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Investigating the risk-benefit balance of substituting red and processed meat with fish in a Danish diet

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ABSTRACT

Danish dietary guidelines recommend the Danish population to increase the consumption of fish while decreasing the consumption of red and processed meat to prevent nutrition-related diseases. However, the presence of contaminants in these foods may affect the overall risk-benefit balance of such substitution. We performed a quantitative risk-benefit assessment on substituting red and processed meat with fish in a Danish diet. We modeled the substitution among Danish adults based on data from a Danish dietary survey and compared four alternative scenarios based on varying chemical and nutrient exposures to the current consumption. We quantified the overall health impact of the substitutions in terms of Disability-Adjusted Life Years (DALYs). Approximately 150 DALYs/100,000 individuals could be averted each year if Danish adults consumed 350 g of fish/week (fatty or mix of fatty and lean) while decreasing the consumption of red and processed meat. A lower beneficial impact was observed when consumption of fish was restricted to lean fish (80 DALYs/100,000 averted), and a marked health loss (180 DALYs/100,000) was estimated when consumption was restricted to tuna. Our results show an overall beneficial effect of the substitution if the consumption of large predatory fish is low and at least half is fatty fish.

1. Introduction

Fish consumption and its associated health effects have been extensively studied during the last decades (EFSA Scientific Committee, 2015). The beneficial effects of fish consumption are well established; however, so is the presence of various contaminants in fish such as methyl mercury (MeHg) and dioxins, potentially causing adverse effects on human health (FAO/WHO, 2011). Risk-benefit assessment (RBA) is a tool used for weighting the risks and benefits of food consumption, and several RBAs have addressed the dual role of fish consumption on human health (Becker et al., 2007; Berjia et al., 2012; Cohen et al., 2005; Domingo, 2016; EFSA Scientific Committee, 2015; FAO/WHO, 2011; FDA, 2014; Gao et al., 2015; Hellberg et al., 2012; Hoekstra et al., 2013; Hsi et al., 2016; Jacobs et al., 2017; Persson et al., 2018; Sirot et al., 2012; van der Voet et al., 2007; VKM, 2014; Zeilmaker et al., 2013). By qualitatively or quantitatively weighting the adverse health effects associated with contaminants in fish against the beneficial health effects associated with fish consumption, these RBAs have investigated whether increased fish consumption has a net beneficial or adverse effect on human health. The vast majority only dealt with fish alone and did not take substitution of other foods into consideration. However, increased consumption of fish is expected to lead to a decrease in the consumption of other foods, which may also be associated with risks and benefits that need to be addressed. The Danish food-based dietary guidelines (FBDG) of 2013 recommend an intake of 350 g of fish/week of which 200 g should be fatty fish. At the same time, the intake of red and processed meat is recommended to not exceed 500 g/week, and the intake of processed meat should be limited (Tetens et al., 2013a). One way for individuals that do not reach the recommended fish intake and that surpass the one for meats to fulfill these guidelines would be by substituting red and processed meats with fish.

Quantification of the risk-benefit balance of foods for defining and supporting dietary guidelines has previously been encouraged (Rideout and Kosatsky, 2017). In addition, the need for national estimates of disease burden and risk-benefit balance of food for public health policy has been stressed (Devleesschauwer et al., 2014b; Jacobs et al., 2017).

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Abbreviations

AI	Adequate Intake
Bw	Body weight
CHD	Coronary Heart Disease
CONTAM	Contaminants in the Food Chain
CRC	Colorectal Cancer
DALY	Disability-Adjusted Life Year
DANSDA	Danish National Survey of Diet and Physical Activity
DHA	Docosahexaenoic Acid; dl-PCB: Dioxin-Like Polychlorinated Biphenyls
DW	disability weight
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic Acid
FAO	Food and Agriculture Organization of the United Nations
FBDG	Food-Based Dietary Guidelines
IQ	Intelligence Quotient
LE	Life Expectancy
MeHg	Methyl Mercury
NDA	Dietetic Products, Nutrition, and Allergies
P10	10th Percentile
P50	50th Percentile
P90	90th Percentile
RBA	Risk-Benefit Assessment
RR	Relative Risk
SC	Stomach Cancer
SD	Standard Deviation
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalents
TWI	Tolerable Weekly Intake
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost

The Disability-Adjusted Life Year (DALY) is a composite health metric commonly used in RBA and is also the preferred metric used for the World Health Organization estimates of the global burden of foodborne diseases (Devleesschauwer et al., 2015) and the Global Burden of Disease Study (Hay et al., 2017). It combines information on incidence, severity and duration of a disease or disability (Years Lived with Disability, YLD) with the standard expected Years of Life Lost (YLL) due to premature death and allows for a comparison across diseases (Devleesschauwer et al., 2014a). The difference in the sum of DALYs between a given reference scenario and one or more alternative scenarios gives information on an overall health gain or loss by a theoretical intervention in a population, expressed in loss of healthy life years.

In this study, we quantified the health impact of substituting red and processed meat with fish in the diet of the adult Danish population using DALYs as a common health metric. We compared the current consumption of fish and red and processed meat with four alternative scenarios in which red and processed meat were substituted with fish and the consumption of different fish species was considered.

2. Methods

2.1. Identification of relevant health effects

The relevant health effects associated with consumption of fish and red and processed meat were identified on the basis of official assessments by national and international authorities, regulatory agencies and expert groups within nutrition, toxicology, and medicine (EFSA CONTAM Panel, 2012; EFSA NDA Panel, 2014; EFSA Scientific Committee, 2015; FAO/WHO, 2011; FAO, 2010; JECFA, 2002; Larsen and Nørhede, 2013; Norat et al., 2015, 2010; Nordic Council of Ministers, 2014; Scientific Committee on Food, 2000, 2001; US EPA, 2012; Van Horn et al., 2008; VKM, 2014; WCRF/AICR, 2007). In addition, we performed a literature search for more recent systematic reviews and meta-analyses published after the literature search of the Norwegian Scientific Committee for Food Safety on April 1st, 2014 (VKM, 2014) for fish, and after the search of the Evidence Report behind the Danish FBDG on October 15th, 2012 (Tetens et al., 2013a) for red and processed meat. The search was conducted on June 18th, 2016 and covered articles published up to that date. Health effects were included in the assessment if the epidemiological evidence was graded as "convincing" or "probable" according to the criteria set by the World Health Organization (WHO)/Food and Agriculture Organization of the United Nations (FAO) (WHO, 2003). The evidence for toxicological health effects, however, in many cases cannot be graded higher than "possible" due to the constraints of studies investigating such effects (experimental animal studies, human case-control or cross-sectional studies). We chose to include health effects associated with toxicological hazards that were considered the most sensitive in animals and/or humans as defined for the establishment of health-based guidance values based on No/Lowest Observed Adverse Effect Levels. The health effects included in the RBA are listed in Table 1.

The health effects associated with fish consumption are mainly linked to the presence of nutrients and chemical contaminants in fish. Based on available evidence, we evaluated health effects associated with the chemical contaminants dioxin and dioxin-like (dl-) polychlorinated biphenyls (PCBs) and MeHg, and two n-3 long-chain polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Table 1). The concentration of these compounds varies among fish species, and is dependent on the content of fat and muscle tissue. Specifically, the concentrations of dioxins, EPA and DHA are higher in fatty fish species, whereas MeHg accumulates in muscle tissue and is therefore found at higher concentrations in larger predatory fish species (EFSA CONTAM Panel, 2012; EFSA Scientific Committee, 2015). As identified by the Norwegian Scientific Committee for Food Safety, other contaminants than MeHg, dioxin and dl-PCBs are present in fish, such as polybrominated flame retardants and fluorinated substances. However, exposure to these contaminants from fish was considered very low compared to the toxicity levels of these contaminants, and thus they were not considered as of concern (VKM, 2014).

Various components have been suggested to associate consumption of red and processed meat with cancer, e.g. fat, protein, heme iron, and various contaminants such as N-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons (Bouvard et al., 2015; Domingo and Nadal, 2017; Norat et al., 2010; WCRF/AICR, 2007). However, although mechanistic evidence for the association between these individual components and cancer exists, their contribution to and the mechanism behind the observed association between consumption of red and processed meat and cancer is not known (Bouvard et al., 2015; Norat et al., 2010; WCRF/AICR, 2007). Thus, we chose to base our modeling of the meat-associated health impact on red and processed meat as whole foods in this study (Table 1).

Both fish and red meat are also important sources of various minerals and vitamins. Red meat is an important contributor to the intake of especially B vitamins, iron, zinc, and selenium, and fish is an important source of vitamin D and selenium in the Danish diet (Pedersen et al., 2015). Due to methodological difficulties in assessing deficiency of iron, a particularly central micronutrient present in red meat, from dietary sources, and due to lack of good dose-response relationships to characterize the risks associated with iron deficiency (The Scientific Advisory Committee on Nutrition, 2010) it was not possible to quantify the health impact of potential changes in iron intake due to the

Table 1
Health effects associated with consumption of fish and red and processed meat included in the risk-benefit assessment based on available evidence and expert opinions. Abbreviations: CHD: coronary heart disease; CRC: colorectal cancer; DALY: Disability-Adjusted Life Year, DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; EPA: eicopentaenoic acid; LE_0: life expectancy at age 0; MeHg: methyl mercury; SC: stomach cancer; YLD: Years Lived with Disability; YLL: Years of Life Lost.

Food	Compound	Health effect	Subgroup by exposure	DALY contributions	Note	Reference of systematic reviews
Fish	Whole fish	Enhanced fetal neurodevelopment upon maternal consumption	Women, age 15–49 years	YLD	The beneficial effects on fetal neurodevelopment appear to be associated with whole fish consumption and cannot be explained only by the n-3 long-chain polyunsaturated fatty acids in fish. No recovery of intellectual disability is assumed, thus duration was set to life expectancy at birth, weighted by the number of males and females born in Denmark in 2015 (LE_0 = 80.6 years).	(EFSA NDA Panel, 2014; FAO/WHO, 2011; FDA, 2014)
Fish	MeHg	Compromised fetal neurodevelopment upon maternal exposure	Women, age 15–49 years	YLD	Maternal MeHg exposure during pregnancy is associated with adverse effects on fetal neurodevelopment and has been found to decrease the above stated beneficial effects of whole fish consumption on fetal neurodevelopment. The same assumptions for the DALY calculations as for enhanced fetal neurodevelopment were used.	(EFSA CONTAM Panel, 2012; FAO/WHO, 2011; FDA, 2014)
Fish	DHA + EPA	Decreased risk of fatal CHD	Age ≥ 15 years	YLL	The evidence on an inverse association with fatal CHD appears to be stronger for DHA and EPA than for whole fish consumption. Fatal CHD was assumed to cause immediate death, thus no recovery was included in the model.	(EFSA NDA Panel, 2014; FAO/WHO, 2011; FAO, 2010; Tetens et al., 2013a).
Fish and red + processed meat	Dioxin + dl-PCBs	Decreased fertility in male offspring	Women, age 15–49 years	YLD	One of the most sensitive endpoint observed in both experimental animals and epidemiological studies. Duration of male infertility was set to 29 years based on the assumption that a person will not be aware of the disability before planning to start a family. We considered it unlikely for this to occur before the age of 20. In addition we assumed the same upper fertility age as for women, i.e. age 49.	(JECFA, 2002; Scientific Committee on Food, 2000, 2001; US EPA, 2012; Van Leeuwen et al., 2000; WHO, 2000)
Fish and red + processed meat	Dioxin and dl-PCBs	Hypothyroidism	Age ≥ 15 years	YLD	One of the most sensitive endpoint observed in both experimental animals and epidemiological studies. Hypothyroidism was assumed non-fatal. We assumed that treatment starts within 1 year and removes all symptoms.	(Larsen and Nørhede, 2013; US EPA, 2012; Van Leeuwen et al., 2000)
Red meat	Whole red meat	Increased risk of colorectal cancer	Age ≥ 15 years	YLD + YLL	Red meat consumption has been found to be associated with an increased risk of CRC. The duration of CRC varies depending on the course of disease which is given by the natural disease history model for CRC (see Table S14).	(Bouvard et al., 2015; IARC, 2015; Tetens et al., 2013a; WCRF/AICR, 2007, 2011)
Processed meat	Whole processed meat	Increased risk of colorectal cancer	Age ≥ 15 years	YLD + YLL	Processed meat consumption has been found to be associated with an increased risk of CRC. The same natural disease history model for CRC used for red meat consumption was used (see Table S14).	(Bouvard et al., 2015; IARC, 2015; Tetens et al., 2013a; WCRF/AICR, 2007, 2011)
Processed meat	Whole processed meat	Increased risk of stomach non-cardia cancer	Age ≥ 15 years	YLD + YLL	Processed meat was recently upgraded by World Cancer Research Fund's Continuous Update Project to be *probably* associated with stomach non-cardia cancer. The duration of SC varies depending on the course of disease which is given by the natural disease history model for SC (see Table S14).	(WCRF/AICR, 2016)

substitution. In order to not introduce bias due to inconsistency in included and excluded micronutrients, we chose not to consider the beneficial health effects associated with any micronutrients in this study. Furthermore, it was beyond the scope of the present study to assess acute adverse effects associated with microbiological contaminations potentially present in fish and meat.

2.2. Data used in the model

Consumption data from the Danish National Survey of Diet and Physical Activity (DANSDA), 2011–2013, were used for estimating the individual mean daily consumption of fish and meat in the Danish population (Pedersen et al., 2015). DANSDA is a nation-wide, cross-sectional survey of diet and physical activity in a representative sample of individuals in the Danish population, drawn from random sampling from the civil population registration system. The participants answered a pre-coded semi-closed food diary consisting of categories with common foods and dishes in the Danish diet (Knudsen et al., 2011). In our study, data were restricted to individuals that 1) reported for all (consecutive) 7 days, 2) had information on body weight, and 3) were at or above 15 years of age, giving a total population sample of 2811 individuals.

Concentration data for both nutrients and contaminants were obtained from Danish food monitoring (DTU, 2017; Larsen et al., 2002; Petersen et al., 2015b, 2015a). These data represent samples taken from foods of both Danish and non-Danish origin on the Danish market (DTU, 2017; Larsen et al., 2002; Petersen et al., 2015b, 2015a). When information on the number of samples from different sources of food sampling was available, a mean weighted by the number of samples across food sampling sources was applied. If the number of samples was not available, all data sources were given the same weight.

We assumed that fish is the only source of DHA and EPA (see Table S2), even though a limited amount of α-linoleic acid, found in various plant oils, can be converted into DHA and EPA (FAO, 2010). Likewise we did not include DHA and EPA intake from supplements. A minimum daily intake of approximately 250 mg DHA and EPA for adult men and non-pregnant/non-lactating women and 300 mg DHA plus EPA for pregnant/lactating women was recommended by FAO in 2010 (FAO, 2010). The European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies (NDA) proposed the same year to set an adequate intake (AI) of 250 mg DHA plus EPA/day for adults and an additional 100–200 mg preformed DHA/day for pregnant and lactating women (EFSA NDA Panel, 2010).

As for DHA and EPA, fish and other seafood are the only significant source of human MeHg exposure (see Table S5). MeHg is the most common form of organic mercury in food and constitute 80–100% of total mercury in fish and 50–80% in other seafood according to the EFSA Panel on Contaminants in the Food Chain (CONTAM) (EFSA CONTAM Panel, 2012). When concentration data were only available for total mercury, we applied a conservative approach, i.e. we assumed that 100% and 80% of total mercury in fish and shellfish, respectively, is MeHg to avoid underestimating the health impact associated with MeHg exposure through fish consumption. The tolerable weekly intake (TWI) for MeHg was set to 1.3 μg/kg bw by the EFSA CONTAM panel in 2012 (EFSA CONTAM Panel, 2012). The TWI corresponds to a daily exposure of 0.19 μg/kg bw.

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans – hereafter referred to as dioxins – and dl-PCBs are persistent organic pollutants that remain in the environment for long periods of time. Dl-PCBs are PCBs that elicit toxicological responses similar to those by the most toxic congener of dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (FAO/WHO, 2011). Exposure to a mixture of dioxin and dl-PCBs is usually estimated in terms of Toxic Equivalents (TEQs). TEQs are defined as the product of the concentration of each congener by it specific Toxic Equivalency Factor (TEF) (WHO, 2000). The TEF of a compound indicates the potency of the given compound relative to TCDD, which has a reference value of 1 (Ahlborg et al., 1992; IARC, 1997). The exposure to dioxin and dl-PCBs is collectively assessed by using concentration data for total TEQ, based on TEFs set by WHO in 2005 (Van den Berg et al., 2006). Humans are primarily exposed to dioxin and dl-PCBs from animal sources, such as fish, meat, and dairy products but also from other foods and the environment (Larsen and Nørhede, 2013). We only assessed the food-associated exposure to dioxin and dl-PCBs in this study. Concentrations of dioxin and dl-PCBs were given per g of fresh weight for fish and seafood (see Table S5) and per g of fat for other foods (see Table S4). Thus, the absolute concentrations of dioxins and dl-PCBs in other foods than fish were calculated based on the fat contents of these foods. A TWI of 14 pg TEQ/kg bw (corresponding to on average 2 pg TEQ/kg bw/day) was established for dioxin and dl-PCBs by the Scientific Committee on Food, European Commission in 2001 (Scientific Committee on Food, 2001).

Data on incidence and mortality of studied health outcomes/diseases for 2015 were obtained from Danish health registries via the Danish eHealth Authority (The Danish National eHealth Authority, The Danish National eHealth Authority). Population statistics for 2015 were obtained from Statistics Denmark (Statistics Denmark) (see Table S6).

2.3. Alternative scenarios

We defined four alternative scenarios to be compared with the current consumption of fish and meat in the Danish population. The alternative scenarios were based on the recommended minimum weekly intake of 350 g of cooked/prepared fish and a maximum weekly intake of 500 g of cooked red meat and processed meat as advised in the Danish FBDG (Pedersen et al., 2015; Tetens et al., 2013a). Fish and meat intake amounts per individual were given in cooked/prepared weights in DANSDA 2011–2013. To determine food intakes in the alternative scenarios, we gave the dietary guideline on fish the highest priority. Consequently, individual consumptions below 350 g/week were increased to this level whereas no changes were made for individuals already consuming 350 g of fish/week or more. Based on assumptions on portion sizes (see Table S7) we estimated that a fish intake of 350 g/week can be achieved by consuming fish in two hot meals (100 g each) and five cold meals (five half Danish open-faced sandwiches, 30 g each) per week.

The increase in individual fish consumption was compensated by decreasing the consumption of red and processed meat. However, if the decrease in red or processed meat consumption for an individual was larger than the current consumption, meat consumption was set to zero. The consumption of red and processed meat was decreased according to the increase in fish consumption at the individual level by applying substitution factors. The substitution factors relied on the assumption that non-processed red meat is only consumed in hot meals and will be substituted by fish mainly consumed in hot meals, while processed meat is mainly consumed in cold meals and will be substituted by fish normally only consumed in cold meals in a Danish diet. The substitution factors were derived based on differences in typical portion sizes of fish, red meat, and processed meat (see Table S7) (Ygil, 2013). The substitution factor used for substituting red meat with fish consumed in hot meals was 1.07, and the substitution factor for substituting processed meats with fish consumed in cold meals was 3. In other words, e.g. 10 g of processed meat (such as a slice of ham on a Danish open-faced sandwich), would be substituted by 30 g of fish consumed for cold meals (such as pickled herring).

We differentiated between fatty and lean fish, and specifically addressed tuna, a large predatory fish, in the alternative scenarios. Fish species were categorized into *lean fish* (≤5% fat) and *fatty fish* (> 5% fat) (VKM, 2014). *Red meat* was defined as beef, pork, lamb, and goat, and *processed meats* included any meats preserved by smoking, curing, salting, or addition of chemical preservatives (both red meat and poultry) (WCRF/AICR, 2007). Game meat was also considered red meat. The ratio between red and processed meat was kept constant for

each individual in all four alternative scenarios and was determined by the amount of meat consumed before substitution and the type of fish (for cold or hot meals) increased in the alternative scenarios. Thus, the four alternative scenarios only differed from each other in terms of fish species consumed.

The following scenarios were compared to the current Danish consumption of fish (reference scenario):

- Alternative scenario 1: consumption of 350 g of a mix of lean and fatty fish/week
- Alternative scenario 2: consumption of 350 g of fatty fish/week.
- Alternative scenario 3: consumption of 350 g of lean fish/week.
- Alternative scenario 4: consumption of 350 g of tuna/week.

Thus, the fish consumed before substitution was also changed according to these fish species in the alternative scenarios. All alternative scenarios considered the same individual decreases in consumption of red and processed meat as a result of the substitution with fish, which was compared to the current consumption of red and processed meat. The proportions of the individual fish species eaten within each of the four alternative scenarios were based on the current preferences for the major fish species consumed in the Danish population (see Table S8).

2.4. Exposure to food, nutrients and contaminants

Observed individual mean daily consumption over 7 days was calculated based on individual-level consumption data from DANSDA 2011–2013 and considered a representative estimate of habitual (long-term) daily consumption in the Danish adult population (≥age 15 years) (Bingham et al., 1994). In order to keep information on the dish and meal in which the food was consumed, consumption of individual foods was estimated based on data on meals. In other words, we used consumption data at the level of foods as consumed (e.g. pizza), and the intake of individual ingredients was estimated based on recipes (see Table S9, Table S10, and Table S11).

Consumption data for foods other than fish and meat contributing to dioxin exposure were provided on an ingredient level (e.g. milk and dairy products) due to the dispersion of these foods throughout the diet. Ingredient level consumption data were given as (primarily) raw weights (see Table S3).

Before estimating the exposure to contaminants and nutrients, fish and red meat intakes were converted into raw weights, assuming a water loss of 20% for fish and 25% for red meat. We assumed that preparation or cooking of foods does not cause a loss of the contaminants and nutrients in the foods considered in this study (Pedersen et al., 2015). Concentration data for nutrients and contaminants were available for processed meat, thus this type of meat was not converted into raw weights.

Exposure to contaminants was expressed per kg body weight (bw). The individual mean daily exposures to chemicals were estimated by the following equation:

$$\sum_{n} \frac{I_n \cdot C_n}{bw}$$

where I_n is the individual mean daily intake of food n in g/day, C_n is the mean concentration of the chemical in food n (in μg/g for MeHg and pg TEQ/g for dioxin and dl-PCBs) and bw is the body weight of the given individual in kg.

Exposure to nutrients was not expressed per kg bw as for chemicals, but in absolute exposure. The individual mean daily exposure to nutrients was estimated as follows:

$$\sum_{n} I_n \cdot C_n$$

where I_n is the individual mean daily intake of food n in g/day, C_n is the mean nutrient concentration in food n (in mg/g for DHA and EPA).

Exposure modeling was done by sex and 13 age groups (see Table S1). In order to also include individuals above the age of 75 years, the consumption data for 75 year-old participants were additionally extrapolated to ages > 75 years, assuming similar consumption patterns.

Exposure was modeled by combining probabilities of exposure with (positive) exposure amounts. Probability of exposure was described by a Bernoulli distribution and exposure amounts by either a lognormal or Gamma distribution depending on the best fit according to Cramér-von Mises and Anderson-Darling goodness of fit tests. In the alternative scenarios, the empirical distributions were used for describing fish consumption and exposure to DHA and EPA, and MeHg due to a poor fit by both the lognormal and Gamma distributions (see Table S12).

2.5. Calculating disability-adjusted life years

The distribution of observed individual mean daily consumption/exposure was combined with dose-response models to estimate the size of a given health effect associated with fish, red meat and processed meat consumption in the various scenarios. We quantified the disease burden of each health effect in terms of DALYs (YLD + YLL). YLD for health outcome d, sex s, and age a was defined as:

$$YLD_{d,s,a} = AC_{d,s,a} \cdot D_d \cdot DW_d$$

where $AC_{d,s,a}$ is the annual number of cases with health outcome d for sex s and age a, D_d is the duration of health outcome d until remission or death, and DW_d is the disability weight for health outcome d. The disability weight is a measure of good health, ranging from zero (full health) to one (death) (see Table S13) (Devleesschauwer et al., 2014a). YLL for health outcome d, sex s, and age a was defined as:

$$YLL_{d,s,a} = AD_{d,s,a} \cdot SEYLL_{s,a}$$

where $AD_{d,s,a}$ is the annual number of deaths due to health outcome d for sex s and age a and $SEYLL_{s,a}$ is the standard expected years of life lost for sex s and age a (WHO, 2017). Finally the disease burden for health outcome d was summed over sex and age:

$$DALY_d = \sum_{s} \sum_{a} (YLD_{d,s,a} + YLL_{d,s,a})$$

The contributions to the DALY estimates for the various health effects considered in this RBA are listed in Table 1. We applied either a "top-down" or "bottom-up" approach to estimate incidence ($AC_{d,s,a}$) and mortality ($AD_{d,s,a}$) of a disease, depending on the data available to describe an association or causation between consumption of a food or exposure to a compound and the disease (Gibb et al., 2015). When risk estimates (e.g. relative risk [RR]) from epidemiological or human intervention studies were available, we applied a "top-down" approach, starting from the current incidence or mortality in the population, which was combined with RR dose-response functions and exposure distributions to estimate incidence or mortality due to fish or meat consumption (fatal CHD and DHA plus EPA exposure, CRC and red and processed meat consumption, and non-cardia stomach cancer and processed meat consumption). We applied a "bottom-up" approach, using dose-response functions combined with exposure distributions when risk estimates were not available from epidemiological studies (i.e., maternal fish consumption/MeHg exposure and fetal neurodevelopment) and when data from experimental animal studies were applied (i.e., exposure to dioxins and dl-PCBs and hypothyroidism and male infertility). A more detailed description of the methods to calculate DALYs is given in the Supplemental Material (see Supplemental Material A) along with model input parameters (see Table S12), and disability weights (see Table S13).

The health impact of the change in food consumption and compound exposure in each alternative scenario was expressed as the DALY difference for outcome d ($\Delta DALY_{d,alt}$) between the alternative scenario and the reference scenario (current consumption):

$$\Delta DALY_{d,alt} = DALY_{d,alt} - DALY_{d,ref}$$

A ΔDALY > 0 implies a health loss of the intervention, whereas a ΔDALY < 0 implies a health gain. Likewise, the overall health impact of the substitution was expressed as the difference between the sum of DALYs over the diseases associated with the food consumption in the alternative scenario and the sum of DALYs over the diseases associated with the food consumption in the reference scenario:

$$\Delta DALY_{alt} = \sum_{d} (DALY_{d,alt} - DALY_{d,ref})$$

We applied two-dimensional Monte Carlo simulation using the *mc2d* package (Pouillot and Delignette-Muller, 2010) in R version 3.4.1 (R Core Team, 2017) for the DALY calculations, with 100,000 iterations for simulating variability and 1000 iterations for uncertainty. The results of the simulations were reported as the mean of the variability dimension and the median of the uncertainty dimension along with the 95% uncertainty interval around the mean.

2.6. Statistical analysis

Two-tailed pseudo p-values were calculated for the DALY differences between each alternative scenario and the reference scenario to test whether the change was significantly different from zero:

$$p\text{−}value = 2 \cdot \min(Pr(\Delta DALY_{alt} > 0),\ Pr(\Delta DALY_{alt} < 0))$$

Where probabilities (Pr) were estimated as the proportion of the DALY difference simulations above or below zero, respectively. We applied a 5% significance level. The statistical analyses were performed using R version 3.4.1 (R Core Team, 2017).

3. Results

3.1. Substitution of meat with fish

The current mean and median daily consumption of fish were 31.5 g/day and 23.2g/day, respectively, with more than 78% of the study population not reaching the recommended level of 350 g of fish/week (i.e. 50g/day); 14% of the study population had no fish consumption (Table 2). In addition, the consumption of red and processed meat was on average above the recommended maximum intake of 500 g/week (i.e. approximately 70 g/day), with a mean daily intake of 115.2 g/day; 73% of the study population was above the recommended maximum consumption. Because some individuals already consumed more than 50 g of fish/day before substitution (22%), the population mean consumption was slightly higher than the recommended minimum (56.5 g/day) after substitution. After the substitution, the consumption of total red and processed meat was on average decreased by 17 g/day, with a larger decrease for red meat (14.1 g decrease/day) compared to processed meat (2.8 g decrease/day). In contrast to the FBDG for fish, on average the recommended maximum consumption of 500 g of total red and processed meat/week was not met after the substitution (mean weekly consumption: ~690 g/week) with 59% of the study population above the recommended maximum 500 g of total red and processed meat/week.

3.2. Exposure assessment

The four alternative substitution scenarios were compared to the current consumption in the Danish adult diet. The ratio of lean to fatty fish varied between scenarios. The fraction of fatty and lean fish consumed in the alternative scenario 1 was based on the current preferences. The resulting percentage of fatty fish in the alternative scenario 1 was 53% and 44% for fish consumed in cold meals and hot meals, respectively, based on the current preferences (see Table S8). This amounts to approximately 168 g of fatty fish per week, thus just below half of the total fish consumption. Fatty fish constituted 100% in the alternative scenario 2, and lean fish 100% in the alternative scenarios 3 and 4.

Table 3 shows the exposures to DHA and EPA, MeHg, and dioxin and dl-PCBs in the reference scenario and the four alternative scenarios. Table 3 shows that the study population was on average above the AI of 250 mg DHA and EPA/day set by FAO and the EFSA NDA panel (EFSA NDA Panel, 2010; FAO, 2010) before the substitution although half of the population (52%) did not meet the AI. In contrast, the recommendation was reached for the whole population in the alternative scenario 1 and 2, whereas the intake of DHA and EPA was decreased compared to the reference scenario in scenario 3 and 4 (84% and 95% below 250 mg DHA and EPA/day, respectively). The reason for this decrease can be the fact that the individual consumption of fish species before substitution was also changed in the alternative scenarios, thus all fatty fish consumed in the reference scenario was replaced by lean fish in the alternative scenarios 3 and 4. The TWI for MeHg (1.3 μg/kg bw/week) was not exceeded in 99% of the study population in the reference or alternative scenarios except for scenario 4 where 98% exceeded the TWI. For dioxin and dl-PCB exposure, we estimated an increase in the mean exposure in the alternative scenarios 1 and 2, whereas only the fraction of individuals exceeding the TWI for dioxin and dl-PCBs (14 pg TEQ/kg bw/week) was increased in the alternative scenario 2 (from 2% to 5%). However, the TWI was not exceeded in 99% of the study population in the alternative scenarios 1, 3, and 4 (Table 3).

3.3. Disability-adjusted life years

Fig. 1 shows the health impact of the substitution in terms of the total DALY difference for each alternative scenario compared to the reference scenario. An overall health gain was observed in the alternative scenarios 1, 2, and 3, whereas a health loss was observed for the alternative scenario 4 (Fig. 1). The overall DALY difference on the level of the whole population was −6986 DALYs (−8779, −5177) for the alternative scenario 1, -7203 DALYs (−9054, 5422) for the alternative scenario 2, -3741 DALYs (−4834, −2783) for the alternative scenario 3, and 8608 DALYs (3569, 15336) for the alternative scenario 4 per year compared to the reference scenario. The DALY difference estimates were significantly different from zero in all alternative scenarios (pseudo P-values < 0.001). In other words, approximately 7000 healthy life years could be gained each year in Denmark if the whole adult population substituted some of the red and processed meat in the diet with fish to reach the recommended intake of 350 g of fish/week (a mix of fatty and lean, or only fatty fish). In contrast, a smaller health gain was estimated when consuming only lean fish in the recommended amounts and an overall health loss was estimated when consuming only tuna.

The health impact of the substitution in terms of the DALY

Table 2
Consumption amounts of fish, total (red and processed) meat, red meat, and processed meat (g/day) in Danish adults before and after the substitution. Abbreviations: P10: 10th percentile; P50: 50th percentile (median); P90: 90th percentile; SD: standard deviation.

Scenario and food	Mean	SD	P10	P50	P90
Reference scenario					
Fish	31.5	32.1	0.0	23.2	73.4
Total red and processed meat	115.2	67.6	44.6	101.1	202.6
Red meat	76.1	46.2	26.7	68.1	134.5
Processed meat	39.0	38.6	4.3	28.3	86.4
Alternative scenario					
Fish	56.5	18.9	50.0	50.0	73.4
Total red and processed meat	98.2	67.4	26.5	85.0	185.6
Red meat	62.0	46.3	9.5	53.7	121.5
Processed meat	36.2	38.4	0.4	24.9	83.1

Table 3
Daily exposures to DHA and EPA, MeHg, and dioxin and dl-PCBs in the Danish adult population in the reference scenario and the four alternative scenarios. Abbreviations: Bw: body weight; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; EPA: eicosapentaenoic acid; P10: 10th percentile; P50: 50th percentile (median); P90: 90th percentile; SD: standard deviation; TEQ: toxic equivalents.

Compound and scenario	Mean	SD	P10	P50	P90
DHA and EPA (mg/day)[a]					
Reference scenario	408.99	508.40	0.00	226.43	1056.26
Scenario 1	722.57	248.44	632.80	632.80	947.93
Scenario 2	1228.79	415.22	1082.10	1082.10	1609.76
Scenario 3	244.24	81.17	215.81	216.72	315.56
Scenario 4	152.26	50.88	134.69	134.69	197.61
MeHg (µg/kg bw/day)[b]					
Reference scenario	0.029	0.044	0.00	0.017	0.063
Scenario 1	0.050	0.017	0.035	0.048	0.063
Scenario 2	0.053	0.010	0.025	0.033	0.042
Scenario 3	0.068	0.025	0.047	0.064	0.086
Scenario 4	0.36	0.088	0.22	0.30	0.37
Dioxin and dl-PCBs (pg TEQ/kg bw/day)[c]					
Reference scenario	0.73	0.49	0.31	0.61	1.31
Scenario 1	0.94	0.29	0.66	0.89	1.28
Scenario 2	1.29	0.40	0.92	1.21	1.73
Scenario 3	0.61	0.20	0.39	0.58	0.85
Scenario 4	0.72	0.22	0.49	0.68	1.00

[a] The recommended intake of DHA and EPA is 250 mg/day (300 mg/day for pregnant/lactating women) (EFSA NDA Panel, 2010; FAO, 2010).

[b] The tolerable daily intake for MeHg is 0.19 µg/kg bw/day (EFSA CONTAM Panel, 2012).

[c] The tolerable daily intake for dioxin and dl-PCBs is 2 pg TEQ/kg bw/day (Scientific Committee on Food, 2001).

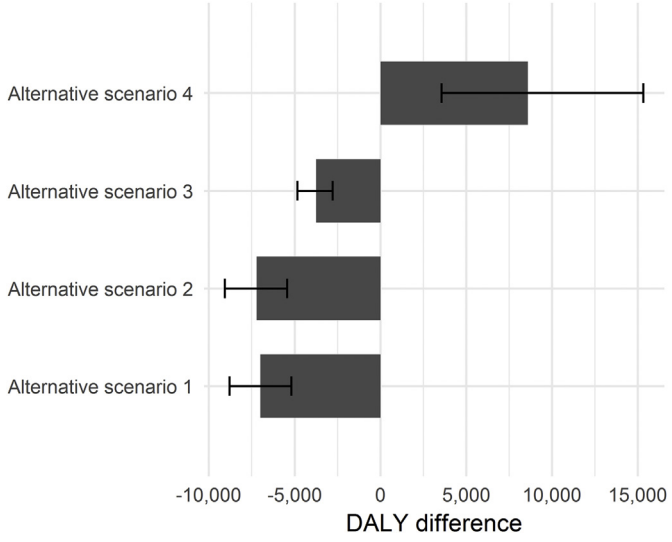

Fig. 1. Difference in Disability-Adjusted Life Years (DALYs) by scenario. DALY difference between the current consumption and the four alternative scenarios for the total Danish adult population (≥ 15 years; 4.7 million individuals). The bars represent the DALY differences between each of the four alternative scenarios and the current consumption as a measure of the health impact of the substitution. Error bars indicate 95% uncertainty intervals.

difference per 100,000 Danish adults (≥15 years) and number of cases of disease are shown for each of the health effects in each scenario in Table 4 and Table 5, respectively. The largest beneficial health impact of the substitution was observed for enhanced neurodevelopment due to maternal fish consumption (alternative scenarios 1–4) and decreased risk of fatal coronary heart disease (CHD) due to an increased intake of DHA and EPA in the alternative scenarios 1–2. The largest adverse health impact of the substitution was observed for scenario 4 due to

Table 4
DALY difference per 100,000 Danish adult individuals per outcome in each alternative scenario compared to the reference scenario (95% uncertainty intervals in parenthesis). Abbreviations: CHD: coronary heart disease; CRC: colorectal cancer; DALY: disability-adjusted life years; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; EPA: eicosapentaenoic acid; IQ: intelligence quotient; MeHg: methyl mercury.

Scenario	Fish consumption			Processed meat		Red meat	Dioxin & dl-PCBs		Total ΔDALY per 100,000
	Increase in IQ (whole fish)	Decrease in IQ (MeHg)	Fatal CHD (DHA + EPA)	CRC	Non-cardia stomach cancer	CRC	Male infertility (dioxin and dl-PCBs)	Hypothyroidism (dioxin and dl-PCBs)	
Scenario 1	−49.83 (−69.41, −33.82)	5.92 (1.92, 11.17)	−86.81 (−117.80, −56.58)	−4.81 (−6.24, −3.38)	−0.33 (−0.52, −0.12)	−12.83 (−18.79, −6.48)	0.00 (0.00, 0.00)	0.00 (−0.027, 0.00)	−148.99 (−187.18, −110.39)
Scenario 2	−49.83 (−69.41, −33.82)	1.15 (0.036, 2.39)	−86.81 (−117.80, −56.58)	−4.81 (−6.24, −3.38)	−0.33 (−0.52, −0.12)	−12.83 (−18.79, −6.48)	0.00 (0.00, 0.00)	0.00 (−0.012, 0.00)	−153.59 (−192.98, −115.70)
Scenario 3	−49.83 (−69.41, −33.82)	11.13 (3.69, 21.11)	−23.97 (−24.63, −19.82)	−4.81 (−6.24, −3.38)	−0.33 (−0.52, −0.12)	−12.83 (−18.79, −6.48)	0.00 (0.00, 0.00)	0.00 (−0.028, 0.00)	−79.85 (−103.19, −59.41)
Scenario 4	−49.83 (−69.41, −33.82)	88.28 (27.33, 184.03)	161.51 (89.22, 262.68)	−4.81 (−6.24, −3.38)	−0.33 (−0.52, −0.12)	−12.83 (−18.79, −6.48)	0.00 (0.00, 0.00)	0.00 (−0.028, 0.00)	183.01 (75.75, 326.31)

Table 5
Extra number of cases by health outcome in each alternative scenario compared to the reference scenario (95% uncertainty intervals in parenthesis).Abbreviations: CHD: coronary heart disease; CRC: colorectal cancer; DALY: disability-adjusted life years; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; EPA: eicosapentaenoic acid; IQ: intelligence quotient; MeHg: methyl mercury.

Scenario	Fish consumption			Processed meat	Red meat		Dioxin & dl-PCBs	
	Intellectually disabled (IQ < 85) due to whole fish consumption	Intellectually disabled (IQ < 85) due to MeHg exposure	Fatal CHD	CRC	Non-cardia stomach cancer	CRC	Male infertility	Hypothyroidism
Scenario 1	−1665 (−1967; −1357)	177 (67; 313)	−174 (−564; −10.91)	−30.7 (−182; −5.16)	−1.02 (−5.19; −0.18)	−88.0 (−1250, −40.9)	0.00 (0.00; 0.00)	0.00 (−56.81; 0.00)
Scenario 2	−1665 (−1967; −1357)	39 (5.2; 73)	−174 (−564; −10.91)	−30.7 (−182; −5.16)	−1.02 (−5.19; −0.18)	−88.0 (−1250, −40.9)	0.00 (0.00; 0.00)	0.00 (−26.73; 0.00)
Scenario 3	−1665 (−1967; −1357)	322 (127; 590)	9.50 (−410; 226)	−30.7 (−182; −5.16)	−1.02 (−5.19; −0.18)	−88.0 (−1250, −40.9)	0.00 (0.00; 0.00)	0.00 (−61.55; 0.00)
Scenario 4	−1665 (−1967; −1357)	2508 (830; 4897)	563 (30.20; 854)	−30.7 (−182; −5.16)	−1.02 (−5.19; −0.18)	−88.0 (−1250, −40.9)	0.00 (0.00; 0.00)	0.00 (−61.55; 0.00)

increased risk of compromised neurodevelopment associated with increased maternal MeHg exposure and increased risk of fatal CHD due to a decreased intake of DHA and EPA.

The relative contribution of the individual health effects to the overall DALY difference estimate is visually presented in Fig. 2.

4. Discussion

In this study we estimated the risk-benefit balance of substituting red and processed meat with fish in a Danish adult diet and investigated the health impact of consuming different types of fish (mix, lean, fatty and predatory) to fulfill the intake recommended by the Danish FBDG. To our knowledge, this is the first RBA that quantifies the health impact of substitution of foods in terms of DALYs. We found that on a population level up to 7000 healthy years of life could be gained if all Danish adults increased their fish consumption to 350 g/week and correspondingly lowered the consumption of red and processed meat. Our results show that consumption of a mix of the average preferred fish species in Denmark or consumption of only fatty fish would be associated with the highest benefit in these amounts. In contrast, consuming only lean fish would be associated with a smaller health gain, and an overall health loss was estimated when consuming 350 g of tuna/week. By quantifying the health impact of adherence to dietary guidelines, our study provides evidence for national public health policy making.

Our results show that women in the fertile age are a particularly sensitive subgroup in the population when considering the health effects associated with fish consumption. Three out of eight health effects included in the RBA specifically concern this subgroup. Particularly the effects on fetal neurodevelopment (MeHg and whole fish consumption) contribute to the overall DALY difference in the various substitution scenarios compared to the reference scenario. The adverse effects on male fertility due to changes in prenatal dioxin and dl-PCB exposure resulting from the substitution appear to be insignificant and almost negligible. Maternal hypothyroidism has been associated with adverse effects on fetal neurodevelopment (Boas et al., 2006; Haddow et al., 1999; US EPA, 2012), which we did not account for in our model due to the lack of a clear dose-response relationship. Despite an increase in the mean exposure to dioxin and dl-PCBs in the alternative scenarios 1–2, our model estimated no extra cases of hypothyroidism in these scenarios, thus no increased dioxin-induced negative impact on neurodevelopment after substitution was anticipated.

The overall health impact of the substitutions we investigated was mainly attributed to the increased fish consumption and the change in fish species consumed, whereas the decrease in consumption of red and processed meat appeared to only explain a minor part of the total DALY difference (Table 4 and Fig. 2). As the guideline on limiting red and processed meat consumption to below 500 g/week was not met in more than half of the study population after substitution, this is not surprising. Likewise, a larger part of the health impact of the decrease in meat consumption was attributed to the decrease in red meat when compared to the decrease in processed meat consumption. Although processed meat is associated with increased risk of both non-cardia stomach cancer and CRC, and red meat is only associated with increased risk of CRC (and with a lower RR than processed meat (WCRF/AICR, 2011)), the larger decrease in consumption of red meat (mean change: 14.1 g/day) when compared to the decrease in consumption of processed meat (mean change: 2.8 g/day) showed a larger effect on the overall health impact of the substitution. Meanwhile, as mentioned in section 2.1. both fish and meat are important contributors to the intake of various micronutrients in the Danish diet. Thus, although only adverse health effects were included for consumption of red and processed meat in this study, we emphasize that this food group is also an important source of vitamins and minerals (Pedersen et al., 2015). However, another study investigated the impact on macro- and micronutrient intake when decreasing the consumption of red and processed meat and substituting with other foods, including fish, in the Nordic

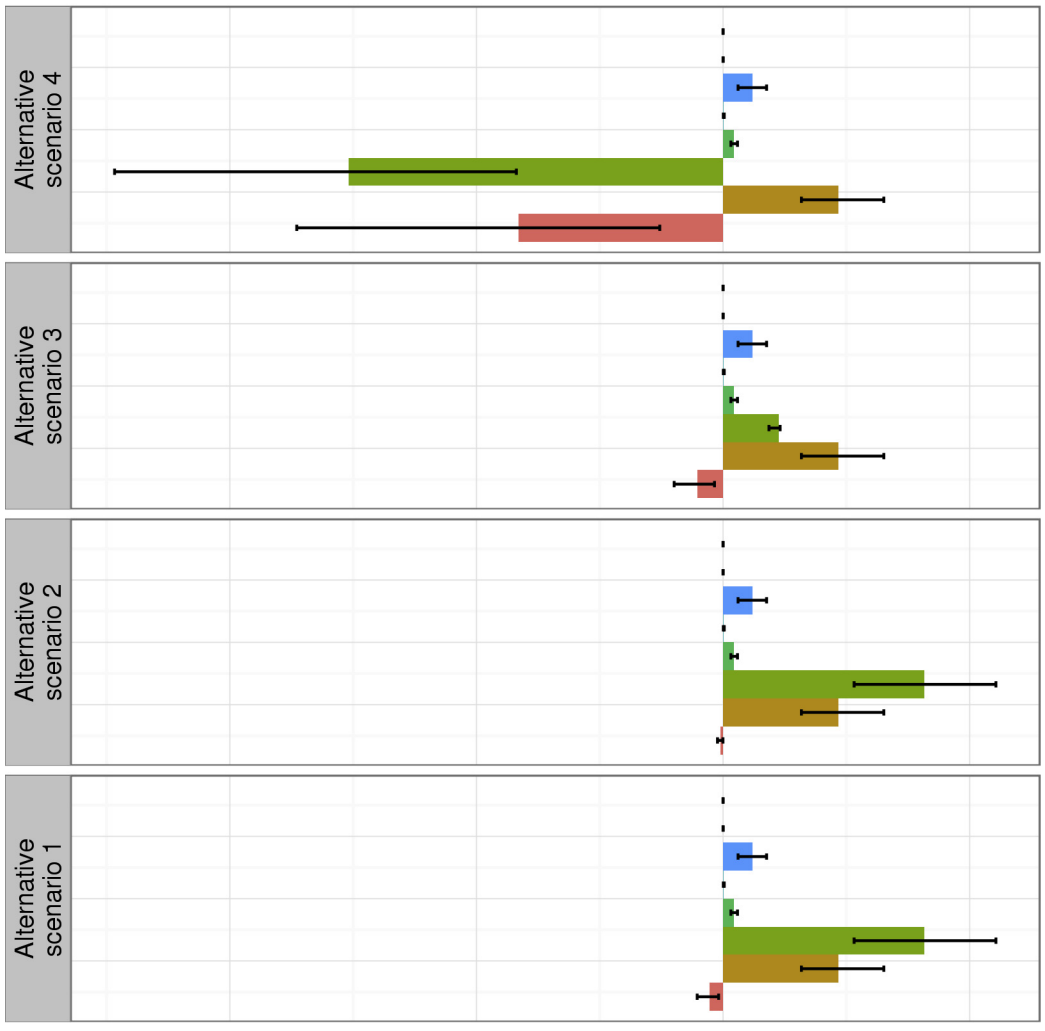

Fig. 2. Difference in Disability-Adjusted Life Years (DALYs) by scenario and outcome. Contribution of each health outcome to the overall DALY difference estimates for each alternative scenario for the total Danish adult population (≥ 15 years; 4.7 million individuals). Each bar represents the health impact of the substitutions on individual health effects. Error bars indicate 95% uncertainty intervals.
Abbreviations: CRC: colorectal cancer; DALY: disability-adjusted life years; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; DW: disability weight; EPA: eicosapentaenoic acid; MeHg: methyl mercury.

diet, and showed no marked changes in intake (Tetens et al., 2013b). It was noted that vitamin D and iron intakes were already below the recommendations in the Nordic countries, and did not change considerably due to the decrease in red and processed meat consumption.

The differences in the health impact between the four alternative scenarios are explained mainly by the ratio of fatty to lean fish. Fatty fish constituted approximately 50% of all fish consumed in the alternative scenario 1, 100% in the alternative scenario 2, and 0% in the alternative scenarios 3 and 4. The scenarios that considered a higher consumption of fatty fish led to a higher intake of the fatty acids, DHA and EPA, which are associated with a decreased risk of fatal CHD (Mozaffarian and Rimm, 2006). In addition, these scenarios also led to a lower exposure to MeHg (Table 3). This may be explained by the lower MeHg concentrations in the most frequently consumed fatty fish in Denmark compared to the most frequently consumed lean fish (see Table S5 and Table S8). Despite a higher consumption of fish in the alternative scenarios 3 and 4, the mean intake of DHA and EPA decreased compared to the current consumption due to the lower concentration of these fatty acids in lean fish. Thus, the overall health loss observed in the alternative scenario 4 cannot be attributed only to the higher exposure to MeHg (mean exposure: 0.36 μg/kg bw/day compared to 0.029 μg/kg bw/day in the reference scenario) and the associated adverse effects on fetal neurodevelopment but also particularly to a decreased intake of DHA and EPA in this scenario (mean intake: 152.26 mg/day compared to 408.99 mg/day in the reference scenario), leading to a higher incidence of fatal CHD. We note that the concentration data for DHA and EPA in tuna that we applied for the exposure modeling were only based on canned tuna (Table S2).

The studies behind the dose-response relationships used for modeling the beneficial effects of fish consumption described upper limits of fish consumption above which no further benefit was observed (FAO/WHO, 2011; Hibbeln et al., 2007; Mozaffarian and Rimm, 2006). Both limits (30.5 g of fish/day for beneficial neurodevelopmental effects and 250 mg DHA and EPA/day for fatal CHD prevention) correspond to approximately 200 g of fish/week, in the latter case exclusively fatty fish (Dietary Guidelines Advisory Committee, 2010). According to the Danish FBDG, around 200 g of the recommended 350 g of fish/week should be fatty (Tetens et al., 2013a). Our study was inconclusive in determining the increased benefit of consuming 350 g of fish/week relative to only 200 g of fatty fish/week. Such increase in benefit was expected to be primarily related to the increase in micronutrient intake (e.g. vitamin D) and a decreased consumption of red and processed meat. We did not quantify the effects of changes in micronutrient intake due to the substitutions, which could however have helped clarifying the size of the increased benefit.

To our knowledge, no quantitative RBAs of red and processed meat consumption have been conducted. The burden of disease of high consumption of red and processed meat has been estimated by the Global Burden of Disease Study (GBD, 2016 Risk Factor Collaborators, 2017; Lim et al., 2012) and was also recently addressed in a national Norwegian burden of disease study (Sælensminde et al., 2016). Both studies quantified the health loss due to the current consumption of red and processed meat compared to a theoretical minimum risk exposure level (14.3 g of red meat/day and 7.2 g of processed meat/day). Norwegian high red meat consumption only constituted a small fraction of the total burden of dietary risk factors (approximately 84 DALYs/100,000 per year) however, processed meat was estimated to be the fourth leading cause of diet-associated disease in Norway, causing approximately 400 DALYs/100,000 per year (Sælensminde et al., 2016). Other health effects than CRC were included in the study (ischemic heart disease, diabetes mellitus, and CRC, and not non-cardia stomach cancer for processed meat) and the burden of CRC due to consumption of red and processed meat only constituted approximately 40 DALYs/100,000 per year and 46 DALYs/100,000 per year, respectively. Meanwhile, differences in e.g. definition of consumption scenarios, disease model, incidence, and mortality make it difficult to make a valid comparison between these results and ours. Had we included the same health effects as in the above mentioned studies, we may have had estimated a larger impact of the substitution of red and processed meat. However, we did not find the evidence strong enough for inclusion in our study.

The risks and benefits associated with fish consumption have been extensively studied over the past decade (Becker et al., 2007; Berjia et al., 2012; Cohen et al., 2005; Domingo, 2016; EFSA Scientific Committee, 2015; FAO/WHO, 2011; FDA, 2014; Gao et al., 2015; Hellberg et al., 2012; Hoekstra et al., 2013; Hsi et al., 2016; Jacobs et al., 2017; Persson et al., 2018; Sirot et al., 2012; van der Voet et al., 2007; VKM, 2014; Zeilmaker et al., 2013). All RBAs of fish have reached conclusions coherent with the outcome of our RBA, estimating that nutritional benefits generally outweighed the toxicological risks of fish consumption in the general population at moderate intakes and when exposures to contaminants were low. Hoekstra et al. reached similar overall results when investigating the impact of increasing the Dutch fish consumption to 200 g and 500 g/week (Hoekstra et al., 2013). Hoekstra and colleagues also accounted for variability in the final DALY difference and found that, on average, (young) Dutch women experience a smaller benefit of the increase in fish consumption compared to Dutch men, primarily due to health loss of unborn children. Van der Voet et al. also accounted for variability in an RBA of substituting a fraction of Dutch red meat consumption with fish by estimating individual probabilities of being below the Dutch AI of DHA and EPA (0.45 g/day) and above the tolerable daily intake for dioxin (2 pg/kg bw/day) (van der Voet et al., 2007). By simultaneously modeling the probabilities of transgressing these limits, they found a substitution of 25% of red meat with either salmon or a mix of fatty fish to be the most optimal scenario.

In an RBA of fish, Zeilmaker et al. found great variation in the risk-benefit balance among 33 fish species. This study focused on neurodevelopmental effects in unborn children attributed to maternal fish consumption and found an overall adverse effect of maternal fish consumption for the majority of the fish species considered (Zeilmaker et al., 2013). Zeilmaker and colleagues based their dose-response model describing beneficial neurodevelopmental effects of fish consumption on the maternal intake of DHA. However, according to the EFSA NDA panel, the beneficial neurodevelopmental effects of fish consumption during pregnancy cannot be solely attributed to this fatty acid (EFSA NDA Panel, 2014). By basing our model on maternal fish consumption, we also covered the beneficial neurodevelopmental effects of other nutrients in fish such as iodine (EFSA NDA Panel, 2014). This may explain why the adverse effects of MeHg on neurodevelopment outweighed the beneficial effects of maternal fish consumption in the RBA by Zeilmaker et al., but not in our study, except when consuming large predatory fish species in high quantities. Furthermore, the beneficial effect of fish consumption on neurodevelopment observed in our RBA is likely an underestimate of the true beneficial effect, as the dose-response relation we applied was not adjusted for maternal MeHg exposure (exposure assumed equal to the mean exposure in the British population of 0.05 μg/kw/day) (FDA, 2014; Hibbeln et al., 2007). However, results from an American observational cohort showed that increased maternal fish intake was associated with a higher beneficial effect in the child when adjusting for maternal MeHg exposure (Oken et al., 2008b). The same study showed that the association between MeHg exposure and adverse neurodevelopmental effects were strengthened when adjusting for maternal fish intake. To be able to investigate potential limitations of increasing consumption of various types of fish with varying MeHg concentrations with a certain safety margin, we chose to apply a conservative approach and model both the non-MeHg adjusted beneficial effects of fish consumption and the adverse effects of MeHg exposure. Even though we may overestimate the adverse effects of MeHg, our model supports the findings from other cohort studies, including a Danish birth cohort that found an overall beneficial effect of maternal fish consumption on fetal

neurodevelopment when exposures to MeHg are low (Oken et al., 2005, 2008b; 2008a). However, our study adds insight in terms of the potential consequences of changing preferences towards large predatory fish species such as tuna. The monitoring data used in this study clearly showed that the concentration of MeHg in tuna was particularly higher than other (smaller) predatory fish species consumed in Denmark with around a 10-fold higher MeHg concentration (Table S5). While tuna showed a concentration of 0.31 μg MeHg/g fresh weight, fish such as cod, pollock, mackerel, Greenland halibut, flounder, and eel had concentrations in the range 0.052–0.072 μg/g fresh weight. WHO

Table 6
Unquantified sources of uncertainty of the final DALY difference estimates. Abbreviations: bw: body weight; CRC: colorectal cancer; DALY: disability-adjusted life year; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; DW: disability weight; EPA: eicosapentaenoic acid; IQ: intelligence quotient; RBA: risk-benefit assessment; RR: relative risk.

	Source of uncertainty	Impact
Health outcome	Identification of relevant compounds	There may be other compounds with adverse/beneficial effects present in fish and red and processed meat that have not been accounted for in this RBA.
	Identification of relevant health effects	There may be other health effects associated with consumption of fish and red and processed meat which was not included in this RBA.
	Identification of relevant subgroups	There may be other relevant subgroups in relation to the health effects considered in this RBA.
Exposure assessment	Uncertainty in consumption data	Over- or under-estimation of consumption. We did not exclude under- and over-reporters in the dietary survey. In addition, we did not adjust for within-individual variability in consumption which may cause overestimation of upper and lower tails of distributions of consumption amounts.
	Uncertainty in concentration data	There may be large uncertainty associated with measuring nutrient and contaminant concentrations in food. In addition, food processing was not accounted for in our exposure assessment.
	Uncertainty in substitution model	The established substitution factors are associated with uncertainty which causes uncertainty in the exposure assessment in the alternative scenarios and around the final DALY difference estimate.
	Choice of model to describe exposure distributions	May over- or under-estimate exposures.
	Uncertainty in measured bw	We applied measured (non self-reported) bw data and uncertainty would therefore primarily be associated with the scale used in the dietary survey.
Health impact characterization	Choice of dose-response modeling of animal data	Uncertainty is associated with the fitted dose-response model to describe dioxin and dl-PCB induced health effects which may lead to uncertainty around the dose estimated to cause an adverse effect in rats.
	Interspecies extrapolation	We did not quantify the uncertainty associated with extrapolation factors applied to convert dioxin and dl-PCB effect doses in animal to humans; however, the uncertainty may be large.
	Intraspecies extrapolation	We did not quantify the uncertainty associated with extrapolation factors applied to account for within species variability in sensitivity to dioxin and dl-PCBs.
	Choice of critical effect size for dioxin-induced health effects	Large uncertainty is associated with establishing a single estimate of a critical effect size used for dioxin dose-response modelling, leading to additional uncertainty around the critical effect dose for dioxin-induced health effects. We most likely overestimated the risks.
	Choice of distributions to describe uncertainty around critical effect dose for dioxin-induced health effects	Uncertainty is associated with the assumptions on the PERT distribution being suitable to describe the uncertainty around the critical effect dose for dioxin-induced health effects.
	RR estimates based on epidemiological observational studies	The RR estimates describing the association between food consumption and disease, derived from observational studies, may already be based on underlying food substitutions. This causes uncertainty around the overall health impact of the substitution.
	Dose-response models based on epidemiological data	Large uncertainty is associated with the assumption on linearity of the RR dose-response relations applied. Furthermore, upper limits of dose-response relations (fish and IQ; DHA + EPA and fatal CHD) are very uncertain as well and likewise it is uncertain if there may be upper/lower limits for the other RR dose-response models applied above/below which there is no effect. We most likely underestimated the benefits associated with the substitution.
DALY estimation	Choice of distributions to describe uncertainty around DWs	Uncertainty is associated with the assumptions on the PERT distribution being suitable to describe the uncertainty around the DWs.
	Choice of onset and duration of disease	Large uncertainty associated with the assumptions on onset and duration of disease which may lead to either over- or under-estimation of the final DALY estimates. Likewise, we assumed no time-lag from exposure to disease which is also associated with great uncertainty. In contrast to all other health effects considered, for the dioxin-induced health effects we applied lifetime probabilities and not annual probabilities of disease, causing an overestimation of the risks associated with dioxin exposure.
	Overlapping cases of disease/co-morbidity	We did not account for the fact that cases of disease may count double in the DALY estimates, e.g. cases of CRC and non-cardia stomach cancer attributed a high processed meat consumption which impacts both. However, it unlikely that an individual will be diagnosed with both cancer types within the same year. We expect this to cause an over-estimation of the disease incidences causing an over-estimation of the final DALY estimates for each scenario (reference and alternative scenarios) which may impact the final DALY difference estimate as well.
Overall evaluation of unquantified uncertainty		In general, we applied a conservative approach when making assumptions favoring especially toxicological risks associated with consumption of fish. However, uncertainties around e.g. unidentified compounds or health effects may as well cause an underestimation of risks.

particularly highlighted shark, king mackerel, and swordfish, in addition to tuna as large predatory fish which may have high concentrations of MeHg (WHO, 2008). Data on consumption of these fish species were not given in DANSDA, indicating a low intake in Denmark, and thus leaving tuna as the main concern for the Danish population.

In line with our findings, a recent risk assessment of MeHg exposure from fish consumption in five European countries found that frequent consumption of large predatory fish species, and in particular consumption of tuna, poses a potential risk of exceeding the TWI for MeHg (Jacobs et al., 2017). The authors recommended substituting large predatory and lean fish species with small fatty fish to increase benefits and decrease risks associated with fish consumption, coherent with the overall message of our RBA. Though others have stressed the risks of increasing the consumption of fatty fish species due to higher concentrations of dioxins and dl-PCBs (Sioen et al., 2008), we did not estimate an increased risk of dioxin-associated health effects when consuming 350 g of fatty fish/week compared to the current fish consumption.

Our substitution model was based on deterministic approaches, assuming that all individuals would substitute in the same manner. Thus, our model did not take variability in the substitution or in fish and meat preferences into account apart from individual baseline consumption. However, the Danish population may be very heterogeneous in the behavior concerning food substitution and in addition may also vary in what foods to substitute. The data, assumptions and models applied in this RBA all contribute to the uncertainty in the overall health impact of the substitutions we investigated. We were able to quantify some but not all of this uncertainty. Table 6 lists the sources of unquantified uncertainty in our study and explains the potential impact on the final results. We generally applied a conservative approach and overestimated especially toxicological risks. Still, the impact and direction of other sources of uncertainties are difficult to characterize.

5. Conclusions

In conclusion, our findings support the recommendations on increasing consumption of fish while decreasing consumption of red and processed meat in the Danish population. We considered the health effects associated with consumption of fish, red and processed meat and with exposure to contaminants and two fatty acids in these foods. We found that up to approximately 7000 healthy life-years could be gained each year in Denmark if all adult individuals increased the consumption of fish to 350 g/week and at the same time decreased the consumption of red and processed meat. The largest benefit was estimated when at least half of the total amount of fish consumed was fatty. Our study also showed that especially women who plan to become pregnant in the near future should limit the consumption of large predatory fish species such as tuna. However, it is important to stress that our findings show that this subgroup should not limit the consumption of small and fatty fish species to below 200–350 g/week, as the beneficial effects appear to outweigh the adverse effects of MeHg and dioxins at these amounts.

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Appendix A. Supplementary data

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Transparency document

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