjoberg et al. 2010). Similarly in the present work, arterial stiffness decreased along with increasing serum omega-3 PUFAs among the men in Health 2000 survey. In contrast, an increase in arterial stiffness measured by β-stiffness index along with increasing contaminant concentrations was observed among the men in the Fishermen study. This contradictory finding is indirectly supported by several previous observational studies where serum PCDD/Fs, serum PCBs, and blood mercury were associated with elevated blood pressure (Uemura et al. 2009; Valera et al. 2009; Chang et al. 2011; Goncharov et al. 2011), which is strongly associated with arterial stiffness. In the present work, there was a tendency towards increasing blood pressure among the men with high fish consumption and in addition, fish consumption was positively correlated with sodium chloride intake (Spearman correlation coefficient around 0.4). Thus, fish-related sodium chloride intake together with high exposure to environmental contaminants and their consequent effect on blood pressure could, at least partially, explain the observed increase in arterial stiffness.

Several observational studies among healthy individuals have reported an inverse association between fish consumption or serum omega-3 PUFAs and IMT (Ebbesson et al. 2008; Sala-Vila et al. 2010) or the prevalence of atherosclerotic plaque in the coronary artery (He et al. 2008; Heine-Broring et al. 2010). In the present work, the risk of carotid artery plaque tended to decrease across tertiles of environmental contaminants among the men in the Fishermen study. This observation implies that despite the potential adverse effects on insulin sensitivity and arterial elasticity, high exposure to environmental contaminants may not be able to cancel out the beneficial effect of omega-3 PUFAs on the plaque formation and the overall effect remains beneficial. Regarding the RR estimates, however, it should be noted that the number of cases was probably underestimated since ultrasonography was performed only from one segment of the right common carotid artery.

6.4.6 Conclusion

Overall, the results of this cross-sectional study contribute to the growing body of evidence that the hypotriglyceridemic and anti-inflammatory effects of fish-derived omega-3 PUFAs has a pivotal role in the cardiovascular benefits of fish consumption. Other beneficial effects of omega-3 PUFAs were seen in glucose-insulin metabolism and arterial stiffness. Our results also suggest that high dietary exposure to fish-derived environmental contaminants might decrease insulin sensitivity and arterial elasticity assuming that the exposure is high enough to cancel out the beneficial effect of omega-3 PUFAs. At the same time, the overall effect on carotid artery plaque formation appeared not to be harmful regardless of high exposure to environmental contaminants.

Table 1. Characteristics of the study participants

| | Health 2000 sub-study | | | | Fishermen sub-study | | | |
| | Men (n=532) | | Women (n=641) | | Men (n=123) | | Women (n=132) | |
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Dietary data[a]								
Fish consumption (g/day)	35	33–38	36	34–38	64	56–72	50	45–56
Vegetable consumption (g/day)	189	178–201	256	244–268	169	150–189	255	230–282
Fruit and berry consumption (g/day)	114	103–126	186	173–201	139	119–162	180	150–216
Oil consumption (g/day)	7.7	7.4–8.1	7.3	7.1–7.6	8.2	7.6–8.9	7.7	7.2–8.3
Alcohol intake (g/day)	4.5	4.1–5.0	1.8	1.7–2.0	7.2	5.9–8.6	2.6	2.1–3.2
Salt intake (g/day)	11	10–11	9.9	9.6–10	9.6	9.1–10	8.5	8.1–8.9
Serum omega-3 PUFAs (% FAs)[b]	3.6	3.5–3.8	3.7	3.6–3.8	6.3	5.8–6.8	6.4	6.0–6.8
Environmental contaminants								
Serum PCDD/F+PCB-TEq (pg/g fat)[c]	-	-	-	-	98	84–114	54	47–62
Blood MeHg (ng/ml)	-	-	-	-	3.8	3.2–4.4	2.3	2.0–2.6
Traditional risk factors								
Age (years)	57	57–58	58	57–58	52	50–54	48	46–50
Smoking (%)								
Never smoker	36	-	64	-	41	-	65	-
Occasional or former smoker[d]	42	-	21	-	37	-	22	-
Daily smoker	22	-	15	-	22	-	13	-
Physical activity (%)								
Sufficient	37	-	38	-	30	-	31	-
Intermediate[e]	28	-	30	-	27	-	32	-
Sedentary	35	-	32	-	43	-	37	-
BMI (kg/m²)	27	27–28	26	26–27	27	27–28	26	25–27
Waist circumference (cm)	99	98–100	87	86–88	98	96–100	85	83–87
Systolic blood pressure (mmHg)	140	139–142	134	132–135	134	131–137	122	119–126
Diastolic blood pressure (mmHg)	87	86–88	81	81–82	85	83–86	78	77–80
Serum HDL cholesterol (mmol/l)	1.4	1.4–1.4	1.7	1.6–1.7	1.5	1.4–1.6	1.7	1.6–1.7
Serum non-HDL cholesterol (mmol/l)	4.0	3.9–4.0	3.8	3.7–3.9	4.1	4.0–4.3	3.6	3.4–3.8
Serum triglycerides (mmol/l)	1.3	1.3–1.4	1.1	1.1–1.2	1.2	1.1–1.3	1.0	0.97–1.1
Serum glucose (mmol/l)	6.0	5.9–6.1	5.5	5.5–5.6	5.7	5.5–5.8	5.3	5.2–5.3
Serum insulin (mU/l)	8.9	8.5–9.3	7.6	7.3–7.9	6.0	5.4–6.7	5.9	5.3–6.6

(Table 1. Continued)

HOMA-IR index[f]	2.4	2.2–2.5	1.9	1.8–1.9	1.5	1.3–1.7	1.4	1.2–1.5
HOMA-%B index[g]	74	71–77	77	75–80	57	52–62	69	63–76
Inflammatory markers								
Serum CRP (mg/l)	1.5	1.4–1.6	1.4	1.3–1.5	1.3	1.1–1.5	1.3	1.1–1.6
Serum TNF-α (ng/l)	5.6	5.5–5.8	5.3	5.2–5.5	-	-	-	-
Serum IL-6 (ng/l)	1.6	1.5–1.7	1.4	1.3–1.5	-	-	-	-
Vascular markers[h]								
Carotid artery IMT (mm)[i]	0.82	0.80–0.83	0.77	0.76–0.78	0.80	0.76–0.84	0.74	0.71–0.77
Plaque in carotid artery (%)[j]	17	-	11	-	26	-	15	-
Carotid artery stiffness								
Compliance (%/10 mmHg)[k]	0.80	0.76–0.84	0.84	0.80–0.88	0.79	0.68–0.92	0.95	0.86–1.1
Elastic modulus (kPa)[l]	830	788–874	741	707–777	796	683–928	624	565–689
β-stiffness index[m]	3.6	3.6–3.6	3.6	3.6–3.6	3.6	3.5–3.7	3.5	3.4–3.6
Medications (% of users)								
Insulin	1.7[n]	-	0.78[n]	-	4.1	-	2.3	-
Oral glucose lowering drugs	4.3[o]	-	1.9[o]	-	4.9	-	2.3	-
Lipid modifying drugs	14[p]	-	10[p]	-	18	-	12	-
Blood pressure lowering drugs	22[q]	-	23[q]	-	19	-	15	-

Abbreviations: ATC, anatomical therapeutic chemical; BMI, body mass index; CRP, C-reactive protein; FA, fatty acid; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IMT, intima-media thickness; IR, insulin resistance; IL-6, interleukin 6; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-p-dioxin and dibenzofuran; PUFA, polyunsaturated fatty acid; TEq, toxic equivalent quantity; TNF-α, tumour necrosis factor α

[a] based on a food frequency questionnaire
[b] the sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA)
[c] the sum of World Health Organization's toxic equivalent quantities for dioxins and PCBs
[d] smoked two days ago at the minimum but within previous 10 years
[e] mildly exhausting physical activity on free-time (duration at least 20 minutes) at least 2–3 times/week and physical activity while commuting (duration less than 30 minutes) daily
[f] insulin resistance index
[g] pancreatic beta cell function
[h] Health 2000 sub-study: men n=406, women n=499; Fishermen sub-study: men n=84, women n=90
[i] three end-diastole images from lateral interrogation angle at least 1 cm away from the origin of the bulb
[j] the prevalence of a focal raised lesion of >1.5 mm in size in at least one of the images of the carotid bulb
[k] ability of the artery to expand according to pulse pressure
[l] Young's elastic modulus, arterial stiffness independent of arterial wall thickness
[m] arterial stiffness relatively independent of blood pressure
[n] ATC code A10A
[o] ATC code A10B
[p] ATC code C10A
[q] ATC codes C02–C09

Table 2. Model-adjusted* geometric means for traditional CVD risk factors and inflammatory markers by tertiles of fish consumption and serum omega-3 PUFAs in the Health 2000 sub-study and the Fishermen sub-study

| | Health 2000 sub-study | | | | | | | | Fishermen sub-study | | | | | | | |
| | Men (n=532) | | | | Women (n=641) | | | | Men (n=123) | | | | Women (n=132) | | | |
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend
Fish consumption (g/day)																
Traditional risk factors																
BMI (kg/m²)	26.9	27.2	27.5	0.22	26.7	26.0	26.4	0.66	27.0	27.1	28.3	0.15	25.5	26.7	26.7	0.33
Waist (cm)	98.2	98.5	99.5	0.31	88.3	86.7	86.9	0.33	95.7	96.9	100	0.07	82.7	86.9	86.0	0.25
Systolic BP (mmHg)	143	142	140	0.26	138	134	134	0.07	130	137	137	0.22	121	123	127	0.15
Diastolic BP (mmHg)	89	87	86	0.02	82	82	82	0.50	83	88	85	0.52	77	79	81	0.11
HDL (mmol/l)	1.41	1.42	1.34	0.10	1.63	1.67	1.74	0.02	1.50	1.54	1.42	0.27	1.64	1.65	1.66	0.82
Non-HDL (mmol/l)	4.01	3.97	3.93	0.47	3.92	3.77	3.74	0.11	4.12	4.10	4.24	0.62	3.49	3.65	3.57	0.80
Triglycerides (mmol/l)	1.34	1.29	1.32	0.91	1.23	1.10	1.05	<0.01	1.27	1.11	1.15	0.54	1.03	1.00	1.09	0.51
Glucose (mmol/l)	5.94	6.05	5.99	0.67	5.53	5.52	5.54	0.92	5.49	5.75	5.81	0.09	5.25	5.28	5.24	0.89
Insulin (mU/l)	8.44	9.08	9.22	0.17	8.22	7.44	7.11	<0.01	5.58	5.62	6.89	0.12	5.76	6.56	5.47	0.60
HOMA-IR index	2.23	2.44	2.45	0.19	2.02	1.82	1.75	0.01	1.36	1.44	1.78	0.08	1.34	1.54	1.27	0.62
HOMA-%B index	71.8	73.8	76.3	0.29	82.5	76.2	73.3	0.01	57.2	51.5	62.2	0.38	67.3	76.2	64.8	0.63
Inflammatory markers																
CRP (mg/l)	1.53	1.48	1.54	0.93	1.50	1.36	1.31	0.24	1.41	1.27	1.14	0.36	1.41	1.12	1.47	0.75
TNF-α (ng/l)	5.89	5.60	5.40	0.05	5.49	5.23	5.29	0.41	-	-	-	-	-	-	-	-
IL-6 (ng/l)	1.67	1.62	1.57	0.48	1.46	1.33	1.41	0.77	-	-	-	-	-	-	-	-
Serum omega-3 PUFA concentration (% FAs)																
Traditional risk factors																
BMI (kg/m²)	27.0	27.5	27.0	0.67	27.2	26.2	25.7	<0.01	26.5	27.8	28.1	0.10	25.9	25.6	27.5	0.11
Waist (cm)	99.0	99.6	97.7	0.18	89.7	86.7	85.5	<0.01	94.3	98.6	100	0.03	84.3	84.4	86.9	0.28
Systolic BP (mmHg)	142	143	141	0.53	137	135	134	0.08	131	138	135	0.43	123	121	127	0.33
Diastolic BP (mmHg)	89	87	87	0.14	82	82	82	0.64	83	87	85	0.63	79	79	79	0.92
HDL (mmol/l)	1.34	1.36	1.46	<0.01	1.58	1.67	1.80	<0.01	1.51	1.49	1.46	0.57	1.64	1.71	1.60	0.60

(Table 2. Continued)

Non-HDL (mmol/l)	4.01	3.91	3.98	0.85	3.94	3.74	3.76	0.08	4.18	4.18	4.09	0.71	3.50	3.75	3.47	0.79
Triglycerides (mmol/l)	1.45	1.33	1.17	<0.01	1.28	1.10	1.00	<0.01	1.32	1.26	0.97	0.01	1.10	1.06	0.96	0.13
Glucose (mmol/l)	6.00	6.05	5.93	0.33	5.56	5.50	5.52	0.61	5.62	5.69	5.74	0.51	5.22	5.16	5.40	0.07
Insulin (mU/l)	8.98	9.58	8.21	0.05	8.14	7.65	6.97	<0.01	5.74	5.79	6.48	0.36	5.87	5.43	6.49	0.39
HOMA-IR index	2.40	2.57	2.17	0.05	2.01	1.87	1.71	<0.01	1.43	1.46	1.65	0.34	1.36	1.24	1.55	0.29
HOMA-%B index	74.3	78.2	69.6	0.12	81.7	78.7	71.7	<0.01	55.2	54.8	60.3	0.44	70.2	66.8	70.9	0.88
Inflammatory markers																
CRP (mg/l)	1.57	1.57	1.42	0.26	1.59	1.32	1.28	0.03	1.22	1.38	1.22	0.91	1.12	1.61	1.29	0.68
TNF-α (ng/l)	5.81	5.73	5.35	0.03	5.74	5.46	4.84	<0.01	-	-	-	-	-	-	-	-
IL-6 (ng/l)	1.76	1.72	1.40	<0.01	1.57	1.45	1.20	<0.01	-	-	-	-	-	-	-	-

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FA, fatty acid; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; IL-6, interleukin 6; PUFA, polyunsaturated fatty acid; TNF-α, tumour necrosis factor α

Fish consumption (g/day):
[a] men: n=177, mean=14, range 0–30; women: n=213, mean=16, range 0–31
[b] men: n=178, mean=39, range 31–50; women: n=214, mean=38, range 32–47
[c] men: n=177, mean=77, range 51–276; women: n=214, mean=71, range 48–417
[d] men: n=41, mean=31, range 3.9–47; women: n=44, mean=26, range 0.54–41
[e] men: n=42, mean=65, range 48–89; women: n=44, mean=52, range 42–67
[f] men: n=40, mean=131, range 90–463; women: n=44, mean=93, range 68–282

Serum omega-3 PUFA concentration (% FAs):
[a] men: n=177, mean=2.4, range 1.0–3.0; women: n=213, mean=2.4, range 0.72–3.1
[b] men: n=177, mean=3.5, range 3.1–4.3; women: n=216, mean=3.7, range 3.2–4.3
[c] men: n=178, mean=5.7, range 4.4–12; women: n=212, mean=5.6, range 4.4–12
[d] men: n=41, mean=4.1, range 2.6–5.0; women: n=44, mean=4.4, range 3.2–5.5
[e] men: n=41, mean=6.1, range 5.1–7.4; women: n=44, mean=6.4, range 5.6–7.5
[f] men: n=41, mean=10, range 7.5–23; women: n=44, mean=9.4, range 7.6–23

Epidemiological studies on
fish consumption and
cardiovascular health

Table 3. Model-adjusted* geometric means for vascular markers and a risk ratio (RRs) for the presence of carotid artery plaque by tertiles of fish consumption and serum omega-3 PUFAs in the Health 2000 sub-study and the Fishermen sub-study

| | Health 2000 sub-study | | | | | | | | Fishermen sub-study | | | | | | | |
| | Men (n=406) | | | | Women (n=499) | | | | Men (n=84) | | | | Women (n=90) | | | |
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend
								Fish consumption (g/day)								
Vascular markers																
IMT (mm)	0.81	0.81	0.80	0.48	0.77	0.77	0.76	0.32	0.78	0.81	0.80	0.90	0.72	0.72	0.77	0.15
Compliance (%/10 mmHg)	0.79	0.76	0.84	0.29	0.83	0.87	0.85	0.80	0.88	0.69	0.81	0.90	0.96	0.91	0.99	0.75
Elastic modulus (kPa)	844	856	792	0.36	746	701	738	0.93	720	903	777	0.89	647	668	562	0.24
β-stiffness index	3.61	3.66	3.55	0.32	3.60	3.58	3.60	0.92	3.56	3.66	3.60	0.88	3.50	3.57	3.49	0.84
RR for plaque	1.00	0.82	1.09	0.71	1.00	0.49	0.54	0.11	1.00	3.06	1.70	0.55	1.00	1.38	1.00	0.96
								Serum omega-3 PUFA concentration (% FAs)								
Vascular markers																
IMT (mm)	0.81	0.81	0.81	079	0.78	0.76	0.76	0.20	0.79	0.81	0.79	0.82	0.72	0.74	0.75	0.40
Compliance (%/10 mmHg)	0.76	0.75	089	0.01	0.85	0.83	0.88	0.40	1.07	0.72	0.65	0.03	1.01	0.97	0.88	0.25
Elastic modulus (kPa)	866	889	743	0.01	728	750	708	0.56	597	870	971	0.04	592	617	665	0.36
β-stiffness index	3.67	3.63	3.52	0.01	3.58	3.63	3.57	0.71	3.42	3.63	3.78	0.04	3.50	3.51	3.56	0.58
RR for plaque	1.00	0.81	0.71	0.20	1.00	1.19	1.06	0.92	1.00	1.12	0.64	0.44	1.00	1.26	3.03	0.05

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: FA, fatty acid; IMT, intima-media thickness; PUFA, polyunsaturated fatty acid; RR, risk ratio

Fish consumption (g/day):

[a] men: n=177, mean=14, range 0–30; women: n=213, mean=16, range 0–31
[b] men: n=178, mean=39, range 31–50; women: n=214, mean=38, range 32–47
[c] men: n=177, mean=77, range 51–276; women: n=214, mean=71, range 48–417
[d] men: n=41, mean=31, range 3.9–47; women: n=44, mean=26, range 0.54–41
[e] men: n=42, mean=65, range 48–89; women: n=44, mean=52, range 42–67
[f] men: n=40, mean=131, range 90–463; women: n=44, mean=93, range 68–282

Serum omega-3 PUFA concentration (% FAs):

[a] men: n=177, mean=2.4, range 1.0–3.0; women: n=213, mean=2.4, range 0.72–3.1
[b] men: n=177, mean=3.5, range 3.1–4.3; women: n=216, mean=3.7, range 3.2–4.3
[c] men: n=178, mean=5.7, range 4.4–12; women: n=212, mean=5.6, range 4.4–12
[d] men: n=41, mean=4.1, range 2.6–5.0; women: n=44, mean=4.4, range 3.2–5.5
[e] men: n=41, mean=6.1, range 5.1–7.4; women: n=44, mean=6.4, range 5.6–7.5
[f] men: n=41, mean=10, range 7.5–23; women: n=44, mean=9.4, range 7.6–23

Epidemiological studies on
fish consumption and
cardiovascular health

Table 4. Model-adjusted* geometric means for traditional CVD risk factors and CRP by tertiles of environmental contaminants in the Fishermen sub-study

Fishermen sub-study

Traditional risk factors	Men (n=123)				Women (n=132)			
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend
	Serum PCDD/F+PCB-TEq concentration (pg/g fat)							
BMI (kg/m²)	26.4	27.9	28.1	0.18	26.5	25.9	26.5	0.91
Waist (cm)	95.5	99.7	97.7	0.60	86.5	84.4	84.8	0.66
Systolic BP (mmHg)	131	142	131	0.67	121	123	128	0.10
Diastolic BP (mmHg)	83	89	83	0.52	76	80	80	0.14
HDL (mmol/l)	1.54	1.47	1.44	0.34	1.68	1.56	1.73	0.42
Non-HDL (mmol/l)	4.34	4.06	4.06	0.39	3.79	3.45	3.48	0.41
Triglycerides (mmol/l)	1.21	1.21	1.10	0.45	1.14	1.01	0.97	0.19
Glucose (mmol/l)	5.61	5.72	5.72	0.62	5.17	5.32	5.28	0.49
Insulin (mU/l)	5.19	6.06	6.85	0.07	6.23	6.06	5.47	0.39
HOMA-IR index	1.30	1.54	1.74	0.09	1.43	1.43	1.28	0.49
HOMA-%B index	50.2	57.6	63.2	0.10	77.1	68.2	63.2	0.17
CRP (mg/l)	1.30	1.48	1.07	0.29	1.50	1.09	1.42	0.94
Traditional risk factors	Blood MeHg concentration (ng/ml)							
BMI (kg/m²)	26.8	27.6	28.0	0.26	25.9	25.9	27.2	0.17
Waist (cm)	95.1	98.1	99.6	0.10	83.9	84.0	88.0	0.08
Systolic BP (mmHg)	135	133	136	0.79	124	121	127	0.30
Diastolic BP (mmHg)	85	85	86	0.67	78	78	80	0.30
HDL (mmol/l)	1.45	1.51	1.50	0.67	1.64	1.69	1.62	0.73
Non-HDL (mmol/l)	4.42	4.00	4.04	0.26	3.49	3.58	3.64	0.57

Epidemiological studies on
fish consumption and
cardiovascular health

(Table 4. Continued)

Triglycerides (mmol/l)	1.22	1.10	1.21	0.86	1.08	1.00	1.03	0.77
Glucose (mmol/l)	5.47	5.72	5.86	0.04	5.24	5.13	5.41	0.04
Insulin (mU/l)	5.60	5.72	6.75	0.15	6.24	5.06	6.56	0.42
HOMA-IR index	1.36	1.46	1.76	0.09	1.45	1.16	1.58	0.30
HOMA-%B index	58.5	52.9	59.1	0.75	73.3	63.5	71.2	0.97
CRP (mg/l)	1.46	1.11	1.28	0.75	0.96	1.56	1.59	0.07

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; IL-6, interleukin 6; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-p-dioxin and dibenzofuran; TEq, toxic equivalent quantity

Serum PCDD/F+PCB-TEq concentration (pg/g fat):
[a] men: n=41, mean=37, range 6.6–69; women: n=44, mean=22, range 7.3–36
[b] men: n=41, mean=106, range 70–155; women: n=44, mean=54, range 37–74
[c] men: n=41, mean=239, range 156–590; women: n=44, mean=128, range 75–433

Blood MeHg concentration (ng/ml):
[a] men: n=41, mean=1.3, range 0.21–2.6; women: n=46, mean=0.96, range 0–1.5
[b] men: n=42, mean=3.5, range 2.7–5.3; women: n=44, mean=2.2, range 1.6–2.9
[c] men: n=40, mean=9.4, range 5.4–60; women: n=42, mean=5.0, range 3.0–20

Table 5. Model-adjusted* geometric means for vascular markers and a risk ratio (RRs) for the presence of carotid artery plaque by tertiles of environmental contaminants in the Fishermen study.

| | Fishermen sub-study | | | | | | | |
| | Men (n=84) | | | | Women (n=90) | | | |
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend
	Serum PCDD/F+PCB-TEq concentration (pg/g fat)							
Vascular markers								
IMT (mm)	0.82	0.78	0.79	0.66	0.74	0.74	0.73	0.62
Compliance (%/10 mmHg)	1.05	0.70	0.68	0.09	1.13	0.82	0.94	0.38
Elastic modulus (kPa)	589	934	917	0.12	529	713	645	0.32
β-stiffness index	3.43	3.62	3.78	0.07	3.35	3.69	3.53	0.37
RR for plaque	1.00	0.76	0.47	0.13	1.00	2.67	4.07	0.15
	Blood MeHg concentration (ng/ml)							
Vascular markers								
IMT (mm)	0.82	0.78	0.80	0.86	0.74	0.74	0.73	0.79
Compliance (%/10 mmHg)	1.14	0.65	0.68	0.03	1.06	0.93	0.88	0.13
Elastic modulus (kPa)	544	1011	895	0.05	564	636	685	0.13
β-stiffness index	3.32	3.74	3.76	0.02	3.43	3.55	3.60	0.13
RR for plaque	1.00	0.90	0.36	0.04	1.00	1.50	2.04	0.14

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: IMT, intima-media thickness; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; TEq, toxic equivalent quantity; RR, risk ratio

Serum PCDD/F+PCB-TEq concentration (pg/g fat):
[a] men: n=28, mean=36, range 11–67; women: n=30, mean=22, range 7.3–39
[b] men: n=28, mean=102, range 68–155; women: n=30, mean=54, range 40–74
[c] men: n=28, mean=234, range 156–590; women: n=30, mean=126, range 75–367

Blood MeHg concentration (ng/ml):
[a] men: n=27, mean=1.1, range 0.21–2.2; women: n=32, mean=0.92, range 0–1.5
[b] men: n=30, mean=3.0, range 2.3–3.5; women: n=29, mean=2.0, range 1.6–2.6
[c] men: n=27, mean=6.2, range 3.6–19; women: n=29, mean=4.4, range 2.7–10

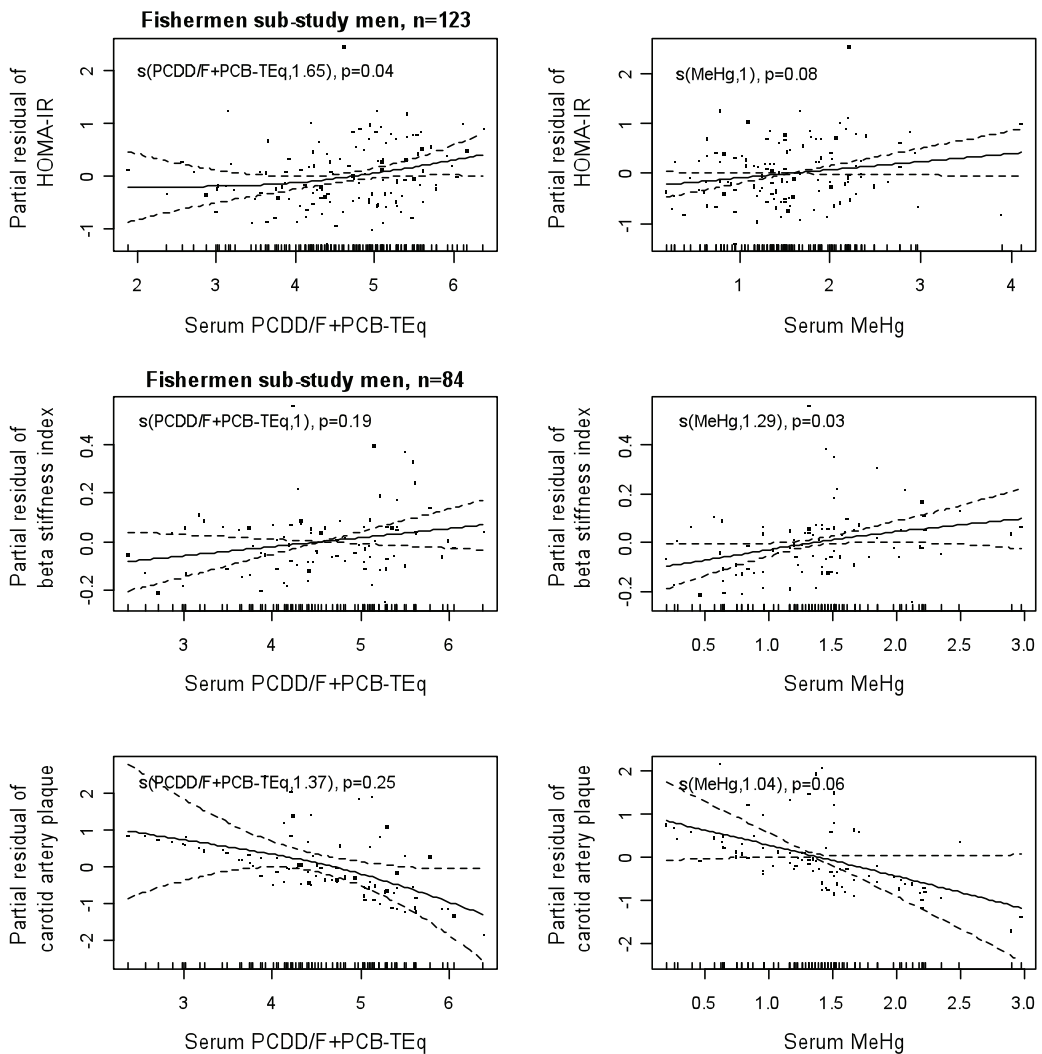Epidemiological studies on fish consumption and cardiovascular health

Figure 1. Smoothed associations between log-transformed serum PCDD/F+PCB-TEq concentration or blood MeHg concentration and log-transformed HOMA-IR index, log-transformed beta stiffness index, and the risk of carotid artery plaque among the Fishermen sub-study men. The figure has been produced by an additive model (AM) with a thin-plate regression spline and adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives. The solid curve is the additive model fit and the dashed curves represent the approximate 95% confidence interval. The fit is named as s(log_PCDD/F+PCB-TEq, edf) or s(log_MeHg, edf), where edf is the estimated degrees of freedom describing the wigginess of the fit. The plotted points are partial residuals.

Abbreviations: HOMA, homeostasis model assessment; IR, insulin resistance; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; TEq, toxic equivalent quantity

Appendix

Abbreviations and formulas for the parameters of homeostasis model assessment (HOMA) and ultrasonography

Abbreviation	Name	Formula / Definition
HOMA-IR[a,b]	Insulin resistance index	= [serum insulin (mU/l) * serum glucose (mmol/l)] / 22.5
HOMA-%B[a,b]	Beta cell function	= [20 x serum insulin (mU/l)] / [serum glucose (mmol/l) - 3.5]
IMT[a]	Intima-media thickness (mm)	= average of three end-diastole CCA IMT measurements
CAC[a,c]	Carotid artery compliance (%/10 mmHg)	= ability of the artery to expand according to pulse pressure (elasticity) = 100*10*[(ADC/DAD)/PP]
YEM[a,c]	Young's elastic modulus (kPa)	= arterial stiffness independent of arterial wall thickness = 0.1333*[EP*DAD/(2*IMT)]
SI[a,c]	β-stiffness index	= arterial stiffness relatively independent of blood pressure = Ln(SBP/DBP)/(ADC/DAD)
ADC	Arterial diameter change (mm)	= SAD–DAD
DAD	Diastolic arterial diameter (mm)	= average of three diastolic CCA diameter measurements
PP	Pulse pressure (mmHg)	= systolic blood pressure–diastolic blood pressure
EP[c]	Peterson's elastic modulus (kPa)	= 0.1333*(PP*DAD)/ADC
SAD	Systolic arterial diameter (mm)	= average of three systolic CCA diameter measurements

[a] reported in the present work

[b] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412–419.

[c] Selzer RH, Mack WJ, Lee PL, Kwong-Hu H, Hodis HN. Improved common carotid elasticity and intima-media thickness measurements from computer analysis of sequential ultrasound frames. Atherosclerosis 2001; 154:185–193.

Acknowledgements

References

Airaksinen R, Rantakokko P, Eriksson JG, Blomstedt P, Kajantie E, Kiviranta H. Association between type 2 diabetes and exposure to persistent organic pollutants. Diabetes Care. 2011; 34(9):1972-1979.

Airaksinen R, Turunen AW, Rantakokko P, Mannisto S, Vartiainen T, Verkasalo PK. Blood concentration of methylmercury in relation to food consumption. Public Health Nutr. 2010; 14(3):480-489.

Bjerregaard P, Dewailly E, Ayotte P, Pars T, Ferron L, Mulvad G. Exposure of Inuit in Greenland to organochlorines through the marine diet. J Toxicol Environ Health. 2001; 62(2):69-81.

Bushkin-Bedient S, Carpenter DO. Benefits versus risks associated with consumption of fish and other seafood. Rev Environ Health. 2010; 25(3):161-191.

Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006; 83(6 Suppl):1505S-1519S.

Calder PC, Yaqoob P. Omega-3 polyunsaturated fatty acids and human health outcomes. Biofactors. 2009; 35(3):266-272.

Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr. 2006; 83(6 Suppl):1499S-1504S.

Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Dioxin exposure and insulin resistance in Taiwanese living near a highly contaminated area. Epidemiology. 2010; 21(1):56-61.

Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance. J Hazard Mater. 2011; 185(2-3):749-755.

Choi AL, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. Crit Rev Toxicol. 2008; 38(10):877-893.

Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol. 2008; 167(7):847-858.

Damsgaard CT, Frokiaer H, Andersen AD, Lauritzen L. Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men. J Nutr. 2008; 138(6):1061-1066.

Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ. Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. Am J Clin Nutr. 2002; 76(1):85-92.

Ebbesson SO, Roman MJ, Devereux RB, Kaufman D, Fabsitz RR, Maccluer JW, et al. Consumption of omega-3 fatty acids is not associated with a reduction in carotid atherosclerosis: the Genetics of Coronary Artery Disease in Alaska Natives study. Atherosclerosis. 2008; 199(2):346-353.

Ebbesson SO, Tejero ME, Nobmann ED, Lopez-Alvarenga JC, Ebbesson L, Romenesko T, et al. Fatty acid consumption and metabolic syndrome components: the

GOCADAN study. J Cardiometab Syndr. 2007; 2(4):244-249.

Everett CJ, Frithsen I, Player M. Relationship of polychlorinated biphenyls with type 2 diabetes and hypertension. J Environ Monit. 2011; 13(2):241-251.

Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. Atherosclerosis. 2009; 205(2):538-543.

Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006; 91(2):439-446.

Giacco R, Cuomo V, Vessby B, Uusitupa M, Hermansen K, Meyer BJ, et al. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? Nutr Metab Cardiovasc Dis. 2007; 17(8):572-580.

Goncharov A, Pavuk M, Foushee HR, Carpenter DO. Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. Environ Health Perspect. 2011; 119(3):319-325.

Hall WL. Dietary saturated and unsaturated fats as determinants of blood pressure and vascular function. Nutr Res Rev. 2009; 22(1):18-38.

He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease--eat fish or take fish oil supplement? Prog Cardiovasc Dis. 2009; 52(2):95-114.

He K, Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, et al. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2009; 103(9):1238-1243.

He K, Liu K, Daviglus ML, Mayer-Davis E, Jenny NS, Jiang R, et al. Intakes of long-chain n-3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis. Am J Clin Nutr. 2008; 88(4):1111-1118.

Heine-Broring RC, Brouwer IA, Proenca RV, van Rooij FJ, Hofman A, Oudkerk M, et al. Intake of fish and marine n-3 fatty acids in relation to coronary calcification: the Rotterdam Study. Am J Clin Nutr. 2010; 91(5):1317-1323.

Heistaro S. Methodology report. Health 2000 Survey. National Public Health Institute. Report No.: B26/2008. Available at: http://www.terveys2000.fi/doc/methodolog yrep.pdf

Hennig B, Oesterling E, Toborek M. Environmental toxicity, nutrition, and gene interactions in the development of atherosclerosis. Nutr Metab Cardiovasc Dis. 2007; 17(2):162-169.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006; 332(7544):752-760.

Jorgensen ME, Borch-Johnsen K, Bjerregaard P. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. Diabetologia. 2008; 51(8):1416-1422.

Jula A, Marniemi J, Ronnemaa T, Virtanen A, Huupponen R. Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: a randomized controlled trial. Arterioscler Thromb Vasc Biol. 2005; 25(9):1952-1959.

Kalogeropoulos N, Panagiotakos DB, Pitsavos C, Chrysohoou C, Rousinou G, Toutouza M, et al. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. Clin Chim Acta. 2010; 411(7-8):584-591.

Karlstrom BE, Jarvi AE, Byberg L, Berglund LG, Vessby BO. Fatty fish in the diet of patients with type 2 diabetes: comparison of the metabolic effects of foods rich in n-3 and n-6 fatty acids. Am J Clin Nutr. 2011; 94(1):26-33.

Kern PA, Said S, Jackson WG, Jr., Michalek JE. Insulin sensitivity following agent

orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Clin Endocrinol Metab. 2004; 89(9):4665-4672.

Kiviranta H, Ovaskainen ML, Vartiainen T. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environ Int. 2004; 30(7):923-932.

Kiviranta H, Vartiainen T, Tuomisto J. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 2002; 110(4):355-361.

Lara JJ, Economou M, Wallace AM, Rumley A, Lowe G, Slater C, et al. Benefits of salmon eating on traditional and novel vascular risk factors in young, non-obese healthy subjects. Atherosclerosis. 2007; 193(1):213-221.

Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs DR, Jr. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One. 2011; 6(1):e15977.

Lee E, Lee S, Park Y. n-3 Polyunsaturated fatty acids and trans fatty acids in patients with the metabolic syndrome: a case-control study in Korea. Br J Nutr. 2008; 100(3):609-614.

Massaro M, Scoditti E, Carluccio MA, Montinari MR, De Caterina R. Omega-3 fatty acids, inflammation and angiogenesis: nutrigenomic effects as an explanation for anti-atherogenic and anti-inflammatory effects of fish and fish oils. J Nutrigenet Nutrigenomics. 2008; 1(1-2):4-23.

Mostad IL, Bjerve KS, Bjorgaas MR, Lydersen S, Grill V. Effects of n-3 fatty acids in subjects with type 2 diabetes: reduction of insulin sensitivity and time-dependent alteration from carbohydrate to fat oxidation. Am J Clin Nutr. 2006; 84(3):540-550.

Mozaffarian D. Fish, mercury, selenium and cardiovascular risk: current evidence and unanswered questions. Int J Environ Res Public Health. 2009; 6(6):1894-1916.

Männistö S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-

control study on breast cancer. J Clin Epidemiol. 1996; 49(4):401-409.

Nestel P, Shige H, Pomeroy S, Cehun M, Abbey M, Raederstorff D. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans. Am J Clin Nutr. 2002; 76(2):326-330.

Nigam A, Frasure-Smith N, Lesperance F, Julien P. Relationship between n-3 and n-6 plasma fatty acid levels and insulin resistance in coronary patients with and without metabolic syndrome. Nutr Metab Cardiovasc Dis. 2009; 19(4):264-270.

Niiranen T, Jula A, Kantola I, Moilanen L, Kahonen M, Kesaniemi YA, et al. Home-measured blood pressure is more strongly associated with atherosclerosis than clinic blood pressure: the Finn-HOME Study. J Hypertens. 2007; 25(6):1225-1231.

Nogi A, Yang J, Li L, Yamasaki M, Watanabe M, Hashimoto M, et al. Plasma n-3 polyunsaturated fatty acid and cardiovascular disease risk factors in Japanese, Korean and Mongolian workers. J Occup Health. 2007; 49(3):205-216.

Ohsawa M, Itai K, Onoda T, Tanno K, Sasaki S, Nakamura M, et al. Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. Atherosclerosis. 2008; 201(1):184-191.

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, et al. Validity of a food frequency questionnaire varied by age and body mass index. J Clin Epidemiol. 2006; 59(9):994-1001.

Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ Health. 2009; 8(Sept 19):39.

Ramel A, Martinez A, Kiely M, Morais G, Bandarra NM, Thorsdottir I. Beneficial effects of long-chain n-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. Diabetologia. 2008; 51(7):1261-1268.

Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the

roles of n-3 fatty acids in health and disease. J Am Diet Assoc. 2009; 109(4):668-679.

Rizza S, Tesauro M, Cardillo C, Galli A, Iantorno M, Gigli F, et al. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. Atherosclerosis. 2009; 206(2):569-574.

Sala-Vila A, Cofan M, Perez-Heras A, Nunez I, Gilabert R, Junyent M, et al. Fatty acids in serum phospholipids and carotid intima-media thickness in Spanish subjects with primary dyslipidemia. Am J Clin Nutr. 2010; 92(1):186-193.

Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of type 2 diabetes. Nutrition, Metabolism & Cardiovascular Diseases. 2011; 21(Suppl 2):B32-B48.

Sipila K, Kahonen M, Salomaa V, Paivansalo M, Karanko H, Varpula M, et al. Carotid artery intima-media thickness and elasticity in relation to glucose tolerance. Acta Diabetol. 2011; (May 21):DOI 10.1007/s00592-00011-00291-z.

Sjoberg NJ, Milte CM, Buckley JD, Howe PR, Coates AM, Saint DA. Dose-dependent increases in heart rate variability and arterial compliance in overweight and obese adults with DHA-rich fish oil supplementation. Br J Nutr. 2010; 103(2):243-248.

Thorseng T, Witte DR, Vistisen D, Borch-Johnsen K, Bjerregaard P, Jorgensen ME. The association between n-3 fatty acids in erythrocyte membranes and insulin resistance: the Inuit Health in Transition Study. Int J Circumpolar Health. 2009; 68(4):327-336.

Turunen AW, Männistö S, Kiviranta H, Marniemi J, Jula A, Tiittanen P, et al. Dioxins, polychlorinated biphenyls, methylmercury and omega-3 polyunsaturated fatty acids as biomarkers of fish consumption. Eur J Clin Nutr. 2010; 64(3):313-323.

Turunen AW, Männistö S, Suominen AL, Tiittanen P, Verkasalo PK. Fish consumption in relation to other foods in the diet. Br J Nutr. 2011; 10(106):1570-1580.

Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Mannisto S, et al. Mortality in a cohort with high fish consumption. Int J Epidemiol. 2008; 37(5):1008-1017.

Uemura H, Arisawa K, Hiyoshi M, Kitayama A, Takami H, Sawachika F, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. Environ Health Perspect. 2009; 117(4):568-573.

Valera B, Dewailly E, Poirier P. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. Hypertension. 2009; 54(5):981-986.

Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev. 2010; 68(5):280-289.

Wang S, Ma AQ, Song SW, Quan QH, Zhao XF, Zheng XH. Fish oil supplementation improves large arterial elasticity in overweight hypertensive patients. Eur J Clin Nutr. 2008; 62(12):1426-1431.

Wood SN. Generalized additive models: An introduction with R. Chapman and Hall; 2006.

7 Mortality in a cohort with high fish consumption

Turunen AW,[1] Verkasalo PK,[1] Kiviranta H,[1] Pukkala E,[2] Jula A,[3] Männistö S,[4] Räsänen, R[1] Marniemi J,[3] Vartiainen T[1,5]

[1] National Public Health Institute, Department of Environmental Health, Kuopio, Finland
[2] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland
[3] National Public Health Institute, Department of Health and Functional Capacity, Turku, Finland
[4] National Public Health Institute, Department of Health Promotion and Chronic Disease Prevention, Helsinki, Finland
[5] University of Kuopio, Department of Environmental Sciences, Kuopio, Finland

Abstract

Background: Our aim was to assess the mortality of fishermen and fishermen's wives in Finland, presuming that the mortality reflects their high consumption of contaminated fish.

Methods: All Finnish fishermen, registered since 1980, were identified from the Professional Fishermen Register (N=6410), and the fishermen's wives from the national population register (N=4260). The cohorts were individually linked with cause-of-death data until 2005 at Statistics Finland. The follow-up started in the year after the first registration as a fisherman and at marriage (if later) for the wives. The standardised mortality ratios (SMRs) were calculated based on the national mortality rates. In addition, blood samples and food frequency questionnaire data were collected from a volunteer sample.

Results: The average fish consumption and serum concentrations of fish-derived fatty acids and environmental contaminants were higher among the fishermen and their wives than among the general population from the same region. The fishermen and their wives had lower mortality from all causes (SMR 0.78, 95% confidence interval (CI) 0.73–0.82, and 0.84, 0.76–0.93, respectively), and ischaemic heart diseases (0.73, 0.65–0.81, and 0.65, 0.50–0.83) than the general population. Mortality from cerebrovascular diseases and malignant neoplasms was decreased among the fishermen (0.67, 0.52–0.85, and 0.90, 0.80–1.01), but not among the wives. In addition, the fishermen's mortality from water transport accidents was extremely high (8.31, 5.65–11.79).

Conclusions: The fishermen and their wives had lower mortality from many natural causes. The high intakes of environmental contaminants in fish were not seen as excess mortality.

7.1 Introduction

Dietary fish contains beneficial nutritional compounds, such as long-chain polyunsaturated fatty acids (omega-3 PUFAs), and vitamin D. High fish consumption and high omega-3 PUFA intake may protect against fatal coronary heart disease (Brouwer et al. 2006; Mozaffarian and Rimm 2006), ischaemic stroke (Skerrett and Hennekens 2003; He et al. 2004) and certain cancers (Caygill and Hill 1995; Fernandez et al. 1999; Augustsson et al. 2003; Terry et al. 2003; Leitzmann et al. 2004; Saadatian-Elahi et al. 2004; Norat et al. 2005). Conversely, fish may also contain various persistent environmental contaminants, for instance polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs, called dioxins in this work), and polychlorinated biphenyls (PCBs). The most toxic dioxin congener, 2,3,7,8-tetrachlorodibentzo-*p*-dioxin (TCDD) is carcinogenic (IARC International Agency for Research on Cancer 1997) and may also have harmful effects on the cardiovascular system (Pesatori et al. 1998).

In northern Europe, the Baltic Sea area is heavily contaminated with persistent organic pollutants (Hallikainen et al. 2004). For example, big Baltic herring and wild salmon often exceed the maximum level of World Health Organisation (WHO) toxic equivalent quantity (8 pg WHO-$_{PCDD/F-PCB}$-TEq per g fresh weight) (Commission of the European Communities 2006). In our previous study, Finnish Baltic Sea fishermen had at least twofold serum concentrations of dioxins and PCBs than the general male population (Kiviranta et al. 2000; Kiviranta et al. 2002). These concentrations were comparable to those found in Seveso, Italy, after the industrial accident (Needham et al. 1997), and considerably higher than for example, concentrations among the Canadian Inuit (Ayotte et al. 1997) or the frequent fish consumers in the Great Lakes area in the United States (Falk et al. 1999).

Previous epidemiological data on the health behaviour of Finnish professional fishermen are scarce. Based on high serum concentrations of persistent organic pollutants, we presumed that high fish consumption is an important characteristic of Finnish fishermen's diet (Kiviranta et al. 2000; Kiviranta et al. 2002). Regarding fishermen's health, mortality from occupational accidents is presumed to be high, but less is known about mortality from natural causes (disease mortality), which reflects both life habits and work-related exposures. This study aims to assess cause-specific mortality in a cohort of Finnish professional fishermen and their wives.

7.2 Methods

7.2.1 Materials

Mortality study

In this longitudinal study, the cohort consisted of Finnish professional fishermen (n=6410) and their wives (n=4260). The fishermen were identified from the Professional Fishermen Register (Ministry of Agriculture and Forestry 1994), which was maintained by the Finnish Game and Fisheries Research Institute under the Ministry of Agriculture and Forestry from the early 1980s to 1995. The regional Employment and Economic Development Centres (TE-Centres) have kept the register since 1995, when Finland joined the European Union (EU). The Professional Fishermen Register automatically includes all fishermen, who own a fishing vessel. In addition, all fishermen are obligated to notify the agricultural industry district (regional TE-Centre) before taking up fishing activities. All maritime and freshwater area fishermen who had entered the register at least once between 1980 and 2002 were included in the study cohort.

A fisherman's wife was defined as a woman married to a fisherman at the time of the registration of the fisherman, or later. The wives were identified from the Population Information System of the Population Register Centre (for more information, see http://www.vaestorekisterikeskus.fi/vrk/home.nsf/www/populati-oninformationsystem). Spouses cohabiting without marriage could not be identified from the population register.

The cohort was linked with Statistics Finland's national cause-of-death data (Statistics Finland 2004) from 1980 to 2005 by unique personal identity codes (for more information, see http://www.stat.fi/til/ksyyt/index_en). To enable easy production of time series over the years, Statistics Finland transfers the original cause-of-death codes to a standard 54-category list of causes of death. This list was used in the present study.

Fish consumption and life habit study

In the mortality study, we did not have data on life habits. Therefore, we conducted a cross-sectional sub-sample study. We first drew a national sample of 4487 fishermen, their wives, and other family members from the registers to conduct a health questionnaire study. From 1429 respondents, 309 volunteers living at the southern and south-western sea coast of Finland (Helsinki and Turku regions) attended a health examination between August 2004 and May 2005. Of those, 88 were fishermen and 94 were fishermen's wives, aged 45–74 years (the Fishermen study). For comparison, we used data from the population-based Health 2000 health examination survey (Aromaa and Koskinen 2004) (n=6986). The study subjects from the supplemental study on cardiovascular disease and diabetes (n=1526),

conducted between October 2001 and December 2002, represented the regional general Finnish population. Data were available from 313 males and 361 females, aged 45–74 years, from Helsinki and Turku regions (the Health 2000 survey).

The health examination protocols were similar in the Fishermen study and in the Health 2000 survey. Diet was assessed by a validated self-administered semi-quantitative 128-item food frequency questionnaire (FFQ) designed to cover the diet over the preceding 12 months (Paalanen et al. 2006). Dietary data was processed in the Fineli Finnish Food Composition Database (National Public Health Institute 2007). During the health examinations, fasting blood samples were collected to analyse serum concentrations of nutrients and environmental contaminants, and anthropometric measures were taken to assess body composition. Serum total fatty acid composition was analysed using gas chromatography (capillary column, flame ionisation detector) (Jula et al. 2005), and the concentration of 25-hydroxy-derivative of vitamin D (25-hydroxy-cholecalciferol) was analysed by radioimmunoassay. A high resolution mass spectrometer equipped with a gas chromatograph was used to analyse 17 dioxin and 37 PCB congeners from serum (Kiviranta et al. 2002). The analyses were performed at the National Public Health Institute's accredited testing laboratory in Turku and Kuopio (Code T077, EN ISO/IEC 17025).

To analyse environmental contaminants, serum samples were not available from the Health 2000 survey. Therefore, results from the National Public Health Institute's case-control study on soft tissue sarcoma (Tuomisto et al. 2004), conducted from 1997 to 1999, were used instead. In this work, we re-calculated the concentrations of dioxins and PCBs analysed from adipose tissue for 47 male and 41 female controls (appendicitis patients), aged 45–74 years, living at the southern and south-western sea coast of Finland (the Sarcoma study) (Kiviranta et al. 2005). Adipose tissue concentrations are comparable with those measured from serum fat (Schecter et al. 1991).

7.2.2 Statistical analyses

In the mortality study, calculation of person-years started at the beginning of the year after the first registration (any year between 1981 and 2002) to the Professional Fishermen Register for the fishermen, and at marriage (if later) for the wives. The follow-up ended at death, at emigration, or on December 31st 2005, whichever came first. The observed numbers of deaths and person-years at risk were calculated separately by gender and five-year age group for four calendar periods (1980–86, 1987–93, 1994–99 and 2000–05). The expected numbers of deaths were calculated by multiplying the number of person-years in each stratum by the corresponding national mortality rate during the period of observation. The standardised mortality ratios (SMRs) were calculated as the ratio of the observed to the expected deaths

with 95% confidence intervals (CI) based on the Poisson distribution for observed deaths. After considering the annual SMRs, the first three years of the follow-up were excluded from the analysis to eliminate the healthy population selection effect (Vinni and Hakama 1980). On the grounds of biological and epidemiological evidence, the most relevant causes of death were chosen for closer review from the 54-category list.

In the fish consumption and life habit study, means for fish consumption, intakes of fish-derived omega-3 PUFAs (g/day, age- and energy-adjusted), alcohol intake (percentage of total daily energy intake, age-adjusted), and serum concentrations of two omega-3 PUFAs (i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), percentage of serum fatty acids, age-adjusted), vitamin D (nmol/l, age-adjusted), and toxic equivalent quantities (Van den Berg et al. 1998) for dioxins ($WHO_{PCDD/F}$-TEq, pg/g fat, age-adjusted) and PCBs (WHO_{PCB}-TEq, pg/g fat, age-adjusted) were calculated separately for men and women. The variables for body mass index (BMI, kg/m^2), smoking, frequency of hangovers, and physical activity both on free-time and at work were each divided into three categories. Age-adjusted estimates for prevalence were calculated for BMI (<25, 25–29, ≥ 30 kg/m^2), smoking (never smoker, occasional or former smoker, daily smoker), the frequency of hangovers during the last year (no hangovers, 1–6 hangovers, >6 hangovers), physical activity at free-time (exercise ≥ 4 times/week, 1–3 times/week, ≤ 3 times/month), and physical activity at work (heavy exertion, moderate exertion, mainly sedentary).

7.3 Results

7.3.1 Mortality study

The study cohort provided ~128 000 person-years at follow-up (Table 1). The average follow-up time was 12 years.

The fishermen had 22% lower all-cause mortality than the general male population (Table 2). There were 27% and 33% deficits in the fishermen's mortality from ischaemic heart diseases and cerebrovascular diseases, respectively. Mortality from all malignant neoplasms was slightly decreased by 10%. The statistically non-significant SMR estimates were <1 for cancers of the colon, rectum and anus, stomach, and larynx, trachea and lung, slightly >1 for cancers of the lymphoid, haematopoietic and related tissue, and close to unity for prostate cancer. Deficits were also observed in other causes of death, such as diabetes (by 57%), dementia and Alzheimer's disease (by 46%), all diseases of the respiratory system (by 42%), alcohol related diseases and accidental poisonings by alcohol (by 41%), and suicide (by 39%). Mortality from accidents and violence was close to unity. In contrast, the

fishermen had 3-fold mortality from drowning and over 8-fold mortality from water transport accidents when compared with the general male population.

The fishermen's wives had 16% lower all-cause mortality and 35% lower ischaemic heart disease mortality than the general female population (Table 2). The SMR estimates for cerebrovascular diseases and all cancers were close to unity. The statistically non-significant SMR estimates were <1 for cancers of the stomach, breast, larynx, trachea and lung, and lymphoid, haematopoietic and related tissue, and >1 for cancers of the colon, and rectum and anus. A 68% deficit was seen in mortality from all diseases of the respiratory system.

Further, the SMR estimates for all causes, ischaemic heart diseases, cerebrovascular diseases and cancers were <1 in almost all age groups (Table 3).

7.3.2 Fish consumption and life habit study

The fishermen consumed 85% more fish and had 59% higher intake of fish-derived omega-3 PUFAs than males of the Health 2000 survey (Table 4). The serum concentrations of EPA and DHA were twofold, and vitamin D concentration was 40% higher among the fishermen. The concentrations of dioxins and PCBs in serum fat were twofold among the fishermen when compared with those of the Sarcoma study males.

The fishermen's wives consumed 45% more fish and had 29% higher intake of fish-derived omega-3 PUFAs than females of the Health 2000 survey (Table 4). The serum EPA concentration was 67% higher, DHA concentration was twofold, and vitamin D concentration was 30% higher among the fishermen's wives. The concentrations of dioxins and PCBs in serum fat were ~20% higher among the fishermen's wives than among the Sarcoma study females.

When compared with the males and females of the Health 2000 survey, the fishermen and their wives had higher prevalence of obesity (BMI≥30), lower prevalence of current daily smoking, and lower frequency of hangovers. Alcohol intake as a proportion of total energy intake was slightly higher among the fishermen than among the males of the Health 2000 survey. The prevalence of free-time regular and sufficient physical activity (exercise ≥4 times/week) was lower, whereas the prevalence of heavy exertion at work was considerably higher among the fishermen than among the Health 2000 males. Among the females of the Fishermen study and the Health 2000 survey, alcohol intake and physical activity both during free-time and work did not differ considerably.

7.4 Discussion

In the present study, the fishermen had decreased mortality from all-causes, ischaemic heart diseases, cerebrovascular diseases, cancers, diabetes, dementia and Alzheimer's disease, diseases of the respiratory system, alcohol related diseases and accidental poisonings by alcohol, and suicide when compared with the general male population. Further, they had almost twofold fish consumption, 1.6-fold fish-derived omega-3 PUFA intake, 1.4-fold serum vitamin D concentration, and twofold serum EPA, DHA, dioxin, and PCB concentrations when compared with the males of the general population sub-sample. Similarly, the fishermen's wives had lower mortality from all causes, ischaemic heart diseases, and respiratory diseases than the general female population. Their fish consumption, omega-3 PUFA intake, and serum concentrations of vitamin D, EPA, DHA, dioxins, and PCBs were higher than those of the females of the general population sub-sample.

In Finland, administrative registers, such as Population Information System and cause-of-death register, have good coverage and validity (Gissler and Haukka 2004), and the automated record linkage procedure is based on unique personal identity codes. Although the determination principles of the underlying cause of death may slightly vary by time, region, social class, and occupation (Pukkala 1995), the variation among the fishermen and their wives is likely to be similar to the variation in the general population. The automatic registration based on fishing vessel register and the notification obligation by law since 1995 have improved the file coverage of the Professional Fishermen Register close to 100%.

The majority of the Finnish fishermen live at the south-western sea coast of Finland, but we do not have reference mortality rates for that region and for a comparable time period. Thus, we evaluated the magnitude of the potential effect of geographical variation in the mortality by using the Small Area Statistics on Health System (Kokki et al. 2002). In short, we calculated the SMRs (adjusted for socio-economic status) for the population living within 20 km from the Finnish coastline in the year 1980, excluding fishermen and their wives. The size of the population was ~0.9 million persons, and it provided 20 million person-years during the follow-up from 1981 to 2005. Mortality was 3% lower from all causes and 7% lower from ischaemic heart diseases among those living at the coastal areas than among the general population of Finland. Cancer mortality did not differ between the coastal areas and the rest of Finland. Hence, the use of regional reference mortality rates would not have changed the SMR estimates notably.

We evaluated the potential for healthy population selection effect (Vinni and Hakama 1980) in our cohort by calculating the SMRs separately for each year from the beginning of the follow-up. The healthy population selection effect was distinctive during the first three years of the follow-up, and the annual SMR estimates stabilised to their long-term level after the third year. For example, the

SMR estimate for all diseases among the fishermen was 0.39 (0.24–0.60), 0.41 (0.26–0.62), and 0.57 (0.40–0.79) during the first 3 years, and stabilised after the third year at the level around 0.75. Therefore, the first three years of the follow-up were excluded from the mortality analyses. In the previous studies on fishermen, the healthy population selection effect has not been actively controlled. It can be speculated that decreased mortality especially among the Canadian (Neutel 1989) fishermen is partially explained by the healthy population selection effect.

In the longitudinal mortality study, we did not have data on confounding factors, such as diet, smoking, alcohol consumption, and physical activity. Instead, we assessed life habits in small volunteer samples of the study populations. In general, volunteers tend to be more health conscious than the average population, and therefore, the results from the Fishermen study sub-sample may not be fully generalisable to all Finnish fishermen and their wives (and similarly, the results from the Health 2000 survey sub-sample may not be fully generalisable to the general population). However, comparisons between the two similarly selected volunteer samples will at least diminish the bias.

Our results on mortality among the Finnish fishermen and their wives are in line with the reported associations between high fish consumption or high omega-3 PUFA intake and reduced all-cause mortality (Bucher et al. 2002; Mozaffarian and Rimm 2006), fatal coronary heart disease (summarised in several reviews (Sidhu 2003; Ruxton et al. 2004; Brouwer et al. 2006; Mozaffarian and Rimm 2006)), and ischaemic stroke (Skerrett and Hennekens 2003; He et al. 2004). In previous studies in cohorts with high fish consumption, a decreased ischaemic heart disease risk has been reported for the Greenland (Kromann and Green 1980) and the Alaskan (Davidson et al. 1993) Inuit and the residents of a Japanese fishing village (Hirai et al. 1989). Overall, results from five previous fishermen studies are quite inconsistent. Compared with the Finnish fishermen, only the Swedish (Hagmar et al. 1992) (0.88, 0.78–0.99) and Canadian (Neutel 1989) (0.80, 0.76–0.85) fishermen seem to have a similarly decreased mortality from all causes. Regarding diseases of the circulatory system, only the Canadian (Neutel 1989) fishermen have decreased mortality from ischaemic heart diseases (0.72, 0.65–0.80) and cerebrovascular diseases (0.67, 0.51–0.86). Among the Swedish (Hagmar et al. 1992) and Italian (Mastrangelo et al. 1995) fishermen, the SMR estimates for diseases of the circulatory system show statistically non-significant decreases. On the contrary, all-cause and ischaemic heart disease mortality is increased among the Danish (Jensen 1996) and Icelandic (Rafnsson and Gunnarsdottir 1994) fishermen.

The lack of decrease or increase in cancer mortality can be seen as a reflection of the unclear net effect of fish consumption on cancer risk. For example, fish or omega-3 PUFAs (Caygill and Hill 1995; Fernandez et al. 1999; Augustsson et al. 2003; Terry et al. 2003; Key et al. 2004; Leitzmann et al. 2004; Saadatian-Elahi et al. 2004; Norat et al. 2005) and vitamin D (Garland et al. 2006) are suspected to have a protective effect against cancer, but TCDD is a human carcinogen (IARC

115

International Agency for Research on Cancer 1997). With regard to the previous studies, only the Swedish (Hagmar et al. 1992) (0.77, 0.58–1.02) and Canadian (Neutel 1989) (0.92, 0.83–1.02) fishermen and the Swedish fishermen's wives from the West coast (Rylander and Hagmar 1995) (0.96, 0.87–1.06) seem to have similar cancer mortality when compared with the Finnish fishermen and their wives. The Italian (Mastrangelo et al. 1995), Danish (Jensen 1996), and Icelandic (Rafnsson and Gunnarsdottir 1994) fishermen have increased cancer mortality.

Decreased mortality from diabetes, diseases of the respiratory system and dementia and Alzheimer's disease is in line with the findings that omega-3 PUFAs (Nettleton and Katz 2005) and vitamin D (Garland et al. 2006) may protect against diabetes and/or its fatal complications, and omega-3 PUFAs may protect from inflammatory diseases (Ruxton et al. 2004) and dementia (Issa et al. 2006). In the previous studies, diabetes mortality is reported only among the Canadian (Neutel 1989) fishermen (0.33, 0.13–0.68), and it is similar when compared with the Finnish fishermen. In the Seveso study, the SMR estimate for diabetes is >1 (Bertazzi et al. 2001). Regarding respiratory diseases, the Canadian (Neutel 1989) fishermen seem to have a similarly decreased mortality (0.39, 0.28–0.54) than the Finnish fishermen. The decreased SMR estimate for respiratory diseases among the Italian (Rafnsson and Gunnarsdottir 1994) fishermen and the slightly increased SMR estimates among the Danish (Jensen 1996) and Icelandic (Rafnsson and Gunnarsdottir 1994) fishermen are statistically non-significant.

Extremely high mortality from water transport accidents and drowning among the fishermen was expected due to fishermen's working conditions on fishing vessels. The observed decreased mortality from suicides could be linked with a recent finding suggesting that high intake of omega-3 PUFAs may affect mental health by protecting from depression and other mental disorders (Sidhu 2003; Ruxton et al. 2004). However, suicides among professional fishermen are likely to be partly misclassified as water transport accidents and drowning. Regarding the previous studies, mortality from occupational accidents is reported only for the Swedish (Hagmar et al. 1992) (11.1, 5.33–20.4), Canadian (Neutel 1989) (8.50, 6.87–10.4) and Danish (Jensen 1996) (4.75, 3.91–5.71) fishermen, and the results are in line with the results of the present study. Suicide mortality is reported only for Canadian (Neutel 1989) and Danish (Jensen 1996) fishermen but those ~10% decreases are statistically non-significant.

With regard to the Finnish fishermen's life habits, their high fish consumption, relatively low prevalence of daily smoking, low frequency of hangovers, and high frequency of physical activity at work are in line with the observed decreases in mortality from many chronic diseases and the absence of increased SMR estimates for cancers. High physical activity at work may partly compensate for the risk caused by high BMI and low prevalence of regular and sufficient free-time physical activity. In addition, BMI may not be a good measure of body composition in a population with heavy physical exertion.

Regarding the comparability of the fishermen studies, the SMR estimates are expected to vary by country due to differences in national characteristics of professional fishing (e.g., type of the vessel, working methods, distance to the shore, and work shift hours) and professional fishermen's life habits (e.g., smoking, fish consumption and other dietary habits, alcohol drinking patterns, and physical activity). For example, the reported high smoking prevalence among the Italian (Mastrangelo et al. 1995) fishermen could explain their increased mortality from many cancers and a slightly increased SMR estimate for all causes. Increased lung cancer mortality among the Danish (Jensen 1996) and Icelandic (Rafnsson and Gunnarsdottir 1994) fishermen indicates high smoking prevalence, which agrees with their increased mortality from the majority of the reported causes. Further, fish consumption may not be as important characteristic of fishermen's diet in other countries as it is in Finland.

The SMR estimates in different countries may also vary depending on how study population and reference population are defined. With regard to the Icelandic study (Rafnsson and Gunnarsdottir 1994), fishermen and sailors are grouped together, which makes that study less suitable for comparisons. In the Danish study (Jensen 1996), the general population in labour force is used as a reference population, which could be an additional explanation for the increased estimates. Moreover, due to differences in national reference mortality levels, comparisons of mortality patterns should ideally be based on both relative mortality ratios and absolute mortality rates.

7.5 Conclusions

To conclude, the Finnish fishermen and their wives are a population with high fish consumption and high serum concentrations of dioxins and PCBs. In this study, they had lower mortality from all causes, ischaemic heart diseases, and respiratory diseases than the respective general male and female populations. The fishermen (but not their wives) also had decreased mortality from cerebrovascular diseases, diabetes, dementia and Alzheimer's disease, and suicide. The high intakes of environmental contaminants in fish were not seen as excess mortality. It is possible that exposure to environmental contaminants was not high enough to cause excess mortality, or the beneficial health effects of fish consumption (or some other factor) outweighed the potential hazardous health effects.

Table 1. Numbers (N) and proportions (%) of the fishermen and their wives in the Fishermen study by age at the beginning of the follow-up, and person-years at risk by age at follow-up during 1980–2005

Age (years)	Fishermen				Fishermen's wives			
	Persons		Person-years[a]		Persons		Person-years[a]	
	N	%	N	%	N	%	N	%
All ages	6410	100	77 233	100	4260	100	50 958	100
<20	158	3	115	0	10	0	0	0
20–29	816	13	2567	3	507	12	725	1
30–39	1536	24	9825	13	1174	28	6047	12
40–49	1695	26	18 269	24	1163	27	12 710	25
50–59	1292	20	20 663	27	841	20	14 013	28
60–69	691	11	15 547	20	441	10	10 420	20
70–79	197	3	8330	11	110	3	5651	11
80+	25	0	1917	2	14	0	1393	3

[a] calculated after exclusion of the first three years of the follow-up

Table 2. Observed numbers of deaths (Obs) and standardised mortality ratios (SMR) with 95% confidence intervals (CI) for selected causes among the fishermen and their wives in the Fishermen study, during 1980–2005 (after exclusion of the first three years of the follow-up)

Cause of death[a]	Fishermen (n=6410)			Fishermen's wives (n=4260)		
	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	962	0.78	0.73–0.82	355	0.84	0.76–0.93
All diseases[b]	840	0.75	0.70–0.79	335	0.84	0.76–0.93
Diseases of the circulatory system	412	0.75	0.68–0.82	140	0.81	0.68–0.94
Ischaemic heart diseases	269	0.73	0.65–0.81	62	0.65	0.50–0.83
Other heart diseases	41	1.08	0.77–1.46	13	0.88	0.47–1.51
Cerebrovascular diseases	67	0.67	0.52–0.85	46	0.95	0.70–1.27
Other diseases of the circulatory system	35	0.85	0.59–1.18	19	1.23	0.74–1.92
Neoplasms	267	0.90	0.79–1.00	120	0.99	0.82–1.17
Malignant neoplasms	263	0.90	0.80–1.01	115	0.97	0.80–1.15
Colon	8	0.52	0.23–1.03	10	1.30	0.62–2.39
Rectum and anus	8	0.82	0.35–1.60	8	2.13	0.92–4.19
Stomach	16	0.82	0.47–1.33	2	0.30	0.04–1.08
Prostate	36	0.99	0.69–1.36	-	-	-
Breast	-	-	-	18	0.80	0.47–1.25
Larynx, trachea and lung	72	0.80	0.63–1.01	8	0.70	0.30–1.38
Lymphoid, haematopoietic and related tissue	33	1.28	0.88–1.79	10	0.83	0.40–1.53
Endocrine, nutritional and metabolic diseases	8	0.60	0.26–1.18	6	0.87	0.32–1.89
Diabetes mellitus	5	0.43	0.14–0.99	5	0.83	0.27–1.94
Dementia and Alzheimer's disease	19	0.54	0.33–0.85	27	1.14	0.75–1.66
Diseases of the respiratory system	58	0.58	0.44–0.75	8	0.32	0.14–0.62
Pneumonia	26	0.53	0.35–0.78	5	0.32	0.10–0.74
Bronchitis and emphysema	27	0.66	0.44–0.96	1	0.18	0.00–1.01
Alcohol related diseases and accidental poisoning by alcohol	34	0.59	0.41–0.82	5	0.58	0.19–1.36
Accidents and violence[c]	110	0.95	0.78–1.13	18	0.74	0.44–1.16
Accidents[c]	80	1.17	0.93–1.45	15	1.01	0.56–1.66
Traffic accidents	5	0.44	0.14–1.02	4	1.30	0.35–3.32
Water transport accidents	31	8.31	5.65–11.79	0	0.00	0.00–24.54
Accidental falls	9	0.37	0.17–0.70	10	1.51	0.73–2.78
Drowning	17	3.05	1.78–4.88	0	0.00	0.00–6.05
Accidental poisonings[d]	2	0.30	0.04–1.08	1	0.58	0.01–3.22
Suicides	24	0.61	0.39–0.91	3	0.38	0.08–1.11
Assault	4	1.02	0.28–2.61	0	0.00	0.00–3.76
No death certificate	1	1.07	0.03–5.94	1	2.98	0.08–16.61

[a] for International Classification of Diseases (ICD) codes, see http://statfin.stat.fi/statweb/
[b] including accidental poisoning by alcohol
[c] excluding accidental poisoning by alcohol
[d] excluding poisonings by alcohol

Table 3. Observed (Obs) numbers of deaths and standardised mortality ratios (SMR) with 95% confidence intervals (CI) for selected causes by age group among the fishermen and their wives in the Fishermen study, during 1980–2005 (after exclusion of the first three years of the follow-up)

Cause of death[a]	Fishermen (n=6410)			Fishermen's wives (n=4260)		
	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes						
<50	73	0.75	0.59–0.95	21	0.81	0.50–1.24
50–59	128	0.73	0.61–0.85	35	0.73	0.51–1.01
60–69	230	0.72	0.63–0.81	68	0.78	0.60–0.98
70–79	321	0.80	0.71–0.88	114	0.82	0.67–0.97
80+	210	0.86	0.75–0.97	117	0.98	0.81–1.16
Ischaemic heart diseases						
<50	4	0.33	0.09–0.83	2	1.80	0.22–6.51
50–59	24	0.51	0.33–0.76	2	0.49	0.06–1.75
60–69	87	0.82	0.66–1.01	10	0.58	0.28–1.06
70–79	105	0.81	0.66–0.96	21	0.56	0.35–0.85
80+	49	0.67	0.50–0.88	27	0.77	0.51–1.12
Cerebrovascular diseases						
<50	1	0.23	0.01–1.29	1	0.58	0.01–3.22
50–59	9	0.92	0.42–1.75	4	1.12	0.31–2.88
60–69	11	0.51	0.25–0.91	5	0.61	0.20–1.42
70–79	26	0.70	0.46–1.03	13	0.74	0.39–1.26
80+	20	0.75	0.46–1.15	23	1.34	0.85–2.00
Malignant neoplasms						
<50	9	0.80	0.37–1.52	9	0.97	0.44–1.83
50–59	33	0.83	0.57–1.16	16	0.74	0.42–1.20
60–69	66	0.74	0.57–0.93	36	1.04	0.73–1.43
70–79	104	0.98	0.80–1.17	34	0.93	0.64–1.29
80+	51	1.14	0.85–1.50	20	1.26	0.77–1.93

[a] for International Classification of Diseases (ICD) codes, see http://statfin.stat.fi/statweb/

Table 4. Age- and energy-adjusted means for fish consumption and the intake of fish-derived omega-3 PUFAs, age-adjusted means for serum concentrations of EPA, DHA, vitamin D, dioxins, and PCBs, and age-adjusted prevalence of certain life-style factors among volunteers, aged 45–74 years, from the Fishermen study (during 2004–2005), the Health 2000 survey (during 2001–2002), and the Sarcoma study (during 1997–1999, only for dioxin and PCB analyses)

	Fishermen (n=88)	Men, Health 2000 survey (n=313)	Fishermen's wives (n=94)	Women, Health 2000 survey (n=361)
FFQ				
Fish consumption (g/day)	89	48	64	44
Fish-derived omega-3 PUFA intake (g/day)	1.4	0.88	0.98	0.76
Alcohol intake (ethanol, % of total energy intake)	3.7	3.0	1.4	1.5
Serum sample analyses				
Eicosapentaenoic acid (EPA, % FAs)	2.4	1.2	2.0	1.2
Docosahexaenoic acid (DHA, % FAs)	4.3	2.2	4.6	2.1
Vitamin D (nmol/l)	71	50	65	50
Dioxins ($WHO_{PCDD/F}$-TEq, pg/g fat)[a]	94[c]	45[d]	59[c]	47[d]
PCBs (WHO_{PCB}-TEq, pg/g fat)[b]	69[c]	35[d]	40[c]	33[d]
Health examination				
BMI				
<25 kg/m^2 (%)	23	29	31	36
25–29 kg/m^2 (%)	47	47	39	39
≥30 kg/m^2 (%)	30	24	30	25
Health questionnaire				
Smoking (missing=1)				
Never smoker (%)	47	35	69	61
Occasional or former smoker (%)	36	40	19	23
Daily smoker (%)	17	25	12	16
Alcohol consumption pattern (missing=91)				
No hangovers during the last year (%)	45	39	79	73
1–6 hangovers during the last year (%)	43	45	19	24
>6 hangovers during the last year (%)	12	16	2.0	3.0

(Table 4. Continued)

Physical activity (free-time) (missing=7)				
Exercise ≥4 times/week (%)	18	28	28	27
Exercise 1–3 times/week (%)	43	45	52	52
Exercise ≤3 times/month (%)	39	27	20	21
Physical activity (work) (missing=245)				
Heavy exertion (%)	61[e]	31[f]	29[e]	26[f]
Moderate exertion (%)	17[e]	19[f]	26[e]	26[f]
Mainly sedentary (%)	22[e]	50[f]	45[e]	48[f]

[a] WHO toxic equivalent quantity for polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs, dioxins)
[b] WHO toxic equivalent quantity for polychlorinated biphenyls (PCBs)
[c] measured from serum fat, samples were not available from all Fishermen study subjects (n_{men}=83, n_{women}=77)
[d] serum samples were not available from the Health 2000 survey subjects, adipose tissue concentrations were recalculated from the Sarcoma study (n_{men}=47, n_{women}=41)
[e] for current or previous work
[f] for current work only

Key messages

- The Finnish fishermen and their wives are a population with high fish consumption and high serum concentrations of dioxins and PCBs.
- The Finnish fishermen and their wives had lower mortality from all causes, ischaemic heart diseases, and respiratory diseases than the general population.
- In this study, high consumption of contaminated fish was not reflected as excess mortality.
- The health benefits of fish consumption seem to outweigh the potential health hazards even if dietary fish is highly contaminated.

Acknowledgements

References

Aromaa A, Koskinen S. Health and functional capacity in Finland. Baseline Results of the Health 2000 Health Examination Survey. National Public Health Institute. Report No.: B12/2004. Available at: http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2004b12.pdf

Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, et al. A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev. 2003; 12(1):64-67.

Ayotte P, Dewailly E, Ryan JJ, Bruneau S, Lebel G. PCBs and dioxin-like compounds in plasma of adult Inuit living in Nunavik (Arctic Quebec). Chemosphere. 1997; 34(5-7):1459-1468.

Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, et al. Health effects of dioxin exposure: a 20-year mortality study. AmJEpidemiol. 2001; 153(11):1031-1044.

Brouwer IA, Geelen A, Katan MB. n-3 Fatty acids, cardiac arrhythmia and fatal coronary heart disease. Prog Lipid Res. 2006; 45(4):357-367.

Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. AmJMed. 2002; 112(4):298-304.

Caygill CP, Hill MJ. Fish, n-3 fatty acids and human colorectal and breast cancer mortality. Eur J Cancer Prev. 1995; 4(4):329-332.

Commission of the European Communities. Commission Regulation (EC) setting maximum levels for certain contaminants in foodstuffs. 1881/2006. Available at: http://eur-lex.europa.eu/en/index.htm

Davidson M, Bulkow LR, Gellin BG. Cardiac mortality in Alaska's indigenous and non-Native residents. Int J Epidemiol. 1993; 22(1):62-71.

Falk C, Hanrahan L, Anderson HA, Kanarek MS, Draheim L, Needham L, et al. Body burden levels of dioxin, furans, and PCBs among frequent consumers of Great Lakes sport fish. The Great Lakes Consortium. Environ Res. 1999; 80(2 Pt 2):S19-S25.

Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr. 1999; 70(1):85-90.

Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, et al. The role of vitamin D in cancer prevention. Am J Public Health. 2006; 96(2):252-261.

Gissler G, Haukka J. Finnish health and social welfare registers in epidemiological research. Norsk Epidemiologi. 2004; 14(1):113-120.

Hagmar L, Linden K, Nilsson A, Norrving B, Akesson B, Schutz A, et al. Cancer incidence and mortality among Swedish Baltic Sea fishermen. Scand J Work Environ Health. 1992; 18(4):217-224.

Hallikainen A, Kiviranta H, Isosaari P, Vartiainen T, Parmanne R, Vuorinen PJ. Concentrations of dioxins, furans, dioxin-like PCB compounds and polybrominated diphenyl ethers in domestic fresh water and salt water fish. National Food Agency of Finland. Report No.: 1/2004.

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke. 2004; 35(7):1538-1542.

Hirai A, Terano T, Tamura Y, Yoshida S. Eicosapentaenoic acid and adult diseases in Japan: epidemiological and clinical aspects. J Intern Med Suppl. 1989; 225(731):69-75.

IARC International Agency for Research on Cancer. Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. Monographs on the evaluation of carcinogenic risks to human Report No.: 69. Available at: http://monographs.iarc.fr/ENG/Monographs/vol69/volume69.pdf

Issa AM, Mojica WA, Morton SC, Traina S, Newberry SJ, Hilton LG, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. Dement Geriatr Cogn Disord. 2006; 21(2):88-96.

Jensen OC. Mortality in Danish fishermen. Bull Inst Marit Trop Med Gdynia. 1996; 47(1-4):5-10.

Jula A, Marniemi J, Ronnemaa T, Virtanen A, Huupponen R. Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: a randomized controlled trial. Arterioscler Thromb Vasc Biol. 2005; 25(9):1952-1959.

Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. Public Health Nutr. 2004; 7(1A):187-200.

Kiviranta H, Tuomisto JT, Tuomisto J, Tukiainen E, Vartiainen T. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in the general population in Finland. Chemosphere. 2005; 60(7):854-869.

Kiviranta H, Vartiainen T, Tuomisto J. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 2002; 110(4):355-361.

Kiviranta H, Vartiainen T, Verta M, Tuomisto JT, Tuomisto J. High fish-specific dioxin concentrations in Finland. Lancet. 2000; 355(9218):1883-1885.

Kokki E, Pukkala E, Verkasalo P, Pekkanen J. Small Area Statistics on Health (SMASH): A system for rapid investigations of cancer in Finland. In: Briggs D, Forer P, Järup L, Stern R, editors. GIS for emergency preparedness and health risk reduction. Dordrecht: Kluwer Academic Publishers; 2002.

Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950-1974. Acta Med Scand. 1980; 208(5):401-406.

Leitzmann MF, Stampfer MJ, Michaud DS, Augustsson K, Colditz GC, Willett WC, et al. Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr. 2004; 80(1):204-216.

Mastrangelo G, Malusa E, Veronese C, Zucchero A, Marzia V, Boscolo Bariga A. Mortality from lung cancer and other diseases related to smoking among fishermen in north east Italy. Occup Environ Med. 1995; 52(3):150-153.

Ministry of Agriculture and Forestry. Decision of the Ministry of Agriculture and Forestry on the Registers of the Fishing Industry. 1575/1994. Available at: http://www.finlex.fi/en/laki/kaannokset/1994/en19941575.pdf

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006; 296(15):1885-1899.

National Public Health Institute. Fineli Finnish Food Composition Database [cited 12.6.2007]. Available at: http://www.fineli.fi

Needham LL, Gerthoux PM, Patterson DG, Jr., Brambilla P, Turner WE, Beretta C, et al. Serum dioxin levels in Seveso, Italy, population in 1976. Teratog Carcinog Mutagen. 1997; 17(4-5):225-240.

Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005; 105(3):428-440.

Neutel CI. Mortality in commercial fishermen of Atlantic Canada. Can J Public Health. 1989; 80(5):375-379.

Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst. 2005; 97(12):906-916.

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, et al. Validity of a food frequency questionnaire varied by age and body mass index. J Clin Epidemiol. 2006; 59(9):994-1001.

Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA. Dioxin exposure and non-malignant health effects: a mortality study. Occup Environ Med. 1998; 55(2):126-131.

Pukkala E. Cancer risk by social class and occupation. A survey of 109,000 cancer cases among Finns of working age. Basel: S. Karger AG; 1995.

Rafnsson V, Gunnarsdottir H. Mortality among Icelandic seamen. Int J Epidemiol. 1994; 23(4):730-736.

Ruxton CH, Reed SC, Simpson MJ, Millington KJ. The health benefits of omega-3 polyunsaturated fatty acids: a review of the evidence. J Hum Nutr Diet. 2004; 17(5):449-459.

Rylander L, Hagmar L. Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochlorine compounds. ScandJWork EnvironHealth. 1995; 21(6):419-426.

Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer. 2004; 111(4):584-591.

Schecter A, Papke O, Ball M, Ryan JJ. Partitioning of Dioxins and Dibenzofurans - Whole-Blood, Blood-Plasma and Adipose-Tissue. Chemosphere. 1991; 23(11-12):1913-1919.

Sidhu KS. Health benefits and potential risks related to consumption of fish or fish oil. Regul Toxicol Pharmacol. 2003; 38(3):336-344.

Skerrett PJ, Hennekens CH. Consumption of fish and fish oils and decreased risk of stroke. Prev Cardiol. 2003; 6(1):38-41.

Statistics Finland. Causes of death 2004. Report No.: 2005:1.

Terry PD, Rohan TE, Wolk A. Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence. Am J Clin Nutr. 2003; 77(3):532-543.

Tuomisto JT, Pekkanen J, Kiviranta H, Tukiainen E, Vartiainen T, Tuomisto J. Soft-tissue sarcoma and dioxin: A case-control study. Int J Cancer. 2004; 108(6):893-900.

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife.

Environ Health Perspect. 1998; 106(12):775-792.

Vinni K, Hakama M. Healthy worker effect in the total Finnish population. Br J Ind Med. 1980; 37(2):180-184.

8 Discussion

8.1 Methodological considerations

In the cross-sectional studies described in Chapters 4–6, two separate study populations were used. The unique Fishermen study population consisted of professional Baltic Sea fishermen and their family members with high fish consumption and high exposure to fish derived environmental contaminants. From the nationally representative Health 2000 survey, the larger sample used in Chapter 5 represented the general population of Finland and the smaller sample used in Chapters 4 and 6 was a sub-sample of the general population. The multidisciplinary data included, e.g., food consumption recorded by a calibrated FFQ on whole diet, blood concentrations of various nutrients, environmental contaminants, and markers of health status, carotid artery ultrasound recording, and anthropometric and other basic measurements.

In the register-based mortality study with a 25-year follow-up that was described in Chapter 7, the national cause-of-death data were used as a reference. A small cross-sectional fish consumption and life habit study was used to compensate for the lack of data on fish consumption and confounding factors in the register-based study. Data on fish consumption was available from the Fishermen study and from a regional sample of the Health 2000 survey, whereas data on serum concentrations of environmental contaminants was available only from the Fishermen study and thus, data from a regional sample of controls of the Sarcoma study were used for comparison.

8.1.1 Study population, size, and setting

The Fishermen study population consisted of an occupational group of professional fishermen and their family members, which limits the generalisability of the results. Furthermore, volunteers tend to be more health conscious than the average population, which may, for instance, complicate the detection of effects best observable among high-risk individuals. In addition, the volunteers came from convenience samples, referring to individuals living within a reasonable distance from the study locations, which may further limit the generalisability of the results. The results from the Fishermen study are generalisable only to countries where dioxin and PCB exposure is specific to fish consumption. However, generalisability is not the main concern since the central idea of the present work was to study particularly a population with high exposure to environmental contaminants and draw conclusions based on the idea that if we cannot detect an increased risk in a

highly exposed population, it is likely that populations with lower exposures are also safe.

The number of participants in the Fishermen study was determined by the available resources to perform environmental chemistry analyses, as at the time of the study, these analyses were very expensive and time consuming. The resulting small study population led to a lack of statistical power to establish associations. For example, many linear trends that were observed in the means of cardiovascular risk factors did not reach statistical significance. Hence, the true shapes of the studied associations were examined visually by plotting the results of an additive model with a thin-plate regression spline that allows the data to "speak for themselves" as the smoothing function does not assume a rigid form for the dependence. The message was strengthened also by repeating the analyses, when possible, in a larger and more heterogeneous population representing the general population of Finland.

Observational studies alone cannot establish causality. Especially the cross-sectional setting is always susceptible to reverse causality bias since time order of the events cannot be determined. Despite this inherent limitation, the results of the present work are able to serve as additional support to previous findings when interpreted in conjunction with biological plausibility and prior evidence. In addition, studying the health effects in ordinary living conditions instead of an artificial setting can be seen as an important advantage of observational studies.

8.1.2 Dietary data

Although an FFQ is considered the primary method for assessing a long-term diet in large epidemiological studies, it has some inherent limitations, such as reliance on respondent's memory and susceptibility to both under- and over-reporting depending on foods. The FFQ used in the present work has been calibrated previously, and its reproducibility (interclass correlation 0.63) and validity (Pearson correlation 0.51) regarding fish consumption were judged to be satisfactory (Männistö et al. 1996). In another previous calibration study on the same FFQ, fish consumption was observed to be over-reported approximately by 40% among men and by 80% among women (Paalanen et al. 2006). The evident over-reporting is not necessarily a problem since an FFQ is designed only to rank individuals according to their habitual diet and not to measure absolute intake. However, measurement error in fish consumption typically attenuates the studied associations towards the null. This could explain why associations observed between biomarkers and cardiovascular risk factors were not always observable when fish consumption was used instead of biomarkers. Comparisons between the Fishermen study and the Health 2000 survey were warranted since the same FFQ was used in both studies.

The lipid content of fish varies markedly depending on species, and thus, the separation of total fish consumption into fatty and lean fish might be necessary.

Fatty fish consumption may estimate better fatty acid and vitamin D intake and exposure to fat-soluble contaminants. In our data, however, fatty fish consumption yielded correlation coefficients of the same magnitude with serum omega-3 PUFA concentration and similar associations with cardiovascular risk factors when compared with total fish consumption. In addition, information on fish species, e.g., division of predatory and herbivore fish, would be useful when assessing exposure to non-fat-soluble contaminants such as MeHg. In the present work, the lack of information on fish species was not problematic as contaminants were analysed from blood samples.

In some studies, the health benefits of fish consumption have been observed to be dependent on cooking method in a way that baked or broiled fish has been associated with decreased disease risk and fried fish has been associated with zero effect or an increased risk of disease (Mozaffarian et al. 2003; He 2009; Belin et al. 2011). Ideally, fish consumption data should contain information also on food preparation methods since typical methods differ substantially between countries. For example, heavy processing (e.g., battering and deep-frying) is common especially in the UK and USA (Myint et al. 2006). In the present work, data on cooking method was not collected in the FFQ. However, according to unpublished data from the health questionnaire, the only heavily processed fish dish listed, fish fingers accounted for only 1% of the total fish consumption in the Fishermen study. Pan-frying was the most common single cooking method for fish (25% of all fish dishes were prepared by pan-frying) but healthier methods, namely cooking and oven-baking, were together as common as pan-frying. In addition, the use of vegetable oils was positively associated with fish consumption both in the Fishermen study and the general population, which indicates healthy cooking methods and dietary habits associated with fish consumption.

Ultimately, the quality of the dietary data is determined by the quality of the database used to calculate food consumption and nutrient intake from the frequency data. Regarding the present work, the national food composition database Fineli and the dietary intake calculation software Finessi are comprehensive, frequently updated, and quality-controlled (Reinivuo et al. 2010) and thus, the technical quality of the dietary data can be considered as good.

8.1.3 Complexity of the research question

The complex interrelations between CVD and diabetes and their lifestyle-related biological risk factors, dietary risk factors, and genetic risk factors make it difficult to distinguish the specific effects of fish consumption and omega-3 PUFA intake (Kromhout 2001). Due to complexity, regression models typically include a high number of covariates, which may cause instability in the estimates. Further, the separation of confounders and mediators is not straightforward. For instance, body

mass index (BMI) probably mediates various cardiovascular effects of both omega-3 PUFAs and endocrine disrupting contaminants, and is also a potential effect modifier. Furthermore, the possibility of residual confounding resulting from imprecision in measurement or unmeasured factors is always a concern.

Variability and intricacy of diet causes difficulties in identifying the specific health effects of individual dietary components (Chung et al. 2008). Nutrients can have both synergistic and antagonist effects with each other and simultaneous exposure to a complex mixture of compounds can lead to unexpected interactions that can obscure modest effects. In addition, fish typically contains both beneficial and hazardous compounds that may have opposing effects on the same outcomes. The following negative confounding leads to the underestimation of beneficial or hazardous effects (Choi et al. 2008; Stern and Korn 2011). Benefits and risks are tightly linked, mutually confounding, and cannot be considered in isolation.

The unique population where the potential harmful effects of contaminants are most likely to be seen due to high fish consumption and high exposure to environmental contaminants is one of the strengths of the present work. The background concentrations of environmental contaminants are usually low, and hence, the hazards may not be observable in general populations. Another strength is the multidisciplinary data, including actual biological concentrations of nutrients and environmental contaminants together with dietary data on food consumption and nutrient intake. In the scientific literature, the effects of beneficial nutrients and environmental contaminants have rarely been assessed at the same time, and even if both nutrient and contaminant data are simultaneously included in multivariate analyses, imprecision in their measurement may still bias the results towards the null. In the present work, negative confounding was assessed by including both omega-3 PUFAs and environmental contaminant simultaneously in the models when considering the cardiovascular risk factors, whereas in the mortality study, the net effect of fish consumption was assessed in the high-exposure population.

8.2 Findings on biomarkers and frequency questions reflecting fish consumption

Serum concentrations of omega-3 PUFAs, namely EPA and DHA, are traditional biomarkers of fish consumption. However, they reflect relatively short-term fish intake, especially when measured from serum or plasma fractions with rapid turnover, even though ideally, the biomarker should reflect cumulative intake over an extended period. In addition, EPA and DHA are typically expressed as percentages from total serum fatty acids, which may be problematic since changes in the intake of some other fatty acid affects the percentages of EPA and DHA regardless of their absolute intake. Further, concentration biomarkers are typically

affected by non-dietary factors such as lifestyle, metabolism, and genetics. Despite the limitations, EPA has been found to at least discriminate between habitual fish eaters and non-eaters (Hunter 1998).

In the present work, correlation coefficients between blood concentration of omega-3 PUFAs and fish consumption were approximately at the same level as those reported in earlier studies (Andersen et al. 1999; Philibert et al. 2006; Sun et al. 2007). However, blood concentrations of fish-derived environmental contaminants, namely dioxins, PCBs, and MeHg reflected self-reported habitual fish consumption better than omega-3 PUFAs in a population with high consumption of Baltic fish. This is probably explained by the fact that both dietary data from the FFQ over the preceding year and serum concentrations of persistent environmental contaminants reflect long-term exposure. It appears possible that due to accumulation, fish-derived environmental contaminants may bring out the health effects of fish consumption better than self-reported dietary data. For example, in one recent study, blood MeHg concentration was associated with a decreased risk of AMI whereas fish consumption itself was not (Wennberg et al. 2011). Thus, environmental contaminants could be used to substitute dietary data on fish consumption in those populations where fish is an important source of environmental contaminants. It should be noted, however, that in order to function properly, the biomarker should show sufficient variation between individuals.

The separate frequency questions on fish consumption in the health questionnaire yielded equally good estimates of habitual fish consumption as the previously calibrated FFQ on whole diet. This enables us to use the larger health questionnaire data collected from the Fishermen study population in future epidemiological studies on fish consumption and self-perceived health, although ideally, dietary data should contain information on whole diet and energy intake.

8.3 Findings on diet associated with fish consumption

It has been suggested that at least a part of the postulated beneficial effects of high fish consumption and high omega-3 PUFA intake could be explained by an overall healthier dietary pattern or even a healthier lifestyle associated with fish consumption (Cundiff et al. 2007; Hostenkamp and Sorensen 2009). To the best of our knowledge, however, the specific association between fish consumption and the overall diet has not been the main research question in previous studies. In the present work, fish consumption was positively associated with the consumption of vegetables, fruit, berries, potatoes, vegetable oils, and wine both in a population with high fish consumption and in the general population. The positive association was observable even among the professional fishermen who were originally thought to eat fish merely due to easy availability based on their occupation. Further, red meat

and sausage consumption had a tendency to decrease along with increasing fish consumption. A decreasing trend in red meat was more evident among the fishermen and their wives when compared with the general population possibly because fish consumption in the Fishermen study was high enough to actually replace other sources of protein.

The observed dietary choices associated with fish consumption resemble a health-promoting Mediterranean-style diet (Sofi et al. 2010), which is characterised by high consumption of fruit, vegetables, legumes, and complex carbohydrates, and moderate consumption of fish, olive oil, and red wine. Another similar diet is the recently established Baltic Sea diet, which is based on a traditional Nordic diet (Adamsson et al. 2010) and is characterised by the consumption of vegetables, berries, rye, rapeseed oil, and fish. It seems that the healthy diet associated with fish consumption is relatively universal across western populations regardless of differences in social and cultural circumstances and dietary habits.

Since fish consumption appears to be a surrogate marker for healthy diet, one needs to consider confounding by other foods in the diet when evaluating the health effects of fish consumption. It appears likely that healthy foods associated with fish consumption may reinforce the health benefits of fish consumption. Furthermore, beneficial nutrients both in fish itself and in other healthy foods consumed along with fish might protect against hazardous effects of environmental contaminants. For example, vegetables, fruit, and berries contain antioxidants that can negate oxidative damage caused by environmental contaminants (Hennig et al. 2007). Furthermore, selenium in fish, nuts, and seeds, for example, is thought to be able prevent DNA damage caused PCBs (Ravoori et al. 2010) and oxidative stress caused by MeHg (Mozaffarian 2009). Due to potential joint effects, fish-derived omega-3 PUFAs and other nutrients should ideally be obtained from fish and the associated healthy diet to get the maximum health benefit.

8.4 Findings on cardiovascular risk factors

A disease risk factor is defined as a biological characteristic that precedes and predicts disease outcome and is situated directly on the causal pathway. A risk marker, on the other hand, is a biological indicator of a pathogenic process that may or may not be causal (Balagopal et al. 2011), but in practice, the difference is subtle. For example, insulin resistance and low-grade inflammation could be seen either as risk factors or risk markers for CVD whereas IMT, arterial stiffness, and the prevalence of atherosclerotic plaque can be considered as risk markers or subclinical CVD outcomes. For the sake of simplicity, the term risk factor has been used in the present work to refer to both risk factors and markers.

THL — Research 79/2012   132   Epidemiological studies on
fish consumption and
cardiovascular health

The cardiovascular effects of fish consumption and fish-derived omega-3 PUFAs have been extensively studied and well demonstrated. Except for a modest positive association between fish consumption and the risk of diabetes observed in some studies (Kaushik et al. 2009; van Woudenbergh et al. 2009; Djousse et al. 2011), no adverse cardiovascular effects of fish consumption have been observed. However, some controversy still remains especially regarding the mechanisms and interrelationships between individual CVD risk factors. More importantly, the benefits of fish consumption and omega-3 PUFA intake have rarely been studied in populations with high exposure to fish-derived environmental contaminants, and thus, the net effect of omega-3 PUFAs and environmental contaminants on cardiovascular risk and CVD risk factors is currently unclear. Based on previous literature, the evidence of cardiovascular hazards of fish-derived environmental contaminants is somewhat limited when compared with the large body of evidence on the benefits of fish consumption and omega-3 PUFAs.

In the present work, the previously established hypotriglyceridemic effect of omega-3 PUFAs (Hartweg et al. 2008; Jacobson 2008; Eslick et al. 2009) was seen both in the Fishermen study and in the sub-sample of the general population, which implies that the data operate as expected.

The anti-inflammatory effect of omega-3 PUFAs has been observed in an abundance of previous cross-sectional studies (Pischon et al. 2003; Lopez-Garcia et al. 2004; Ferrucci et al. 2006; Niu et al. 2006; Ohsawa et al. 2008; Farzaneh-Far et al. 2009; He et al. 2009; Micallef et al. 2009; Kalogeropoulos et al. 2010) but not in the majority of interventions (Madsen et al. 2003; Lindqvist et al. 2009; Pot et al. 2009; Skulas-Ray et al. 2011). In the present work, an inverse association between omega-3 PUFAs and inflammatory markers, especially TNF-α and IL-6, was observed in the sub-sample of the general population but not in the Fishermen study population. The reason for the absence of the anti-inflammatory effect in previous intervention studies and in the Fishermen study could be that omega-3 PUFA intake might have been too high to see any effect. Alternatively in the Fishermen study, it could be hypothesised that the concomitant exposure to environmental contaminants was high enough to negate the beneficial effect. This is plausible since it has been suspected that dioxins, PCBs, and MeHg have induced inflammation (Hennig et al. 2005; Hennig et al. 2007; Mozaffarian 2009; Houston 2011; Nyland et al. 2011). In intervention studies, omega-3 PUFA supplementation lacks the combined effect of fish consumption and associated healthy diet that may be necessary to achieve the benefits.

The evidence for a beneficial effect on insulin sensitivity of fish consumption and omega-3 PUFA intake appears controversial. Two meta-analyses on intervention studies have reported no effect of omega-3 PUFAs on glucose homeostasis (Balk et al. 2006) or insulin sensitivity (Akinkuolie et al. 2011). Results from individual studies imply that the inverse association between omega-3 PUFAs and insulin resistance could be observed among high-risk individuals such as those

THL — Research 79/2012　　　**133**　　　Epidemiological studies on
fish consumption and
cardiovascular health

who are overweight (Ramel et al. 2008) or who have metabolic syndrome (Nigam et al. 2009) or diabetes (Karlstrom et al. 2011), but not among healthy individuals (Giacco et al. 2007; Lara et al. 2007; Rizza et al. 2009; Muramatsu et al. 2010). In the present work, a beneficial trend in insulin resistance with increasing serum concentrations of omega-3 PUFAs was observed in the general population sub-sample. This could be explained by the fact that the Finnish general population can be regarded as a high-risk population where the prevalence of obesity, metabolic syndrome, and diabetes are relatively high. Further, a beneficial trend in arterial stiffness along with increasing serum concentrations of omega-3 PUFAs was observed in the general population sub-sample in the present work. This is in line with the growing body of evidence from previous studies (Hjerkinn et al. 2006; Wang et al. 2008a; Anderson et al. 2009; Chong et al. 2010; Sjoberg et al. 2010; Pase et al. 2011).

It appears that moderate fish consumption and omega-3 PUFA intake in the general population sub-sample was enough to bring out the beneficial trends in inflammatory markers, insulin resistance, and arterial stiffness along with increasing fish consumption or serum omega-3 PUFA concentration but the beneficial trends were not clearly seen in the Fishermen sub-study. On the contrary, adverse trends in insulin resistance and arterial stiffness were observed along with increasing concentrations of environmental contaminants among the professional fishermen. Due to the small size of the Fishermen study, the results may have been subject to chance and thus need to be interpreted with particular caution. However, if the differences are true, it appears that the exposure to fish-derived environmental contaminants might have been high enough to cancel out some of the beneficial effects of fish consumption. The observed harmful trends in insulin resistance and arterial stiffness are biologically plausible especially in regard to dioxins and PCBs (Hennig et al. 2007; Carpenter 2008; Alonso-Magdalena et al. 2011) but also in regard to MeHg (Mozaffarian 2009; Houston 2011). Although the overall epidemiological evidence is limited, the harmful effect of PCBs on insulin resistance is relatively well demonstrated (Lee et al. 2007; Uemura et al. 2009; Chang et al. 2010). Hence, the previously observed moderate increases in insulin resistance could be due to concomitant exposure to environmental contaminants among the Inuit (Ebbesson et al. 2007) and high omega-3 PUFA dosage (5.9 g EPA+DPA+DHA per day) among diabetics (Mostad et al. 2006). Thus, modest increases in the risk of type 2 diabetes observed in previous studies (Kaushik et al. 2009; van Woudenbergh et al. 2009; Djousse et al. 2011) might have been caused by either exposure to environmental contaminants or high omega-3 PUFA intake through fish consumption.

At the same time, the risk of carotid artery plaque was not increased among the professional fishermen regardless of high exposure to environmental contaminants. In previous studies, fish consumption and omega-3 PUFA intake have been associated with decreased IMT (Nakamura et al. 2007; Ebbesson et al. 2008;

Sekikawa et al. 2008; Sala-Vila et al. 2010) and decreased prevalence of atherosclerotic plaque (Erkkila et al. 2004; He et al. 2008; Sekikawa et al. 2008; Ueeda et al. 2008; Heine-Broring et al. 2010). It could be argued that even if high exposure to environmental contaminants did negate the beneficial effects of fish consumption on some of the cardiovascular risk factors, the overall effect on CHD pathogenesis in terms of atherosclerotic plaque formation might still be beneficial.

8.5 Findings on mortality

The hypothesised high fish consumption and high exposure to environmental contaminants among the professional fishermen was confirmed in a sub-sample of fishermen and their wives in the present work. Fish consumption and serum concentrations of dioxins and PCBs were almost twofold among the professional fishermen and approximately 1.5-fold among all men in the Fishermen study population when compared with men from the general population. Among the fishermen's wives, fish consumption and serum concentrations of dioxins and PCBs were respectively 50%, 30%, and 20% higher when compared with women from the general population. Regarding all women in the Fishermen study population, fish consumption was 30% higher whereas serum concentrations of dioxins and PCBs were only slightly higher than among the women from the general population in Finland. The reported differences are likely to be reliable since fish consumption data were collected with the same FFQ in both studies. In addition, contaminants were analysed from serum fat in the Fishermen study and from adipose tissue in the Sarcoma study, which are considered comparable despite having different substrates (Schecter et al. 1991).

According to the register-based mortality study, the fishermen and their wives had lower mortality from all causes, IHD, and respiratory diseases than the general population during the follow-up from 1980 to 2005. Age, calendar period, and sex were controlled for in the analyses but data on other confounding factors such as smoking were not available, which is the major cause of residual confounding in register-based studies. Thus, the explanation for the observed low mortality can only be speculated on. Data on fish consumption was not available either, and the assumption about high fish consumption and high serum concentrations of environmental contaminants among the fishermen and their wives was based on results from the small sub-study. However, it can at least be said that the exposure to environmental contaminants was not high enough to cause a marked excess in mortality, or that the beneficial effects were able to overrule the hazardous effects. Hence, it seems that the overall effect of fish consumption is beneficial even when fish is heavily contaminated.

Generally, the most obvious confounder in occupational mortality studies is the healthy worker effect that can be divided into a healthy population selection effect (indicating the selection in entering the work force) and a survivor population effect (indicating the ability to stay within the same occupation) (Vinni and Hakama 1980). In the present work, the healthy population selection effect was distinctive among the professional fishermen during the first three years of the follow-up although after that, the annual standardised mortality ratios (SMRs) stabilised to their long-term level. Thus, the first three years of the follow-up were excluded from the analyses. The survivor population effect was not taken into account in the analyses since the fishermen stayed in the cohort after their first entry into the professional fishermen register.

Spatial differences in mortality are potentially a problem. Especially mortality from IHD has been higher in eastern Finland when compared with western Finland. In the present work, the majority of professional fishermen lived on the south-western sea coast but reference mortality rates for that region and for a comparable time period were not available. Thus, the magnitude of the potential effect of geographical variation in the mortality was evaluated by using the Small Area Statistics on Health System. The SMRs for the population living within 20 km of the Finnish coastline in the year 1980 were calculated, excluding fishermen and their wives and adjusted for socio-economic status. During the follow-up from 1981 to 2005, mortality was 3% lower from all causes and 7% lower from IHD among those living at the coastal areas than among the general population of Finland. Cancer mortality did not differ between the coastal areas and the rest of Finland. Hence, the use of the reference mortality rates for the regions would not have notably changed the SMR estimates.

The hypothesised association between fish consumption and decreased mortality is supported by compelling evidence that has been collated in various meta-analyses (He et al. 2004; Whelton et al. 2004; Filion et al. 2010; Musa-Veloso et al. 2011; Zheng et al. 2011), a quantitative analysis (Konig et al. 2005), systematic reviews (Wang et al. 2006; Leon et al. 2008) and other reviews (Mozaffarian 2008; Di Minno et al. 2010). However, mortality has almost exclusively been studied in populations with average background exposure to fish-derived contaminants. The only mortality study similar to ours was conducted in Sweden among professional fishermen. Decreased mortality from IHD was observed among the Swedish west coast fishermen but not among those fishermen from the east coast of the Baltic Sea area (Mikoczy and Rylander 2009). The blood concentrations of dioxins and PCBs among the east coast fishermen are assessed to be higher than among the west coast fishermen but still, less than half of those among the Finnish Baltic Sea area fishermen. The differences in fish consumption are probably of similar magnitude (Kiviranta H., personal communication 23.8.2011). The absence of decreased IHD mortality among the Swedish Baltic Sea fishermen could be explained by lower fish consumption when compared with the Finnish Baltic Sea fishermen. The decreased

IHD mortality among the Swedish west coast fishermen, on the other hand, might be explained by differences in fish species and the contamination of the fish consumed in the North Sea area.

Previous evidence on the protective effect of high fish consumption or omega-3 PUFA intake is more conclusive for secondary prevention than for primary prevention. For example, hyperlipidemic and diabetic patients seem to benefit the most from omega-3 PUFA intake, and among CVD patients, the main benefit appears to be the reduction in the incidence of sudden cardiac death (Saravanan et al. 2010). Further, the evidence appears strong against fatal CHD events and limited for the much less studied non-fatal CHD events. Although the cardiovascular benefits of omega-3 PUFAs have been thought to be best observable in fatal events, a study on mortality alone is not enough to rule out the possibility of negative health effects from environmental contaminants. To strengthen the evidence, it would be crucial to evaluate whether high exposure to environmental contaminants is reflected in disease incidence among the fishermen and their wives.

8.6 Future perspectives

Risk communication is one of the challenges in the research on the health benefits and risks of fish consumption. Conflicting results and inconsistent messages have created confusion in the general public and the media about the overall health effects of fish consumption. The fear of environmental contaminants has lead to decreases in fish consumption, which likely has a detrimental net effect especially on the cardiovascular health of the general public and threatens the professions of fishermen and fish farmers. In Finland, the consumption of imported fish has increased at the expense of domestic fish, which may also reflect a tendency to avoid environmental contaminants thought to be related primarily to domestic fish. The consumption of domestic fish is currently approximately 30% of total fish consumption. At the same time, dioxins and PCBs are a problem mainly in Baltic herring and wild-caught Baltic salmon that comprise only 9% of domestic fish consumption and only approximately 3% of total fish consumption. The challenge is to reliably inform consumers both about the potential risks, consumption restrictions, vulnerable groups, high-risk areas in the Baltic Sea and inland waters, and the apparently overwhelming health benefits associated with fish consumption. On the other hand, it should be acknowledged that environmental contaminants continue to be a problem since the concentrations of dioxins and PCBs in the Baltic Sea are decreasing only very slowly and mercury emissions have increased in some parts of the world. Currently, the majority of fish consumed in Finland are imported, and thus, the contamination of imported fish should be given even more consideration than previously.

THL — Research 79/2012   137   Epidemiological studies on
fish consumption and
cardiovascular health

Due to the complex nature of the problem, a holistic view is needed when studying the net effect of fish consumption and the concomitant exposure to environmental contaminants. In future studies, both fish consumption or omega-3 PUFA intake and the concentrations of environmental contaminants should be considered simultaneously to produce less confounded estimates (Stern and Korn 2011). Alternatively, whole foods or whole diet could be studied instead of single nutrients to bring out the net effect. On the other hand, there is substantial within-population variation in the response to omega-3 PUFA intake. In future, research may also shift from a holistic view to more complex scenarios where the impacts of multiple gene variants, epigenetic profiles, and other potential mediators are considered in combination (Madden et al. 2011).

9 Conclusions

I   Blood concentrations of omega-3 PUFAs, dioxins, PCBs, and MeHg functioned fairly well as biomarkers of fish consumption. Environmental contaminants appeared to reflect fish consumption better than omega-3 PUFAs probably due to very slow elimination in the human body. Separate frequency questions measured fish consumption equally well as the calibrated food frequency questionnaire and may be used in future epidemiological studies.

II   Fish consumption was positively associated with the consumption of vegetables, fruit, berries, potatoes, vegetable oils, and wine. This was observed even among the professional fishermen who were originally thought to eat fish merely due to easy availability based on their occupation. It is likely that the health benefits of fish consumption may be partially explained by the consumption of other healthy foods and therefore, at least those foods should be controlled for in studies on the health effects of fish consumption.

III   The hypothesised effects of omega-3 PUFAs on cardiovascular risk factors, namely inflammatory markers, insulin resistance, and arterial stiffness were seen in the general population sub-sample, although the effects were not clear in the Fishermen study. On the contrary, high exposure to environmental contaminants seemed to increase insulin resistance and arterial stiffness among the fishermen but the effect on atherosclerosis progression indicated by carotid artery plaque formation appeared not to be harmful.

IV   Presumed high exposure to environmental contaminants was not seen as excess mortality from natural causes such as IHD, which likely implies that the same holds true also in populations with lower exposures, e.g., the general population of Finland.

In summary, fish consumption appeared to be a surrogate marker for healthy diet and thus, the direct beneficial effects of fish consumption may be reinforced by associated healthy dietary habits. This work adds to the current understanding that the beneficial effects of fish consumption and omega-3 PUFA intake outweigh the potential hazardous effects of fish-derived contaminants at least when mortality is considered. Exposure to environmental contaminants may not have been high enough to cause excess mortality even in this high exposure population or the overall effect of fish consumption was beneficial regardless of environmental contaminants. However, high exposure to environmental contaminants may cancel out some of the hypothesised beneficial effects of omega-3 PUFAs on

Epidemiological studies on
fish consumption and
cardiovascular health

cardiovascular risk factors, and the possibility of harmful effects regarding CVD or other diseases cannot be excluded based on the present work.

References

Adamsson V, Reumark A, Fredriksson IB, Hammarstrom E, Vessby B, Johansson G, et al. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). J Intern Med. 2010; 269(2):150-159.

Airaksinen R, Rantakokko P, Eriksson JG, Blomstedt P, Kajantie E, Kiviranta H. Association between type 2 diabetes and exposure to persistent organic pollutants. Diabetes Care. 2011; 34(9):1972-1979.

Akinkuolie AO, Ngwa JS, Meigs JB, Djousse L. Omega-3 polyunsaturated fatty acid and insulin sensitivity: a meta-analysis of randomized controlled trials. Clin Nutr. 2011; 30(6):702-707.

Alonso-Magdalena P, Quesada I, Nadal A. Endocrine disruptors in the etiology of type 2 diabetes mellitus. Nat Rev Endocrinol. 2011; 7(6):346-353.

Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol. 1999; 150(1):75-87.

Anderson SG, Sanders TA, Cruickshank JK. Plasma fatty acid composition as a predictor of arterial stiffness and mortality. Hypertension. 2009; 53(5):839-845.

Baik I, Abbott RD, Curb JD, Shin C. Intake of fish and n-3 fatty acids and future risk of metabolic syndrome. J Am Diet Assoc. 2010; 110(7):1018-1026.

Bakewell L, Burdge GC, Calder PC. Polyunsaturated fatty acid concentrations in young men and women consuming their habitual diets. Br J Nutr. 2006; 96(1):93-99.

Balagopal PB, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation. 2011; 123(23):2749-2769.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006; 189(1):19-30.

Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet. 1971; 1(7710):1143-1145.

Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. Am J Clin Nutr. 1980; 33(12):2657-2661.

Belin RJ, Greenland P, Martin L, Oberman A, Tinker L, Robinson J, et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail. 2011; 4(4):404-413.

Bjerregaard P, Dyerberg J. Fish oil and ischaemic heart disease in Greenland. Lancet. 1988; 2(8609):514.

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. 1989; 2(8666):757-761.

Calder PC. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci (Lond). 2004; 107(1):1-11.

Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006; 83(Suppl 6):1505S-1519S.

Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. Eur J Pharmacol. 2011; 668 (Suppl 1):S50-58.

Carpenter DO. Environmental contaminants as risk factors for developing diabetes. Rev Environ Health. 2008; 23(1):59-74.

Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr. 2006; 83(Suppl 6):1499S-1504S.

Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is

Epidemiological studies on fish consumption and cardiovascular health

associated with decreased plaque inflammation and increased stability. Atherosclerosis. 2010; 212(1):252-259.

Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Dioxin exposure and insulin resistance in Taiwanese living near a highly contaminated area. Epidemiology. 2010; 21(1):56-61.

Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance. J Hazard Mater. 2011; 185(2-3):749-755.

Chateau-Degat ML, Dewailly E, Louchini R, Counil E, Noel M, Ferland A, et al. Cardiovascular burden and related risk factors among Nunavik (Quebec) Inuit: insights from baseline findings in the circumpolar Inuit health in transition cohort study. Can J Cardiol. 2010; 26(6):190-196.

Choi AL, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. Crit Rev Toxicol. 2008; 38(10):877-893.

Choi AL, Weihe P, Budtz-Jorgensen E, Jorgensen PJ, Salonen JT, Tuomainen TP, et al. Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. Environ Health Perspect. 2009; 117(3):367-372.

Chong MF, Lockyer S, Saunders CJ, Lovegrove JA. Long chain n-3 PUFA-rich meal reduced postprandial measures of arterial stiffness. Clin Nutr. 2010; 29(5):678-681.

Chung H, Nettleton JA, Lemaitre RN, Barr RG, Tsai MY, Tracy RP, et al. Frequency and type of seafood consumed influence plasma (n-3) fatty acid concentrations. J Nutr. 2008; 138(12):2422-2427.

Cohen JT, Bellinger DC, Connor WE, Kris-Etherton PM, Lawrence RS, Savitz DA, et al. A quantitative risk-benefit analysis of changes in population fish consumption. Am J Prev Med. 2005; 29(4):325-334.

Commission of the European Communities. Commission Regulation (EC) setting maximum levels for certain contaminants in foodstuffs. 1881/2006. Available at: http://eur-lex.europa.eu/en/index.htm

Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol. 2008; 167(7):847-858.

Cundiff DK, Lanou AJ, Nigg CR. Relation of omega-3 Fatty Acid intake to other dietary factors known to reduce coronary heart disease risk. Am J Cardiol. 2007; 99(9):1230-1233.

De Caterina R. n-3 fatty acids in cardiovascular disease. N Engl J Med. 2011; 364(25):2439-2450.

de Goede J, Geleijnse JM, Boer JM, Kromhout D, Verschuren WM. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and nonfatal coronary heart disease in a large population of Dutch adults with low fish intake. J Nutr. 2010; 140(5):1023-1028.

de Roos B, Mavrommatis Y, Brouwer IA. Long-chain n-3 polyunsaturated fatty acids: new insights into mechanisms relating to inflammation and coronary heart disease. Br J Pharmacol. 2009; 158(2):413-428.

Deutch B, Dyerberg J, Pedersen HS, Aschlund E, Hansen JC. Traditional and modern Greenlandic food - dietary composition, nutrients and contaminants. Sci Total Environ. 2007; 384(1-3):106-119.

Di Minno MN, Tremoli E, Tufano A, Russolillo A, Lupoli R, Di Minno G. Exploring newer cardioprotective strategies: omega-3 fatty acids in perspective. Thromb Haemost. 2010; 104(4):664-680.

Dijkstra SC, Brouwer IA, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Intake of very long chain n-3 fatty acids from fish and the incidence of heart failure: the Rotterdam Study. Eur J Heart Fail. 2009; 11(10):922-928.

Djousse L, Gaziano JM, Buring JE, Lee IM. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. Am J Clin Nutr. 2011; 93(1):143-150.

Donaldson SG, Van Oostdam J, Tikhonov C, Feeley M, Armstrong B, Ayotte P, et al. Environmental contaminants and human health in the Canadian Arctic. Sci Total Environ. 2010; 408(22):5165-5234.

Epidemiological studies on fish consumption and cardiovascular health

Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J Clin Nutr. 1975; 28(9):958-966.

Ebbesson SO, Roman MJ, Devereux RB, Kaufman D, Fabsitz RR, Maccluer JW, et al. Consumption of omega-3 fatty acids is not associated with a reduction in carotid atherosclerosis: the Genetics of Coronary Artery Disease in Alaska Natives study. Atherosclerosis. 2008; 199(2):346-353.

Ebbesson SO, Tejero ME, Nobmann ED, Lopez-Alvarenga JC, Ebbesson L, Romenesko T, et al. Fatty acid consumption and metabolic syndrome components: the GOCADAN study. J Cardiometab Syndr. 2007; 2(4):244-249.

Egert S, Stehle P. Impact of n-3 fatty acids on endothelial function: results from human interventions studies. Curr Opin Clin Nutr Metab Care. 2011; 14(2):121-131.

Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011; 96(7):1931-1942.

Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. Am J Clin Nutr. 2004; 80(3):626-632.

Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol. 2009; 136(1):4-16.

European Commission. Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCBs in food. 2001; CS/CNTM/DIOXIN/20 final. Available at: http://ec.europa.eu/food/fs/sc/scf/out90_en.pdf

European Food Safety Authority. Opinion of the scientific panel on contaminants in the food chain on a request from the Commission related to mercury and methylmercury in food. EFSA Journal. 2004; (34):1-14.

European Food Safety Authority. Opinion of the scientific panel on contaminants in the food chain on a request from the European parliament related to the safety assessment of wild and farmed fish. EFSA Journal 2005; (236):1-118.

Everett CJ, Frithsen IL, Diaz VA, Koopman RJ, Simpson WM, Jr., Mainous AG, 3rd. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. Environ Res. 2007; 103(3):413-418.

FAO/WHO. Report of the joint FAO/WHO expert consultation on the risks and benefits of fish consumption. Report No.: FIPM/R978. Available at: http://www.fao.org/docrep/014/ba0136e/ba0136e00.pdf

Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. Atherosclerosis. 2009; 205(2):538-543.

Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006; 91(2):439-446.

Feskens EJ, Kromhout D. Epidemiologic studies on Eskimos and fish intake. Ann N Y Acad Sci. 1993; 683(Jun 14):9-15.

Filion KB, El Khoury F, Bielinski M, Schiller I, Dendukuri N, Brophy JM. Omega-3 fatty acids in high-risk cardiovascular patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2010; 10(24):1-11.

Fillion M, Mergler D, Sousa Passos CJ, Larribe F, Lemire M, Guimaraes JR. A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. Environ Health. 2006; 5(29):1-9.

Finnish Food Safety Authority Evira. Dietary advice on fish consumption. [cited 31.8.2011]. Available at: http://www.evira.fi/portal/en/food/informati on_on_food/food_hazards/restriction_on_th

e_use_of_foodstuffs/dietary_advice_on_fish_consumption

Finnish Game and Fisheries Research Institute. Commercial Inland Fishery 2008. Report No.: 1/2010. Available at: http://www.rktl.fi/www/uploads/pdf/uudet%20julkaisut/tilastoja_1_2010.pdf

Finnish Game and Fisheries Research Institute. Commercial Marine Fishery 2010. Report No.: 3/2011. Available at: http://www.rktl.fi/www/uploads/pdf/uudet%20julkaisut/rktl_tilastoja_3_11_web.pdf

Finnish Game and Fisheries Research Institute. Fish consumption statistics. [cited 11.8.2011]. Available at: http://www.rktl.fi/english/statistics/economy_and_the/fish_consumption/

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002; 20(8):1493-1499.

Giacco R, Cuomo V, Vessby B, Uusitupa M, Hermansen K, Meyer BJ, et al. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? Nutr Metab Cardiovasc Dis. 2007; 17(8):572-580.

GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999; 354(9177):447-455.

Goncharov A, Haase RF, Santiago-Rivera A, Morse G, McCaffrey RJ, Rej R, et al. High serum PCBs are associated with elevation of serum lipids and cardiovascular disease in a Native American population. Environ Res. 2008; 106(2):226-239.

Goncharov A, Pavuk M, Foushee HR, Carpenter DO. Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. Environ Health Perspect. 2011; 119(3):319-325.

Grandjean P, Henriksen JE, Choi AL, Petersen MS, Dalgard C, Nielsen F, et al. Marine food pollutants as a risk factor for

hypoinsulinemia and type 2 diabetes. Epidemiology. 2011; 22(3):410-417.

Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, et al. Mercury, fish oils, and the risk of myocardial infarction. N Engl J Med. 2002; 347(22):1747-1754.

Ha MH, Lee DH, Jacobs DR. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002. Environ Health Perspect. 2007; 115(8):1204-1209.

Ha MH, Lee DH, Son HK, Park SK, Jacobs DR, Jr. Association between serum concentrations of persistent organic pollutants and prevalence of newly diagnosed hypertension: results from the National Health and Nutrition Examination Survey 1999-2002. J Hum Hypertens. 2009; 23(4):274-286.

Hallikainen A, Airaksinen R, Rantakokko P, Koponen J, Mannio J, Vuorinen P, et al. Environmental pollutants in Baltic fish and other domestic fish: PCDD/F, PCB, PBDE, PFC and OT compounds. Finnish Food Safety Authority Evira. Report No.: 2/2011. Available at: http://www.evira.fi/portal/fi/evira/julkaisut/?a=view&productId=247

Hallikainen A, Rautala T, Karlström U, Kostamo P, Koivisto P, Pohjanvirta R, et al. The chemical contaminants of foodstuffs and household water (in Finnish). Report No.: 15/2010. Available at: http://www.evira.fi/files/products/1289807140773_kemialliset_vaarat_uudistettu_painos290910_web.pdf

Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008; (1):1-64.

He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease--eat fish or take fish oil supplement? Prog Cardiovasc Dis. 2009; 52(2):95-114.

He K, Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, et al. Associations of dietary long-chain n-3 polyunsaturated fatty

acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2009; 103(9):1238-1243.

He K, Liu K, Daviglus ML, Mayer-Davis E, Jenny NS, Jiang R, et al. Intakes of long-chain n-3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis. Am J Clin Nutr. 2008; 88(4):1111-1118.

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004; 109(22):2705-2711.

Heine-Broring RC, Brouwer IA, Proenca RV, van Rooij FJ, Hofman A, Oudkerk M, et al. Intake of fish and marine n-3 fatty acids in relation to coronary calcification: the Rotterdam Study. Am J Clin Nutr. 2010; 91(5):1317-1323.

Heistaro S. Methodology report. Health 2000 Survey. National Public Health Institute. Report No.: B26/2008. Available at: http://www.terveys2000.fi/doc/methodolog yrep.pdf

Hennig B, Oesterling E, Toborek M. Environmental toxicity, nutrition, and gene interactions in the development of atherosclerosis. Nutr Metab Cardiovasc Dis. 2007; 17(2):162-169.

Hennig B, Reiterer G, Majkova Z, Oesterling E, Meerarani P, Toborek M. Modification of environmental toxicity by nutrients: implications in atherosclerosis. Cardiovasc Toxicol. 2005; 5(2):153-160.

Hites RA, Foran JA, Carpenter DO, Hamilton MC, Knuth BA, Schwager SJ. Global assessment of organic contaminants in farmed salmon. Science. 2004; 303(5655):226-229.

Hjerkinn EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen I, Seljeflot I, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. Eur J Cardiovasc Prev Rehabil. 2006; 13(3):325-333.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006; 332(7544):752-760.

Hostenkamp G, Sorensen J. Are fish eaters healthier and do they consume less health-care resources? Public Health Nutr. 2009; 13(4):453-460.

Houston MC. Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. J Clin Hypertens (Greenwich). 2011; 13(8):621-627.

Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA. 2002; 287(14):1815-1821.

Hunter DJ. Biochemical indicators of dietary intake. In: Willett W, editor. Nutritional Epidemiology. 2 ed. New York: Oxford University Press; 1998.

Isosaari P, Hallikainen A, Kiviranta H, Vuorinen PJ, Parmanne R, Koistinen J, et al. Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls, naphthalenes and polybrominated diphenyl ethers in the edible fish caught from the Baltic Sea and lakes in Finland. Environ Pollut. 2006; 141(2):213-225.

Jacobson TA. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. Am J Clin Nutr. 2008; 87(6):1981S-1990S.

Jensen GE, Clausen J. Organochlorine compounds in adipose tissue of Greenlanders and southern Danes. J Toxicol Environ Health. 1979; 5(4):617-629.

Jones OA, Maguire ML, Griffin JL. Environmental pollution and diabetes: a neglected association. Lancet. 2008; 371(9609):287-288.

Jones PJH, Kubow S. Lipids, sterols, and their metabolites. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern nutrition in health and disease. 10 ed. Baltimore/Philadelphia: Lippincott Williams & Wilkins; 2006.

Jorgensen ME, Bjerregaard P, Kjaergaard JJ, Borch-Johnsen K. High prevalence of

145

Epidemiological studies on fish consumption and cardiovascular health

markers of coronary heart disease among Greenland Inuit. Atherosclerosis. 2008; 196(2):772-778.

Kalogeropoulos N, Panagiotakos DB, Pitsavos C, Chrysohoou C, Rousinou G, Toutouza M, et al. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. Clin Chim Acta. 2010; 411(7-8):584-591.

Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010; 375(9709):132-140.

Karlstrom BE, Jarvi AE, Byberg L, Berglund LG, Vessby BO. Fatty fish in the diet of patients with type 2 diabetes: comparison of the metabolic effects of foods rich in n-3 and n-6 fatty acids. Am J Clin Nutr. 2011; 94(1):26-33.

Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willett WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. Am J Clin Nutr. 2009; 90(3):613-620.

Kiviranta H, Ovaskainen ML, Vartiainen T. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environ Int. 2004; 30(7):923-932.

Kiviranta H, Tuomisto JT, Tuomisto J, Tukiainen E, Vartiainen T. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in the general population in Finland. Chemosphere. 2005; 60(7):854-869.

Kiviranta H, Vartiainen T, Tuomisto J. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 2002; 110(4):355-361.

Kiviranta H, Vartiainen T, Verta M, Tuomisto JT, Tuomisto J. High fish-specific dioxin concentrations in Finland. Lancet. 2000; 355(9218):1883-1885.

Konig A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, et al. A quantitative analysis of fish consumption and coronary heart disease mortality. Am J Prev Med. 2005; 29(4):335-346.

Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950-1974. Acta Med Scand. 1980; 208(5):401-406.

Kromhout D. Epidemiology of cardiovascular diseases in Europe. Public Health Nutr. 2001; 4(2B):441-457.

Kromhout D, Bosschieter EB, de Lezenne CC. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med. 1985; 312(19):1205-1209.

Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010; 363(21):2015-2026.

Kumar S, Sutherland F, Rosso R, Teh AW, Lee G, Heck PM, et al. Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial electrophysiology. Heart Rhythm. 2011; 8(4):562-568.

Lara JJ, Economou M, Wallace AM, Rumley A, Lowe G, Slater C, et al. Benefits of salmon eating on traditional and novel vascular risk factors in young, non-obese healthy subjects. Atherosclerosis. 2007; 193(1):213-221.

Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR, Jr. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007; 30(3):622-628.

Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs DR, Jr. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ Health Perspect. 2010; 118(9):1235-1242.

Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr. 2003; 77(2):319-325.

Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish

oil on arrhythmias and mortality: systematic review. BMJ. 2008; 337(a2931):1-8.

Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006; 114(1):82-96.

Lind PM, van Bavel B, Salihovic S, Lind L. Circulating levels of persistent organic pollutants (POPs) and carotid atherosclerosis in the elderly. Environ Health Perspect. 2012; 120(1):38-43.

Lindqvist HM, Langkilde AM, Undeland I, Sandberg AS. Herring (Clupea harengus) intake influences lipoproteins but not inflammatory and oxidation markers in overweight men. Br J Nutr. 2009; 101(3):383-390.

Liu JC, Conklin SM, Manuck SB, Yao JK, Muldoon MF. Long-chain omega-3 fatty acids and blood pressure. Am J Hypertens. 2011a; 24(10):1121-1126.

Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials. Heart. 2011b; 97(13):1034-1040.

Lopez-Garcia E, Schulze MB, Manson JE, Meigs JB, Albert CM, Rifai N, et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. J Nutr. 2004; 134(7):1806-1811.

Madden J, Williams CM, Calder PC, Lietz G, Miles EA, Cordell H, et al. The impact of common gene variants on the response of biomarkers of cardiovascular disease (CVD) risk to increased fish oil fatty acids intakes. Annu Rev Nutr. 2011; 31(Aug 21):203-234.

Madsen T, Christensen JH, Blom M, Schmidt EB. The effect of dietary n-3 fatty acids on serum concentrations of C-reactive protein: a dose-response study. Br J Nutr. 2003; 89(4):517-522.

Matilda Agricultural Statistics. Balance sheet for food commodities. Ministry of Agriculture and Forestry [cited 11.8.2011]. Available at:

http://www.maataloustilastot.fi/en/tilasto/143

Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis. 2009; 204(2):476-482.

Micallef MA, Munro IA, Garg ML. An inverse relationship between plasma n-3 fatty acids and C-reactive protein in healthy individuals. Eur J Clin Nutr. 2009; 63(9):1154-1156.

Mikoczy Z, Rylander L. Mortality and cancer incidence in cohorts of Swedish fishermen and fishermen's wives: updated findings. Chemosphere. 2009; 74(7):938-943.

Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011; 123(20):2292-2333.

Ministry of Agriculture and Forestry. Laki kalastuslain 6 a §:n muuttamisesta (in Finnish). 756/2001. Available at: http://www.finlex.fi/fi/laki/alkup/2001/20010756

Ministry of Agriculture and Forestry. Maa- ja metsätalousministeriön asetus kalataloutta koskevista rekistereistä annetun maa- ja metsätalousministeriön päätöksen 12 §:n muuttamisesta (in Finnish). 1309/2001. Available at: http://www.finlex.fi/fi/laki/alkup/2001/20011309

Mostad IL, Bjerve KS, Bjorgaas MR, Lydersen S, Grill V. Effects of n-3 fatty acids in subjects with type 2 diabetes: reduction of insulin sensitivity and time-dependent alteration from carbohydrate to fat oxidation. Am J Clin Nutr. 2006; 84(3):540-550.

Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. Am J Clin Nutr. 2008; 87(6):1991S-1996S.

Mozaffarian D. Fish, mercury, selenium and cardiovascular risk: current evidence and unanswered questions. Int J Environ Res Public Health. 2009; 6(6):1894-1916.

Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005a; 111(2):157-164.

Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. Circulation. 2005b; 112(13):1945-1952.

Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, Sacks FM, et al. Circulating long-chain omega-3 fatty acids and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. Ann Intern Med. 2011a; 155(3):160-170.

Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. Circulation. 2003; 107(10):1372-1377.

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006; 296(15):1885-1899.

Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick DS, et al. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N Engl J Med. 2011b; 364(12):1116-1125.

Mozaffarian D, Wu JH. Omega-3 Fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011; 58(20):2047-2067.

Munthe J, Wänberg I, Rognerud S, Fjeld E, Verta M, Porvari P, et al. Mercury in Nordic ecosystems. Report No.: B1761. Available at: http://www.ivl.se/download/18.7df4c4e812d2da6a416800071956/B1761.pdf

Muramatsu T, Yatsuya H, Toyoshima H, Sasaki S, Li Y, Otsuka R, et al. Higher dietary intake of alpha-linolenic acid is associated with lower insulin resistance in middle-aged Japanese. Prev Med. 2010; 50(5-6):272-276.

Musa-Veloso K, Binns MA, Kocenas A, Chung C, Rice H, Oppedal-Olsen H, et al. Impact of low v. moderate intakes of long-chain n-3 fatty acids on risk of coronary heart disease. Br J Nutr. 2011; 106(8):1129-1141.

Myint PK, Welch AA, Bingham SA, Luben RN, Wareham NJ, Day NE, et al. Habitual fish consumption and risk of incident stroke: the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study. Public Health Nutr. 2006; 9(7):882-888.

Männistö S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. J Clin Epidemiol. 1996; 49(4):401-409.

Nadir MA, Szwejkowski BR, Witham MD. Vitamin D and cardiovascular prevention. Cardiovasc Ther. 2010; 28(4):e5-12.

Nakamura Y, Ueno Y, Tamaki S, Kadowaki T, Okamura T, Kita Y, et al. Fish consumption and early atherosclerosis in middle-aged men. Metabolism. 2007; 56(8):1060-1064.

National Institute for Health and Welfare. Fineli Finnish Food Composition Database. [cited 14.11.2011]. Available at: http://www.fineli.fi/

National Nutrition Council. Finnish Nutrition Recommendations 2005. National Nutrition Council [cited 8.11.2011]. Available at: http://www.ravitsemusneuvottelukunta.fi/portal/en/nutrition_recommendations/

Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005; 105(3):428-440.

Nigam A, Frasure-Smith N, Lesperance F, Julien P. Relationship between n-3 and n-6 plasma fatty acid levels and insulin resistance in coronary patients with and without metabolic syndrome. Nutr Metab Cardiovasc Dis. 2009; 19(4):264-270.

Niu K, Hozawa A, Kuriyama S, Ohmori-Matsuda K, Shimazu T, Nakaya N, et al. Dietary long-chain n-3 fatty acids of marine origin and serum C-reactive protein concentrations are associated in a population with a diet rich in marine products. Am J Clin Nutr. 2006; 84(1):223-229.

148

Nyland JF, Fillion M, Barbosa F, Jr., Shirley DL, Chine C, Lemire M, et al. Biomarkers of methyl mercury exposure immunotoxicity among fish consumers in Amazonian Brazil. Environ Health Perspect. 2011; 119 (12):1733-1738.

Ohsawa M, Itai K, Onoda T, Tanno K, Sasaki S, Nakamura M, et al. Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. Atherosclerosis. 2008; 201(1):184-191.

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, et al. Validity of a food frequency questionnaire varied by age and body mass index. J Clin Epidemiol. 2006; 59(9):994-1001.

Park K, Mozaffarian D. Omega-3 fatty acids, mercury, and selenium in fish and the risk of cardiovascular diseases. Curr Atheroscler Rep. 2010; 12(6):414-422.

Pase M, Grima N, Sarris L. Do long-chain n-3 fatty acids reduce arterial stiffness? A meta-analysis of randomised controlled trials. Br J Nutr. 2011; 106(7):974-980.

Patel PS, Sharp SJ, Luben RN, Khaw KT, Bingham SA, Wareham NJ, et al. Association between type of dietary fish and seafood intake and the risk of incident type 2 diabetes: the European prospective investigation of cancer (EPIC)-Norfolk cohort study. Diabetes Care. 2009; 32(10):1857-1863.

Paturi M, Tapanainen H, Reinivuo H, Pietinen P. The National FINDIET 2007 Survey. National Public Health Institute. Report No.: B23/2008. Available at: http://www.ktl.fi/attachments/suomi/julkais ut/julkaisusarja_b/2008/2008b23.pdf

Philibert A, Vanier C, Abdelouahab N, Chan HM, Mergler D. Fish intake and serum fatty acid profiles from freshwater fish. Am J Clin Nutr. 2006; 84(6):1299-1307.

Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation. 2003; 108(2):155-160.

Pot GK, Brouwer IA, Enneman A, Rijkers GT, Kampman E, Geelen A. No effect of fish oil supplementation on serum inflammatory markers and their interrelationships: a randomized controlled trial in healthy, middle-aged individuals. Eur J Clin Nutr. 2009; 63(11):1353-1359.

Ramel A, Martinez A, Kiely M, Morais G, Bandarra NM, Thorsdottir I. Beneficial effects of long-chain n-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. Diabetologia. 2008; 51(7):1261-1268.

Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, et al. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 2006; 83(2):221-226.

Ravoori S, Srinivasan C, Pereg D, Robertson LW, Ayotte P, Gupta RC. Protective effects of selenium against DNA adduct formation in Inuit environmentally exposed to PCBs. Environ Int. 2010; 36(8):980-986.

Reinivuo H, Hirvonen T, Ovaskainen ML, Korhonen T, Valsta LM. Dietary survey methodology of FINDIET 2007 with a risk assessment perspective. Public Health Nutr. 2010; 13(6A):915-919.

Richardson ES, Iaizzo PA, Xiao YF. Electrophysiological mechanisms of the anti-arrhythmic effects of omega-3 fatty acids. J Cardiovasc Transl Res. 2011; 4(1):42-52.

Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the roles of n-3 fatty acids in health and disease. J Am Diet Assoc. 2009; 109(4):668-679.

Rignell-Hydbom A, Rylander L, Hagmar L. Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus. Hum Exp Toxicol. 2007; 26(5):447-452.

Rizza S, Tesauro M, Cardillo C, Galli A, Iantorno M, Gigli F, et al. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. Atherosclerosis. 2009; 206(2):569-574.

Sala-Vila A, Cofan M, Perez-Heras A, Nunez I, Gilabert R, Junyent M, et al. Fatty acids in serum phospholipids and carotid intima-media thickness in Spanish subjects with

Epidemiological studies on fish consumption and cardiovascular health

primary dyslipidemia. Am J Clin Nutr. 2010; 92(1):186-193.

Salonen JT, Seppanen K, Lakka TA, Salonen R, Kaplan GA. Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. Atherosclerosis. 2000; 148(2):265-273.

Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. Am J Clin Nutr. 2011; 94(4):973-980.

Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. Lancet. 2010; 376(9740):540-550.

Schecter A, Papke O, Ball M, Ryan JJ. Partitioning of Dioxins and Dibenzofurans - Whole-Blood, Blood-Plasma and Adipose-Tissue. Chemosphere. 1991; 23(11-12):1913-1919.

Sekikawa A, Curb JD, Ueshima H, El-Saed A, Kadowaki T, Abbott RD, et al. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. J Am Coll Cardiol. 2008; 52(6):417-424.

Serebruany VL, Miller M, Pokov AN, Lynch D, Jensen JK, Hallen J, et al. Early impact of prescription Omega-3 fatty acids on platelet biomarkers in patients with coronary artery disease and hypertriglyceridemia. Cardiology. 2011; 118(3):187-194.

Sergeev AV, Carpenter DO. Hospitalization rates for coronary heart disease in relation to residence near areas contaminated with persistent organic pollutants and other pollutants. Environ Health Perspect. 2005; 113(6):756-761.

Sergeev AV, Carpenter DO. Increase in metabolic syndrome-related hospitalizations in relation to environmental sources of persistent organic pollutants. Int J Environ Res Public Health. 2011; 8(3):762-776.

Sjoberg NJ, Milte CM, Buckley JD, Howe PR, Coates AM, Saint DA. Dose-dependent increases in heart rate variability and arterial compliance in overweight and obese adults with DHA-rich fish oil supplementation. Br J Nutr. 2010; 103(2):243-248.

Skerfving S, Bencko V, Vahter M, Schutz A, Gerhardsson L. Environmental health in the Baltic region--toxic metals. Scand J Work Environ Health. 1999; 25(Suppl 3):40-64.

Skulas-Ray AC, Kris-Etherton PM, Harris WS, Vanden Heuvel JP, Wagner PR, West SG. Dose-response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy persons with moderate hypertriglyceridemia. Am J Clin Nutr. 2011; 93(2):243-252.

Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010; 92(5):1189-1196.

Southgate DAT. Meat, fish, eggs and novel proteins. In: Garrow JS, James WPT, Ralph A, editors. Human Nutrition and Dietetics. 10 ed. The Netherlands: Elsevier Churchill Livingstone; 2000.

Stern AH. A review of the studies of the cardiovascular health effects of methylmercury with consideration of their suitability for risk assessment. Environ Res. 2005; 98(1):133-142.

Stern AH, Korn LR. An approach for quantitatively balancing methylmercury risk and omega-3 benefit in fish consumption advisories. Environ Health Perspect. 2011; 119(8).

Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. Am J Clin Nutr. 2007; 86(1):74-81.

Sun Q, Ma J, Campos H, Rexrode KM, Albert CM, Mozaffarian D, et al. Blood concentrations of individual long-chain n-3 fatty acids and risk of nonfatal myocardial infarction. Am J Clin Nutr. 2008; 88(1):216-223.

Theobald HE, Goodall AH, Sattar N, Talbot DC, Chowienczyk PJ, Sanders TA. Low-dose docosahexaenoic acid lowers diastolic blood pressure in middle-aged men and women. J Nutr. 2007; 137(4):973-978.

Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet. 2003; 361(9356):477-485.

Tuomisto J, Vartiainen T, Tuomisto J. Synopsis on dioxins and PCBs. National Institute for Health and Welfare. Report No.: 11/2011. Available at: http://www.thl.fi/thl-client/pdfs/81322e2c-e9b6-4003-bb13-995dcd1b68cb

Tuomisto JT, Tuomisto J, Tainio M, Niittynen M, Verkasalo P, Vartiainen T, et al. Risk-benefit analysis of eating farmed salmon. Science. 2004; 305(5683):476-477.

Tziomalos K, Athyros VG, Mikhailidis DP. Fish oils and vascular disease prevention: an update. Curr Med Chem. 2007; 14(24):2622-2628.

Ueeda M, Doumei T, Takaya Y, Shinohata R, Katayama Y, Ohnishi N, et al. Serum N-3 polyunsaturated fatty acid levels correlate with the extent of coronary plaques and calcifications in patients with acute myocardial infarction. Circ J. 2008; 72(11):1836-1843.

Uemura H, Arisawa K, Hiyoshi M, Kitayama A, Takami H, Sawachika F, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. Environ Health Perspect. 2009; 117(4):568-573.

Undeland I, Lindqvist H, Chen-Yun Y, Falch E, Ramel A, Cooper M, et al. Seafood and health: what is the full story? In: Luten JB, editor. Marine functional food. The Netherlands: Wageningen Academic Publishers; 2009.

Valera B, Dewailly E, Poirier P. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. Hypertension. 2009; 54(5):981-986.

van Bussel BC, Henry RM, Schalkwijk CG, Ferreira I, Feskens EJ, Streppel MT, et al. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. J Nutr. 2011; 141(9):1719-1725.

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect. 1998; 106(12):775-792.

Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, et al. The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci. 2006; 93(2):223-241.

van Woudenbergh GJ, van Ballegooijen AJ, Kuijsten A, Sijbrands EJ, van Rooij FJ, Geleijnse JM, et al. Eating fish and risk of type 2 diabetes: A population-based, prospective follow-up study. Diabetes Care. 2009; 32(11):2021-2026.

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006; 84(1):5-17.

Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med. 2010; 152(5):315-323.

Wang S, Ma AQ, Song SW, Quan QH, Zhao XF, Zheng XH. Fish oil supplementation improves large arterial elasticity in overweight hypertensive patients. Eur J Clin Nutr. 2008a; 62(12):1426-1431.

Wang SL, Tsai PC, Yang CY, Leon Guo Y. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care. 2008b; 31(8):1574-1579.

Weitz D, Weintraub H, Fisher E, Schwartzbard AZ. Fish oil for the treatment of cardiovascular disease. Cardiol Rev. 2010; 18(5):258-263.

Wennberg M, Bergdahl IA, Hallmans G, Norberg M, Lundh T, Skerfving S, et al. Fish consumption and myocardial infarction: a second prospective biomarker

study from northern Sweden. Am J Clin Nutr. 2011; 93(1):27-36.

Verta M, Salo S, Korhonen M, Assmuth T, Kiviranta H, Koistinen J, et al. Dioxin concentrations in sediments of the Baltic Sea--a survey of existing data. Chemosphere. 2007; 67(9):1762-1775.

Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol. 2004; 93(9):1119-1123.

Villegas R, Xiang YB, Elasy T, Li HL, Yang G, Cai H, et al. Fish, shellfish, and long-chain n-3 fatty acid consumption and risk of incident type 2 diabetes in middle-aged Chinese men and women. Am J Clin Nutr. 2011; 94(2):543-551.

Vinni K, Hakama M. Healthy worker effect in the total Finnish population. Br J Ind Med. 1980; 37(2):180-184.

Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. Am J Clin Nutr. 2008; 88(6):1618-1625.

Virtanen JK, Rissanen TH, Voutilainen S, Tuomainen TP. Mercury as a risk factor for cardiovascular diseases. J Nutr Biochem. 2007; 18(2):75-85.

Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, et al. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arterioscler Thromb Vasc Biol. 2005; 25(1):228-233.

World Health Organization. Executive summary - Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). 1998; Available at: http://www.who.int/ipcs/publications/en/exe-sum-final.pdf

Xun P, Hou N, Daviglus M, Liu K, Morris JS, Shikany JM, et al. Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med. 2011; 270(2):175-186.

Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, et al. Mercury and the risk of coronary heart disease in men. N Engl J Med. 2002; 347(22):1755-1760.

Zheng J, Huang T, Yu Y, Hu X, Yang B, Li D. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. Public Health Nutr. 2011; (Sep 14):1-13.

Appendix

Stages of the Fishermen study

Indentification of the study population (October 2003)

Professional Fishermen Register
All fishermen n=7,020 (index persons), *men n= 6,501, women n=519*

Population Information System
All fishermen's spouses and other family members n=35,648

–   Fishermen's spouses n=4,941, *men n=126, women n=4,815*
–   Fishermen's biological children n=11,339
–   Fishermen's biological siblings n=5,083
–   Fishermen's biological siblings' spouses n=4,030
–   Fishermen's biological siblings' children n=9,982

Register studies, n=10,670
mortality, cancer incidence

Male fishermen n=6,410
Fishermen's wives n=4,260

Health questionnaire, n=1,427
(frequency questions on fish consumption, smoking, alcohol consumption, physical activity, self-reported health and well-being)

National random sample n=3,577 (March 2004)
Additional sample from Helsinki area n=300 (June 2004)
Additional sample from Turku area n=501 (April 2005)
–   Questionnaires sended n=4,378
–   Questionnaires returned n=1,317

Newspaper advertisements in Turku area (December 2004 & January 2005)
–   Questionnaires returned n=112

Male fishermen n=398
Fishermen's wives n=430
Other family members n=599

Health examination, n=309
(food frequency questionnaire on whole diet, weight, height, body circumference measures, blood pressure, ultrasound examination of the right common carotid artery, resting electrocardiogram, bioimpedance, blood sampling and chemical analyses (e.g., lipids, glucose, insulin, fatty acids and environmental contaminants such as dioxins, PCBs, MeHg, organotin and perfluorinared compounds))

–   Persons living <150 km from Helsinki n=77 (August 2004)
–   Persons living <150 km from Turku n=232 (January–May 2005)

Male fishermen n=114
Fishermen's wives n=115
Other family members n=80

Epidemiological studies on
fish consumption and
cardiovascular health