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Quantitative risk–benefit assessment of Portuguese fish and other seafood species consumption scenarios

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Abstract

Portugal has high fish/seafood consumption, which may have both risks and benefits. This study aims to quantify the net health impact of hypothetical scenarios of fish/seafood consumption in the Portuguese population using a risk–benefit assessment methodology. Consumption data from the National Food, Nutrition and Physical Activity Survey 2015–2016 (*n* 5811) were used to estimate the mean exposure to methylmercury and EPA + DHA in the current and the alternative scenarios considered. Alternative scenarios (alt) were modelled using probabilistic approaches to reflect substitutions from the current consumption in the type of fish/seafood (alt1: excluding predatory fishes; alt2: including only methylmercury low-level fishes) or in the frequency of weekly fish/seafood consumption (alt3 to alt6: 1, 3, 5 or 7 times a week, replacing fish/seafood meals with meat or others). The overall health impact of these scenarios was quantified using disability-adjusted life years (DALY). In the Portuguese population, about 11 450 DALY could be prevented each year if the fish/seafood consumption increased to a daily basis. However, such a scenario would result in 1398 extra DALY considering the consumption by pregnant women and the respective risk on fetal neurodevelopment. Our findings support a recommendation to increase fish/seafood consumption up to 7 times/week. However, for pregnant women and children, special considerations must be proposed to avoid potential risks on fetal neurodevelopment due to methylmercury exposure.

Key words: Fish/Seafood: Methylmercury: EPA: DHA: Disability-Adjusted Life Years: Dietary recommendations

Portugal has high fish and seafood consumption, and it is among the European countries with the highest intake of fishery and aquaculture products[1,2]. Fish/seafood is nutrient-dense foods, rich in high biological value proteins, *n*-3 long-chain PUFA (LCPUFA) and micronutrients such as iodine, Se and vitamins A and D, but are also a source of contaminants, such as methylmercury (MeHg). Thus, fish/seafood consumption is commonly associated with both benefits and risks concerning human health[3–9].

There is convincing evidence for an effect of *n*-3 LCPUFA from fish/seafood on the reduction of CHD mortality[4,5,10] and the neurodevelopment improvement in infants and young

Abbreviations: DALY, disability-adjusted life year; EFSA, European Food Safety Authority; LCPUFA, n-3 long-chain PUFA; MeHg, methylmercury; RBA, risk–benefit assessment; TWI, tolerable weekly intake.

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children derived from mother's fish consumption during pregnancy[5,10]. Other benefits have also been suggested to be associated with fish consumption, namely, a probable effect on stroke incidence, a possible effect on depression and some, although insufficient, evidence concerning the incidence of some cancers[5].

On the contrary, exposure to MeHg during pregnancy is associated with adverse neurodevelopmental outcomes in infants and young children, since MeHg crosses the placental and blood-brain barriers, causing oxidative damage to the developing fetal central nervous system[11–13]. Convincing evidence from epidemiological studies supports the deleterious effect of MeHg exposure during pregnancy on neurodevelopment and has been used to establish tolerable exposure levels[13]. Thus, several European countries have advised pregnant women to balance their weekly fish intake and to avoid eating large predatory and older fishes, which typically have higher levels of MeHg occurrence[6].

Prior quantitative evidence suggests that the benefits of increasing fish consumption outweigh the risks[3–5,10,14–18]; however, those studies are usually performed in populations where fish consumption is low, contrasting with the Portuguese reality.

Considering the broad variety of contaminants' levels within and between fish/seafood species and the consumption variability in different countries, European Food Safety Authority (EFSA) recommends that each country considers its pattern of fish/seafood consumption, especially the species consumed, and carefully assess the risk of exceeding the tolerable weekly intake (TWI) of methylmercury while obtaining the health benefits from consuming fish/seafood[6].

Thus, this study aims to quantify the health impact of different fish/seafood consumption scenarios on a high fish consumption population through a quantitative risk–benefit assessment (RBA) of several scenarios of fish consumption, combining the selected effects into a composite metric, the disability-adjusted life years (DALY). Furthermore, this study aims to evaluate and characterise the exposure to the hazardous MeHg and beneficial n-3 LCPUFA, namely EPA and DHA, in the Portuguese population using national representative consumption data from the Portuguese National Food and Physical Activity Survey (IAN-AF 2015–2016)[19,20]. Finally, the conclusions of this assessment will be considered to tailor Portuguese consumption advice for ffish/seafood consumption, as a major risk management instrument for fully achieving its beneficial effects whilst limiting the risks of mercury toxicity.

Methods

Study population

For this study, we used data from the IAN-AF 2015–2016 survey. Briefly, IAN-AF 2015–2016 is a national survey of the non-institutionalised Portuguese general population. It is composed of a sample of 5811 individuals from 3 months to 84 years of age that completed two dietary assessments. The sampling frame used to select the participants in this survey was the Portuguese National Health Registry, and the selection was performed by multistage sampling stratified by the seven Statistical Geographic Units of Portugal (NUTS II). Additionally, the sample was weighed according to sex and age group (< 1 year, 1–2 years, 3–9 years, 10–17 years, 18–34 years, 35–64 years, 65–74 years and 75–84 years) to be representative of the Portuguese population. Further details of the IAN-AF 2015–2016 methodology are described elsewhere[19,20].

Data collection and dietary assessment

Two computer-assisted interviews were performed by trained dietitians using an electronic platform designed for the survey ('You eAT&Move'), to collect socio-demographic, health-related, food intake and physical activity data. Data collection procedures followed the European guidelines from the EU-Menu project, to be harmonised with other countries surveys[21].

Dietary assessment of children, aged under 10 years, was accomplished by two non-consecutive, one-day food diaries that were filled in by the main caregiver. Following this, a face-to-face interview was conducted with the caregivers to collect additional details in food description and quantification. For the remaining age groups, dietary intake was obtained by two non-consecutive 24-h recalls, applied in a face-to-face interview separated by 8–15 d.

Detailed information and quantification of foods, recipes and supplements reported by the participants were collected using a validated electronic assessment tool, the eAT24 software[22]. All foods reported by the participants were then categorised into food groups. Recipes were disaggregated into their components, and single food items were allocated to their respective food group.

Ethical standards

IAN-AF 2015–2016 was conducted according to the guidelines laid down in the Declaration of Helsinki and national legislation. All procedures involving human subjects were approved by the Portuguese National Commission for Data Protection and the Ethical Committee of the Institute of Public Health of the University of Porto. The participants were asked to provide their written informed consent and all documents with identification data were treated separately and stored in a different dataset.

Occurrence data of risk–benefit agents

National data on the occurrence of mercury (Hg) and MeHg in fish and seafood captured in Portuguese waters and marketed in Portugal (total n 1188 samples) were retrieved from the Portuguese National Sampling Plan[23] (n 693), carried out on an annual basis by the Portuguese Economic and Food Safety Authority (ASAE) and from databases of other Portuguese entities[8] (n 495). To avoid underestimating MeHg exposure, we used a conservative approach by assuming that 100 % of Hg in fish/seafood is in the form of MeHg. Whenever data were left-censored, we used a middle-bound approach, assuming half of the value of the limit of detection or the limit of quantification.

Regarding EPA and DHA, national data (n 126 samples) were available only for a small share of the fish/seafood species consumed, thus, we retrieved information for raw food items from the FAO/INFOODS Global Food Composition Database for

Fish and Shellfish Version 1·0[24] (n 134) and from the USDA National Nutrient Database for Standard Reference Legacy Release, April 2018 (n 3832)[25].

Occurrence data of MeHg, EPA and DHA were available for more than 90 % of fish/seafood species consumed by the Portuguese population. All the food items included in the occurrence datasets were classified with the FoodEx2 classification system.

Scenarios' definition

Six alternative scenarios of fish/seafood consumption were considered to compare the health risks and benefits with the current fish/seafood consumption, which is considered as the reference scenario. The characteristics of each scenario are described in detail in Table 1.

First, we considered two alternative scenarios where the amount and frequency of fish/seafood were equal to the reference scenario, changing only the type of fish consumed. Thus, in the first alternative scenario (alt1), the consumption of large predatory fish species (see Table 1) was replaced by other fish species. A second, more conservative, alternative scenario (alt2) was defined replacing the consumption of fish/seafood with MeHg levels > 0·25 mg/kg by species with MeHg levels ≤ 0·25 mg/kg (Table 1). All the replacements were implemented according to the probability of consumption of the fish/seafood species within the Portuguese population, according to sex, age group and geographic region.

Another set of scenarios (alt3 to alt6) were created to represent different weekly frequencies of fish/seafood consumption: alt3 – once a week; alt4 – three times/week; alt5 – five times/week; and alt6 – seven times/week. We considered that the majority of fish/seafood consumption occurs mostly at lunch or dinner, and, in the reference scenario, we categorised the meal types at lunch and dinner in three possible categories. The categories considered were 'Fish/Seafood' (i.e. if any item consumed in the meal was from the fish/seafood food group), 'Meat' (i.e. if any item consumed in the meal was from the meat food group) or 'Others' (i.e. if no meat nor fish items were consumed in the meal, this category included egg meals and vegetarian meals). If both meat and fish or seafood items were part of the meal, the classification was based on the food category present in greater amount. Hence, for each alternative scenario, we replaced entire meals with other types to achieve the target weekly frequency of fish/seafood consumption (Table 1). The type of meal to be selected was modelled using a time-homogeneous Markov multistate model[26], in which the ratio between 'Meat' meals and 'Others' meals was kept constant, regardless of the average weekly proportion of 'Fish/seafood' meals priorly defined for each scenario. Then, the content of each entire meal was imputed, at an individual and eating occasion level, based on the consumption of each meal type in the Portuguese population by sex, age group and geographic region.

All the statistical analyses described in this and throughout the following subsections were performed using R software version 3.4.1 for Windows[27]. All results are representative of the Portuguese population and were estimated using the library 'survey'[28] from R software.

Exposure assessment to risk–benefit agents

To assess the exposure to MeHg, EPA and DHA, individual two-day food consumption data from the IAN-AF 2015–2016 was matched to the occurrence data using the FoodEx2 classification hierarchy system. Different values of MeHg, EPA and DHA within the occurrence datasets were randomly assigned each time a food item was reported in IAN-AF survey to deal with variability observed in the occurrence data. The attribution process was as follows. If more than one occurrence value matched a single consumption occasion or FoodEx2 code, one value was randomly selected. On the contrary, if there was not a direct match to one specific consumption occasion, an occurrence value from the closest item was selected, using the FoodEx2 hierarchy. Regarding EPA and DHA, besides fish/seafood consumption occasions, we applied the previously described methodology for the remaining food groups. All analyses were performed at the ingredient level, considering its raw weight. The exposure was then aggregated by day, and the two-day average individual exposure was estimated. The estimated

Table 1. Fish/seafood consumption scenarios characterisation

Scenario	Changes in the frequency of fish/seafood	Changes in the fish/seafood species	Characteristics
Reference	–	–	Current fish/seafood consumption.
Alt1	No	Yes	Large predatory fishes excluded*
Alt2	No	Yes	Methylmercury low-level fish/seafood included†
Alt3	Yes	No	Fish/seafood meal consumption once a week Average weekly proportion of fish/seafood meals = 1/14‡
Alt4	Yes	No	Fish/seafood meal consumption 3 times per week Average weekly proportion fish/seafood meals = 3/14‡
Alt5	Yes	No	Fish/seafood meal consumption 5 times per week Average weekly proportion of fish/seafood meals = 5/14‡
Alt6	Yes	No	Fish/seafood meal consumption once a day Average weekly proportion of fish/seafood meals = 7/14‡

* Large predatory fishes considered: fresh tuna, rays, sharks, swordfish, scabbard fishes.
† Methylmercury low-level fishes: anchovies, Atlantic mackerel, cod, meagre, forkbeard, hake, horse-mackerel, monkfish, perch, pollock, pouting, rays, red mullet, salmon, sardines, Gilthead seabream, European seabass, sole, octopus, squid, mussels, clams, cockle, oyster, shrimp, lobster, crab, canned tuna, canned sardines, canned mackerel.
‡ Two daily meals considered, lunch and dinner, which results in fourteen meals per week.

population exposure was expressed as the mean daily intake for EPA and DHA and as the mean weekly exposure per kg of body weight (bw) for MeHg. Additionally, it was estimated the prevalence of the population at risk due to MeHg exposure, i.e. the percentage of the population that exceeded the TWI of 1·3 μg/kg bw[13].

This imputation process was repeated 10 times for each scenario and results were combined using Rubin's rules[29].

Health effects and disability-adjusted life year calculations

Identification and selection of health effects. To estimate the health impact of the scenarios, we first reviewed official assessments from the European Food Safety Authority (EFSA) and other institutions[5,10,13,30] to identify the most relevant effects associated with fish/seafood, its components, and meat, as the scenarios alt3-alt6 also reflect changes in meat consumption due to substitutions. Then, the health effects (HE) to be included in this RBA were selected based on the degree of evidence on the associations with the foods and components under study. The associations that were graded as convincing in the official reports were included. Finally, the measures of association to be used (Dose-Response/RR) were collected from the literature. Table 2 presents the selected HE, the population group in which the RBA was performed, and the dose-response approach applied.

Quantification of scenarios health impact: DALY estimate. To quantify the health impact of the scenarios, we estimated the burden of disease using DALY for each HE, as expressed in the following equation:

$$\mathrm{DALY_{HE}} = \mathrm{YLD_{HE}} + \mathrm{YLL_{HE}}.$$

YLD stands for years of life lived with disability, calculated as

$$\mathrm{YLD_{HE}} = I_{HE} \times \mathrm{DW_{HE}} \times L_{HE},$$

where I is the annual incidence of the HE in the population, DW is the disability weight for the HE and L is the average duration of the HE until remission or death, in years. A DW represents the magnitude of health loss associated with the outcome and in this paper DWs were derived from the ones computed by the Global Burden of Disease 2017 study (GBD 2017)[34].

YLL stands for years of life lost due to the HE under study and is calculated as

$$\mathrm{YLL_{HE}} = N_{HE} \times RLE,$$

where N is the annual number of deaths associated with the HE and RLE is the remaining life expectancy at the age of death, in years.

DALY for the reference scenario and their respective 95 % confidence interval (CI) were estimated considering the current values of incidence and mortality for the HE in the Portuguese population, assuming that it reflects the current intake of MeHg, EPA and DHA and red/processed meat. Depending on the available data, top-down and bottom-up approaches were applied to estimate the incidence and the mortality of the selected HEs considering the distributions of exposure to MeHg, EPA and DHA and red/processed meat in the different scenarios, as shown in Table 2. For the associations between the intake of EPA + DHA and Coronary Heart Disease (CHD) mortality, and the intake of red and processed meats and colorectal cancer incidence, top-down approaches were applied, since risk estimates (RR) from epidemiological studies were available. For the neurodevelopment outcome in offspring due to the maternal exposure to MeHg and DHA, where no risk estimates were available from the literature, a bottom-up approach was applied using dose-response models. The summary of the RR and dose-response inputs from the literature used is presented in Table 2, and the remaining data inputs used to calculate DALY for each health effect are given in the Appendix.

The difference in DALY between each alternative scenario and the reference scenario (ΔDALYalt), from all the HE, reflects the health impact of the change in the consumption of fish/seafood in each alternative scenario. If, a health loss is expected from the change in fish/seafood consumption. On the contrary, if , the change in fish/seafood consumption for the alternative scenario results in a populational health gain.

Table 2. Health effects associated with the selected foods and components and data inputs for the risk–benefit assessment

Food/Component	Health Effect	Population Subgroup	Risk–benefit Characterisation Approach	RR/Dose–Response
MeHg	Fetal neurodevelopment: decreased IQ due to maternal exposure[5,10,13]	Women at fertile age (15–49 years old)	Bottom-up	–8·5 (95 % CI: –19·5, –1·5) IQ points in offspring/μg MeHg/kg bw/d[31]
DHA	Fetal neurodevelopment: improved IQ due to maternal exposure[5,10]	Women at fertile age (15–49 years old)	Bottom-up	1·3 (95 % CI: 0·85, 1·74) IQ points in offspring/g DHA/d[18,31]
EPA + DHA	CHD mortality[4,5,10]	Adult population (>15 years old)	Top-down	RR_{CHD} = 0·86 (95 % CI: 0·79, 0·92)/100 mg/d (up to an intake of 250 mg/d)[4]
Meat	Colorectal cancer (CRC)[30,32]	Adult population (>15 years old)	Top-down	Red meat: RR_{CRCred} = 1·17 (95 % CI: 1·05, 1·31)/100 g/d. Processed meat: $RR_{CRCproc}$ = 1·18 (95 % CI: 1·10, 1·28)/50 g/d[33]

MeHg, methylmercury; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

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

Bottom-up approach: methylmercury and DHA v. *fetal neurodevelopment.* To assess the effect of maternal exposure to MeHg and DHA on foetal neurodevelopment, we used cognitive impairment as the outcome, measured by the intelligence quotient (IQ). According to IQ definition, we assumed that, in the reference scenario, the Portuguese population IQ follows a normal distribution, with a mean of 100 and a standard deviation of 15, reflecting the current fish/seafood consumption. In the alternative scenarios, the respective changes in the fish/seafood consumption by the mothers will impact children's IQ, according to the dose-response functions used[18,31], causing a shift in the IQ distribution curve across the population of new-born children.

Different IQ values reflect different levels of disability according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[35] and the 10th revision of the International Classification of Diseases (ICD-10)[36]. The five classes of cognitive impairment considered are borderline intellectual functioning (IQ: 70–84), mild intellectual disability (ID) (IQ: 50–69), moderate ID (IQ: 35–49), severe ID (IQ: 20–34) and profound ID (IQ: <20), with each class reflecting a specific DW according to GBD 2017[34] (see online supplementary material, Supplemental Table S5).

To estimate $DALY_{IQ}$ we considered that no increased mortality is expected from this outcome, thus, $YLL_{IQ} = 0$ and also no recovery is expected for a child with a low IQ level, thus the duration of the outcome (L_{IQ}) would be equal to Portuguese life expectancy at birth (80·8 years)[37]. YLL_{IQ}, DWs for the classes and the duration of the effect are equal for all scenarios, thus, the difference in DALY between scenarios depends on the different incidences of each cognitive impairment class in the scenarios. To estimate the number of children within each class of impairment, we combined information of the fertility rates of the Portuguese women by age group[38] (see online supplementary material, Supplemental Table S1) and the number of women at fertile age at each age group[39] (see online supplementary material, Supplemental Table S1), with the probability of impairment, given by the IQ distributions from each scenario.

Uncertainty in dose-response functions and DWs was described as PERT distributions and variability in the exposure to MeHg and DHA for each scenario as Gamma distributions. Second-order Monte Carlo simulation was used for DALY calculations with 1000 simulations for variability and 1000 iterations for uncertainty.

Top-down approach: EPA + DHA v. coronary heart disease mortality (CHD) and Red/Processed Meat v. colorectal cancer (CRC). Regarding the top-down approaches, to account for EPA + DHA and red/processed meat intake variability, we divided the respective distributions into quartiles with each quartile representing an intake class (1–4). The intake of each class was set as the median value within each class. The RR for the effects (Table 2) was used to estimate a RR for each class, assuming a RR of 1 at zero consumption and a log-linear association between exposure and RR[40]. Thus, the log-linear slope, β, and the RR for each class, $j \in \{1,2,3,4\}$, in each scenario, $i \in \{1,2,3,4,5\}$, were calculated according to the following equations:

$$\beta = \frac{\ln RR_{literature}}{Dose}$$

$$RR_i = \exp(\beta \cdot exposure_i)$$

To measure the fraction of DALY due to CHD and colorectal cancer (CRC) that could be altered by a given change in the intake of EPA + DHA and red and processed meat, respectively, the Potential Impact Fraction (PIF) was calculated. PIF was calculated for each alternative scenario by the RR shift methodology[41] which assumes that the interventions are described by a change in the RR of the categories while keeping the proportion in each category constant:

$$PIF = \frac{\sum_{j=1}^{4} RR_{alt} - \sum_{j=1}^{4} RR_{ref}}{\sum_{j=1}^{4} RR_{ref}},$$

where RR_{ref} is the relative risk in the reference scenario and RR_{alt} is the relative risk in each alternative scenario.

To estimate DALY due to CHD deaths in the reference scenario, it was assumed immediate death, thus, $YLD_{CHD} = 0$. Regarding YLL_{CHD} estimate, we used CHD mortality rate in Portuguese population by age group[42] and the number of individuals in each age group[39] (see online supplementary material, Supplemental Table S2) to estimate the number of deaths, and the life-expectancy for the mean age in each age group to estimate *RLE*[37] (see online supplementary material, Supplemental Table S4).

Concerning CRC, the DALY in the reference scenario were estimated using a three-stage model based on the methodological framework proposed by Soerjomataram *et al.*[43], illustrated in Fig. 1, and we assumed that all incident cases pass through a phase of diagnostic and treatment (p_1). Incidence and mortality of CRC in the Portuguese population, for both sexes and several age groups, were retrieved from IARC[44–46] (see online supplementary material, Supplemental Table S3), DWs for the several stages of CRC were retrieved from GBD 2017 study[34] (see online supplementary material, Supplemental Table S5), the average duration of each stage was obtained in the cancer DALY framework study[43] (see online supplementary material, Supplemental Table S6) and the remaining life expectancy in the case of death (*RLE*) was estimated for the mean age at each age group considering the life expectancy for that age in the Portuguese population[37] (see online supplementary material, Supplemental Table S4). Regarding long-term sequelae, we considered that 13 % of CRC survivors will live until death with a stoma, according to what was described by Soerjomataram *et al.*[43].

We calculated the annual DALY change due to the differences in the intake of EPA + DHA and red and processed meat in the alternative scenarios by multiplying the estimated PIFs for each health effect in each alternative scenario by the DALY values previously calculated for the reference scenario. Uncertainty in RR values and DWs was described as PERT

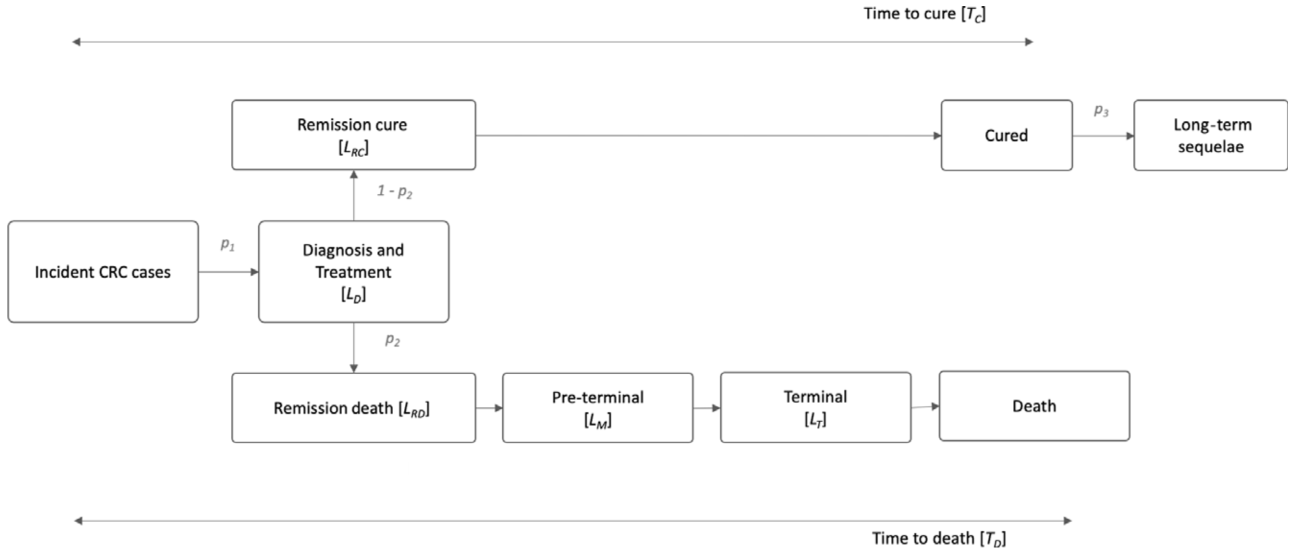

Fig. 1. Three-stage natural history for colorectal cancer (CRC), based on Soerjomataram et al. (2012). L_D: duration of diagnosis and treatment; L_R: duration of remission; L_M: duration of preterminal/metastatic phase; L_T: duration of terminal phase; p_1: incidence of CRC; p_2: case fatality of CRC; p_3: probability of long-term sequelae; Tc=7 years and T_D = 1·6 years.

distributions, and Monte Carlo simulation was used for DALY calculations with 1000 iterations. The DALY estimation is represented by the median and the 95 % CI for uncertainty.

Results

Exposure to risk–benefit assessment agents

Methylmercury. The average MeHg concentration of fish and other seafood samples considered in this study was 0·25 mg/kg (range: 0·00–4·40 mg/kg; median: 0·06 mg/kg). The distribution of MeHg concentrations observed in the different species is presented in Supplemental Fig. S1 (Appendix).

Results on the weekly exposure to MeHg from fish/seafood consumption in the various scenarios are presented in Table 3. The current mean weekly exposure to MeHg is 0·65 µg/kg bw for the Portuguese general population, increasing significantly in children up to 5-years-old. These values are associated with a prevalence of exposure above the TWI of 13·7 % (95 % CI: 12·0, 15·4) for the general population (Table 4), being higher among young children from 2–5 years of age (36·6 %, 95 % CI: 26·9, 46·3). The exposure in the reference scenario represents an average frequency of consumption between 3–5 times/week.

Replacing certain fish species by species with lower MeHg levels (scenarios alt1 and alt2) does not considerably lower the prevalence of exposure higher than the TWI, considering the general population or the different age groups. However, at the regional level, the Madeira region would benefit from the fish species replacement, decreasing the prevalence of exposure above the TWI from 19·6 % (95 % CI: 16·2, 23·0) in the reference scenario to 10·0 % in alt1 (95 % CI: 7·6, 12·3) or 10·3 % (95 % CI: 8·0, 12·5) in alt2 (Table 4). As expected, by reducing the number of fish/seafood consumption occasions to once a week (alt3 scenario), the prevalence of exposure above the TWI decreases to 4·0 % (95 % CI: 3·3, 4·6) in the general population. On the other hand, in the alt5 and alt6 scenarios, the prevalence of population with exposure levels above the TWI increases.

EPA + DHA. The average concentration of EPA + DHA in the fish and other seafood samples used in this study was 0·70 g/100 g (range: 0·00–7·87 g/100 g; median: 0·33 g/100 g). The distribution of EPA + DHA concentrations observed in the different species is presented in Supplemental Fig. S1 (Appendix). Regarding the other food groups, the average concentration of these fatty acids observed was close to 0 g/100 g.

The current mean daily intake of EPA + DHA is 372 mg (95 % CI: 338, 406) for the general Portuguese population (Table 3), which is higher than the value of Adequate Intake (AI), defined for these nutrients (250 mg/d). Replacing fish/seafood consumed with lower MeHg contaminated species (alt2 scenario) slightly increases the mean daily intake of *n*-3 LCPUFA.

Considering the change in the frequency of fish/seafood consumption (scenarios alt3-alt6), consuming it only once a week would significantly decrease mean EPA + DHA intake to an average level lower than the AI. This level would increase when consuming fish/seafood 5 or 7 times a week (Table 3).

Health effects and DALY calculations

Table 5 presents the results of ΔDALY estimates for the alternative scenarios by HE. The scenario that represented a higher change in the burden of disease is the one that represents an average frequency of fish/seafood intake of seven times per week, with an estimated average of 11 445 healthy years saved in one year within the Portuguese population. Additionally, increasing fish consumption to a weekly average of 5 times would also result in an estimated health gain of 5361 healthy years saved per year. The greatest health gain is expected due to the intake of EPA + DHA and decreased risk of CHD mortality. On the contrary, decreasing fish consumption (alt3 and alt4)

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Table 3. Mean exposure to methylmercury (MeHg) (μg/kg bw/week) and EPA + DHA (mg/d) in the Portuguese population for the fish/seafood consumption scenarios and respective 95 % confidence interval (95 % CI)
(Mean values and 95 % confidence intervals)

	Fish/seafood consumption scenarios*													
	Reference		Alt1		Alt2		Alt3		Alt4		Alt5		Alt6	
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI
MeHg (μg/kg bw/week)														
Total	0·65	0·59, 0·70	0·54	0·49, 0·58	0·52	0·48, 0·56	0·19	0·17, 0·22	0·58	0·51, 0·65	0·94	0·86, 1·03	1·36	1·25, 1·47
Women at fertile age (15, 49 years old)	0·58	0·50, 0·67	0·46	0·39, 0·53	0·46	0·39, 0·52	0·15	0·11, 0·19	0·53	0·42, 0·63	0·85	0·71, 0·98	1·29	1·07, 1·51
By age group														
Children (<2 years old)	1·36	1·01, 1·70	1·11	0·81, 1·41	1·09	0·76, 1·43	0·41	0·23, 0·59	1·28	0·94, 1·62	1·92	1·49, 2·36	3·02	2·14, 3·89
Children (2–5 years old)	1·62	1·12, 2·11	1·33	0·94, 1·71	1·38	1·00, 1·76	0·42	0·14, 0·70	1·20	0·77, 1·63	2·06	1·43, 2·69	2·53	1·92, 3·14
Children (6–9 years old)	0·99	0·67, 1·31	0·81	0·60, 1·01	0·87	0·63, 1·11	0·3	0·17, 0·43	0·84	0·52, 1·16	1·29	0·98, 1·59	2·00	1·40, 2·60
Adolescents (10–17 years old)	0·56	0·42, 0·70	0·49	0·36, 0·62	0·50	0·37, 0·63	0·21	0·12, 0·29	0·59	0·43, 0·75	1·00	0·79, 1·20	1·35	1·11, 1·60
Adults (18–64 years old)	0·61	0·54, 0·67	0·49	0·44, 0·54	0·48	0·43, 0·52	0·18	0·15, 0·22	0·53	0·46, 0·61	0·91	0·81, 1·00	1·31	1·17, 1·45
Elderly (≥65 years old)	0·59	0·44, 0·73	0·52	0·37, 0·66	0·47	0·37, 0·56	0·16	0·10, 0·21	0·55	0·33, 0·77	0·74	0·49, 0·99	1·15	0·88, 1·43
By Portuguese region														
North	0·57	0·47, 0·66	0·53	0·44, 0·63	0·51	0·44, 0·58	0·19	0·14, 0·24	0·55	0·42, 0·67	0·94	0·78, 1·11	1·37	1·19, 1·56
Centre	0·66	0·55, 0·78	0·53	0·46, 0·61	0·54	0·46, 0·62	0·18	0·13, 0·23	0·58	0·47, 0·69	0·89	0·77, 1·02	1·29	1·13, 1·46
Lisbon and Tagus Valley	0·69	0·56, 0·82	0·54	0·45, 0·64	0·52	0·44, 0·60	0·19	0·12, 0·25	0·60	0·49, 0·71	0·96	0·82, 1·10	1·39	1·16, 1·62
Alentejo	0·68	0·55, 0·81	0·52	0·41, 0·64	0·52	0·42, 0·62	0·23	0·13, 0·33	0·61	0·46, 0·76	0·95	0·77, 1·13	1·35	1·11, 1·59
Algarve	0·76	0·55, 0·96	0·62	0·49, 0·76	0·59	0·45, 0·74	0·26	0·14, 0·38	0·61	0·48, 0·73	1·00	0·82, 1·18	1·40	1·16, 1·64
Madeira	0·94	0·81, 1·06	0·47	0·41, 0·54	0·48	0·41, 0·55	0·25	0·18, 0·32	0·66	0·58, 0·73	1·10	0·96, 1·24	1·51	1·34, 1·68
Azores	0·62	0·46, 0·78	0·52	0·41, 0·63	0·52	0·41, 0·64	0·17	0·12, 0·23	0·56	0·46, 0·67	0·86	0·63, 1·08	1·32	1·09, 1·55
EPA + DHA (mg/d)														
Total	372	338, 406	377	343, 410	396	361, 431	132	120, 143	314	287, 342	501	455, 546	680	629, 732
Women at fertile age (15–49 years old)	334	277, 391	338	281, 395	354	295, 413	111	92, 129	279	241, 317	453	397, 509	626	560, 692
By age group														
Children (<2 years old)	120	101, 139	121	102, 140	136	114, 158	71	57, 84	123	99, 146	164	138, 189	201	173, 228
Children (2–5 years old)	299	195, 404	303	200, 406	335	218, 451	118	45, 191	215	132, 297	319	227, 411	420	311, 529
Children (6–9 years old)	272	186, 358	275	188, 363	301	199, 403	109	71, 148	197	136, 258	309	241, 377	434	357, 512
Adolescents (10–17 years old)	264	203, 325	265	204, 326	281	218, 344	114	87, 142	234	188, 281	333	286, 380	453	391, 515
Adults (18–64 years old)	382	340, 424	386	344, 428	405	362, 448	137	123, 151	329	291, 367	538	476, 600	719	653, 784
Elderly (≥65 years old)	429	325, 533	435	331, 538	458	354, 562	129	98, 160	343	279, 407	519	427, 611	753	609, 897
By Portuguese region														
North	349	281, 416	349	282, 416	362	293, 431	121	102, 139	305	254, 355	481	408, 554	678	588, 768
Centre	387	326, 449	396	335, 456	419	358, 481	147	119, 175	342	288, 397	542	475, 610	719	635, 803
Lisbon and Tagus Valley	367	298, 436	372	302, 441	390	317, 463	127	105, 149	287	233, 340	475	363, 586	642	528, 756
Alentejo	424	320, 529	431	325, 536	454	346, 561	141	102, 179	359	306, 412	544	469, 619	696	593, 799
Algarve	525	399, 652	529	403, 655	573	449, 697	143	110, 177	369	298, 441	557	487, 627	743	677, 808
Madeira	297	251, 343	316	263, 370	348	282, 413	158	132, 183	333	236, 431	536	477, 596	708	601, 816
Azores	312	259, 366	314	262, 367	351	293, 409	130	109, 150	276	235, 317	447	396, 498	618	576, 659

* Alt1: predatory fishes excluded; Alt2: MeHg low-level fishes included; Alt3: fish/seafood meal consumption once a week; Alt4: fish or seafood meal consumption 3×/week; Alt5: fish or seafood meal consumption 5×/week; Alt6: Fish or Seafood meal consumption 7×/week.

Table 4. Prevalence of methylmercury (MeHg) exposure above the tolerable weekly intake (TWI) in the Portuguese population for the fish/seafood consumption scenarios and respective 95 % confidence interval (95 % CI)
(Mean values and 95 % confidence intervals)

	Fish/seafood consumption scenarios*													
	Reference		Alt1		Alt2		Alt3		Alt4		Alt5		Alt6	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Prevalence > TWI†														
Total	13·7	12·0, 15·4	11·4	9·8, 13·1	11·4	9·7, 13·0	4·0	3·3, 4·6	11·8	10·5, 13·1	19·2	17·8, 20·7	28·0	26·3, 29·8
Women at fertile age (15–49 yearsold)	12·7	9·4, 16·0	10·1	6·9, 13·4	10·0	7·0, 13·0	3·0	2·0, 4·0	10·6	8·3, 12·8	17·3	14·9, 19·7	26·9	23·6, 30·2
By age group														
Children (<2 yearsold)	27·8	21·3, 34·3	26·4	20·1, 32·7	25·5	19·0, 32·0	6·9	4·3, 9·5	20·9	16·7, 25·2	31·5	26·8, 36·2	42·9	37·9, 47·9
Children (2–5 years old)	36·6	26·9, 46·3	34·3	24·9, 43·8	35·9	25·3, 46·4	7·3	2·4, 12·2	23·1	17·1, 29·2	35·6	28·5, 42·7	44·5	36·9, 52
Children (6–9 years old)	22·7	14·8, 30·6	20·5	12·8, 28·2	22·4	14·5, 30·4	6·7	3·7, 9·8	17·1	11·1, 23·1	28·3	22·7, 34	37·8	31·8, 43·9
Adolescents (10–17 yearsold)	11·5	6·4, 16·6	10·2	5·1, 15·3	10·3	5·5, 15·1	4·6	2·9, 6·4	13·5	10·1, 16·8	22·3	18·4, 26·3	31·3	26·6, 36
Adults (18–64 years old)	12·9	11·0, 14·8	10·3	8·5, 12·2	10·2	8·4, 12·0	3·8	2·9, 4·7	11·1	9·6, 12·7	18·7	16·8, 20·6	27·7	25·7, 29·7
Elderly (≥65 years old)	11·6	7·3, 15·9	10·0	5·5, 14·4	9·5	5·3, 13·7	3·1	1·8, 4·4	10·1	7·1, 13·1	14·8	11·6, 18	22·6	18·7, 26·6
By Portuguese region														
North	12·2	9·0, 15·4	11·7	8·4, 15·1	11·4	8·5, 14·4	3·8	2·6, 5·0	11·1	9·0, 13·3	18·7	15·8, 21·5	27·7	24·9, 30·5
Centre	14·3	10·9, 17·6	11·5	8·4, 14·7	11·9	8·5, 15·3	3·6	2·5, 4·8	12·0	9·7, 14·2	18·9	16·2, 21·6	27·1	23, 31·2
Lisbon and Tagus Valley	14·1	9·6, 18·7	11·1	6·5, 15·8	10·5	6·5, 14·6	4·2	2·6, 5·8	11·9	9·1, 14·7	19·7	16·5, 22·9	28·8	24·9, 32·7
Alentejo	14·1	9·6, 18·7	11·1	6·5, 15·8	10·5	6·5, 14·6	4·6	2·8, 6·4	13·3	10·3, 16·2	20·5	16·5, 24·5	28·9	24·4, 33·3
Algarve	15·1	9·9, 20·4	12·7	8·1, 17·4	12·4	7·3, 17·6	4·8	2·8, 6·7	12·1	9·4, 14·8	20·9	17·6, 24·3	29·7	25·1, 34·4
Madeira	19·6	16·2, 23·0	10·0	7·6, 12·3	10·3	8·0, 12·5	4·7	2·9, 6·5	12·8	10·6, 15	21·6	18·3, 24·9	30·3	27·2, 33·4
Azores	12·9	9·7, 16·1	10·7	7·8, 13·6	10·6	7·9, 13·2	3·2	2·1, 4·4	11·4	8·7, 14·1	17·0	12·8, 21·1	25·6	21·9, 29·3

* Alt1: predatory fishes excluded; Alt2: MeHg low-level fishes included; Alt3: fish/seafood meal consumption once a week; Alt4: fish or seafood meal consumption 3×/week; Alt5: fish or seafood meal consumption 5×/week; Alt6: fish or seafood meal consumption 7×/week.
† TWI = 1·3 μg MeHg/kg bw/week.

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Table 5. Total and outcome specific disability adjusted life years difference (ΔDALY) in one year, in the Portuguese population, for each alternative scenario compared with the reference scenario (Mean values and 95 % confidence intervals)

	Fish/seafood consumption scenarios*											
	Alt1		Alt2		Alt3		Alt4		Alt5		Alt6	
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI
ΔDALY HE												
CHD mortality	−124	−257, 9	−730	−1475, 14	12 577	11 941, 13 212	2009	1083, 2935	−4951	−5869, −4033	−10592	−11752, −9433
Fetal neurodevelopment	−316	−384, −249	−348	−396, −300	−725	−801, −648	−40	−140, 60	510	348, 672	1398	1062, 1734
Colorectal cancer	–		–		2254	2207, 2300	1155	1134, 1176	−920	−936, −905	−2251	−2291, −2211
Total ΔDALY	−440		−1078		14 106		3124		−5361		−11445	

DALY, disability adjusted life years; HE, health effects.
* Alt1: large predatory fishes excluded; Alt2: MeHg low-level fishes included; Alt3: fish/seafood meal consumption once a week; Alt4: fish/seafood meal consumption 3×/week; Alt5: fish/seafood meal consumption 5×/week; Alt6: fish/seafood meal consumption 7×/week.

resulted in an increase in the burden of disease with an annual estimate of 14 106 and 3124 lost healthy years, respectively, in the Portuguese population.

Changing fish type consumed, as described for the alternative scenarios alt1 and alt2, resulted in a slight decrease in DALY compared with the reference scenario. Specifically, regarding the HE foetal neurodevelopment, it was found a small but significant decrease in the burden of disease by decreasing consumption of highly MeHg contaminated species. For this HE, the highest health gain was found in alt3.

Discussion

In this study, we estimated the Portuguese exposure to MeHg and EPA + DHA using a national representative sample from IAN-AF 2015–2016. We estimated that about 14 % of the Portuguese population has a MeHg exposure above the established TWI.

A slightly lower prevalence of 11 % in the Portuguese population was reported in a previous study[47], which may be explained due to methodological differences between the two studies. First, Jacobs *et al.*, considered only the adult population (18–75 years old), not considering children, which we found to be the population group at a higher risk. In our study, adults and the elderly had a risk prevalence of 12·9 and 11·6 %, respectively, values closer to the results from Jacobs *et al.* Furthermore, in our study, food consumption was assessed with two 24 h dietary recalls, where participants reported the type of fish, and the specific amount consumed, using food pictures for quantification. Differently from the Jacobs *et al.* study, where a food-frequency questionnaire was applied considering only 32 fish species and an average portion of fish/seafood was used for all intake occasions, in the IAN-AF 2015–2016, average standard portions were used only when no other information was available. Finally, the differences in the occurrence data used may have also contributed to this difference. Regarding MeHg occurrence, we used data from a large number of fish/seafood samples that were available in the Portuguese market, which is a strength of this study. For EPA and DHA the nationally available data was scarcer, thus there was a need to search for data from other sources to increase the accuracy of the assessment. However, a limitation can arise from this, since the fatty acid composition of fish/seafood may vary with the fishing ground and feeding practices of aquaculture products[48,49]. Nevertheless, there was national analytical data available for the most consumed fatty fish species, which we assume to be enough to overcome this limitation. Another important strength of our methodology regarding exposure assessment is the probabilistic approach used to input concentration values to individual eating occasions, rather than a deterministic approach using a point estimate for all individuals. Applying a probabilistic approach acknowledges the variability in the occurrence of food components and the food consumption between and within individuals.

Moreover, in this study, we applied an RBA to estimate the health impact of several hypothetical scenarios of fish consumption in the Portuguese population, considered a population with

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high fish consumption[1,2]. Our results show that the scenario with higher fish/seafood consumption frequency (seven times per week) was the one that represented the highest health gains, and that decreasing fish consumption frequency (once to 3 times per week) would represent a health loss in the Portuguese population. The HE that most contributed to the change in DALY was CHD mortality, which may happen due to its high incidence, as CHD is the second main cause of death in Portugal[37]. Nonetheless, this scenario presented a deleterious impact considering foetal neurodevelopment.

The scenarios reflecting changes in fish/seafood type to low-contaminated species had a lower impact in decreasing the health burden and the change in DALY was significant only for the 'foetal neurodevelopment' effect. This finding may be explained because the majority of fish consumed by the Portuguese population are species typically less contaminated with MeHg, such as cod, hake or salmon. In some regions like Madeira, however, it is expected that these scenarios have a greater impact. In line with findings from a study performed on pregnant women from Madeira[50], our results show that this is the region with the highest prevalence of exposure to MeHg in the reference scenario. We hypothesize that the specific reduction in the risk prevalence estimated in the alternative scenarios alt1 and alt2 observed in Madeira is due to the typical higher consumption of specific predatory fish species (particularly black-scabbardfish and fresh tuna) in that region, also shown in other study[50]. Thus, the change for these scenarios would especially benefit this region.

Our results suggest that official guidelines of fish consumption may recommend daily fish consumption for the general population. However, some population groups, as pregnant women and small children should be a target of special considerations. According to our results, children younger than 5 years old are susceptible to a high prevalence of MeHg exposure above the TWI, particularly in the alternative scenarios with an increased average frequency of fish consumption. Furthermore, there is an increase in the health burden considering the HE 'foetal neurodevelopment' by increasing average fish consumption frequency, suggesting a negative effect on the IQ of children due to maternal fish consumption during pregnancy. This is in line with the findings of the RBA studies from Cohen et al and Zeilmaker *et al.*[18,31], from where we derived the dose-response models for MeHg and DHA effects. On the contrary, another quantitative RBA study considering fish substitutions in Denmark[14], using a different approach, found opposite results concerning neurodevelopment, by applying a dose-response to fish intake as a whole[5,51], instead of only to DHA intake. In fact, according to EFSA, the benefits of fish consumption in neurodevelopment during pregnancy cannot be exclusively attributed to DHA, but also other nutrients such as iodine, thus, we cannot rule out the possibility of underestimation of the neurodevelopment benefits of fish in our study. Additionally, fish/seafood are a source of highly bioavailable selenium (SE)[7–9,52], which may contribute to a beneficial net-effect of fish on neurodevelopment, since previous evidence from animal studies have shown a countereffect of dietary SE in MeHg toxicity[53–57]. Evidence on this protective concurring effect of SE regarding MeHg from epidemiologic studies in humans is, however, conflicting[58–63]. Thus, for this study, we decided to apply a more conservative approach considering only DHA dose-response from randomized clinical trials to isolate its effect, but this may be a limitation since it may produce an underestimation of the benefits of fish/seafood consumption.

An important remark must be done concerning the methodological approach of using foods' raw weights to estimate the exposure to the RBA agents. For MeHg, this is not an issue as there is little impact on the content of mercury in foods after cooking or processing, according to EFSA's Scientific Opinion[13]. On the contrary, regarding EPA and DHA, by considering it in raw food items only, we are overlooking the potential losses (e.g., due to oxidation) caused by heat. Several authors have studied the effect of cooking on n-3 fatty acid profile of different fish species, and while some found a decrease in these fatty acids[64–66], many others described a not very wide variation in fish's fatty acid composition and that n-3 fatty acids were well preserved[67–72]. Thus, we consider this limitation most likely has little impact on our results.

Further limitations of this assessment should be addressed. First, we recognise that not all HE and fish/seafood components were considered for this RBA. Other contaminants such as dioxin and dioxin-like polychlorinated biphenyls may be present in fish/seafood and may pose risks to humans. As already discussed, some nutrients such as iodine, SE and iron, which may have important benefits, were not accounted for in our health impact assessment. Moreover, to quantify the health impact in DALY we rely on available data from different sources and different years. We used the most recently available national data on the incidence and mortality of the HE, fertility rate and life expectancy, which were not all from the same period but were apart only 1–2 years, a timeframe that can be considered short enough to exclude significant changes. Furthermore, there are many sources of uncertainty, namely on dose-response, disability-weights, incidence and mortality rates, and other data, that we tried to account for whenever possible, however, we cannot rule out the possibility of some unquantified uncertainty to impact our results, despite that in general, we used a conservative approach, overestimating the risks. Finally, we used the distribution based on the 2-day average intake to compute the prevalence of inadequate exposure to MeHg, as data shown to be unsuitable to estimate the usual intake. Thus, the obtained prevalence may be slightly overestimated due to a heavy-tailed distribution of the 2-days assessment.

Despite the limitations, our findings, showing greater benefit in the scenarios with average higher fish/seafood consumption frequency, are in line with previous quantitative RBA studies on fish consumption that also showed an overall health benefit of increasing fish consumption[3,5,14,18,73]. However, a quantitative comparison with these studies is not possible due to differences in the alternative scenarios considered and other methodological aspects, namely the components and HE selected for the assessment as well as the model for food substitutions in the alternative scenarios. A relevant strength of our study is the probabilistic approach used to perform the substitutions in the alternative scenarios that allowed to account for variability in food substitution behaviour. It is not expected that all individuals make

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substitutions in the same way, thus the models for the substitutions to achieve the average weekly fish/seafood frequencies in the several alternative scenarios took into account variables such as sex, age group and geographic region. In the scenarios' development, to consider food type and portion sizes for the substitutions, we imputed meals classified as 'Meat', 'Fish/seafood' and 'Others' as they were reported in the survey, by sex, age group and region. This imputation process in the alternative scenarios was performed in a way to vary average 'Fish/seafood' weekly frequency, keeping the ratio between 'Meat' *v.* 'Others' meals the same as the reference scenario, according to sex, age group and region using multistate models. By applying this approach, the replacements were not at random, and we assume a more realistic substitution to build the alternative scenarios rather than a deterministic one, where all individuals replace food in the same manner.

Reflecting on our results and previous evidence from regulatory bodies, as EFSA[10], we consider that for greatly vulnerable population groups (young children and pregnant women), about 3 to 4 weekly meals of fish should be recommended by the Portuguese national guidelines, which are in line with the current national average of consumption. Along with the frequency recommendation of fish/seafood consumption, the choice of smaller non-predatory fish species should be promoted. We found a small but significant decrease in the health burden in the alternative scenarios where selected predatory fish species were excluded, thus we acknowledge that the type of fish has an impact on the health burden and risk prevalence, as shown in previous studies and guidelines[14,47,50,74–77].

Besides the HE considered in this RBA, increasing fish/seafood consumption may also have environmental benefits. Scenarios with higher average fish/seafood frequency have lower levels of meat consumption that has typically higher environmental footprints[78–81]. Thus, considering the relevance of sustainability in our current food systems and the impact of climate change on human health, we acknowledge that further research should focus on quantifying the scenarios' environmental footprint and integrating it in the RBA.

Conclusions

Our findings support a recommendation for the general population to increase fish/seafood consumption up to seven times a week, as it allows to save more than 10k healthy years in the Portuguese population per year. For pregnant women and children, however, the recommendation should not exceed the 3–4 times per week, which is the current frequency of fish/seafood consumption, to avoid potential risks on foetal neurodevelopment due to MeHg exposure. The Portuguese national recommendations should also promote the choice of fish species with lower MeHg levels (as small pelagic fish, i.e., sardine, atlantic horse mackerel, mackerel) to minimise the MeHg exposure, especially in vulnerable populations and regions.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521004773

References

1. European Commission (2018) Facts and Figures on the Common Fisheries Policy : Basic Statistical Data : 2018 Edition. https://op.europa.eu/en/publication-detail/-/publication/cda10e39-ba77-11ea-811c-01aa75ed71a1 (accessed March 2021).
2. EFSA (2020) EFSA Comprehensive European Food Consumption Database.

3. Hoekstra J, Hart A, Owen H, *et al.* (2013) Fish, contaminants and human health: quantifying and weighing benefits and risks. *Food Chem Toxicol* **54**, 18–29.
4. Mozaffarian D & Rimm EB (2006) Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* **296**, 1885–1899.
5. FAO (2011) Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. January 2010. FAO Fish. Aquaculture Report no. 978. https://apps.who.int/iris/handle/10665/44666 (accessed March 2021).
6. EFSA (2015) Statement on the benefits of fish/seafood consumption compared to the risks of methylmercury in fish/seafood. *EFSA J* **13**, 1–36.
7. Cardoso C, Bernardo I, Bandarra NM, *et al.* (2018) Portuguese preschool children: benefit (EPA+DHA and Se) and risk (MeHg) assessment through the consumption of selected fish species. *Food Chem Toxicol* **115**, 306–314.
8. Afonso C, Bernardo I, Bandarra NM, *et al.* (2019) The implications of following dietary advice regarding fish consumption frequency and meal size for the benefit (EPA + DHA and Se) versus risk (MeHg) assessment. *Int J Food Sci Nutr* **70**, 623–637.
9. Cardoso C, Bandarra N, Lourenço H, *et al.* (2010) Methylmercury Risks and EPA + DHA Benefits Associated with Seafood Consumption in Europe. *Risk Anal* **30**, 827–840.
10. EFSA (2014) Scientific Opinion on health benefits of seafood (fish and shellfish) consumption in relation to health risks associated with exposure to methylmercury. *EFSA J* **12**, 3761.
11. Clarkson TW & Magos L (2006) The toxicology of mercury and its chemical compounds. *Crit Rev Toxicol* **36**, 609–662.
12. Farina M, Rocha JBT & Aschner M (2011) Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. *Life Sci* **89**, 555–563.
13. EFSA (2012) Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA J* **10**, 2985.
14. Thomsen ST, Pires SM, Devleesschauwer B, *et al.* (2018) Investigating the risk-benefit balance of substituting red and processed meat with fish in a Danish diet. *Food Chem Toxicol* **120**, 50–63.
15. Wang C, Harris WS, Chung M, *et al.* (2006) *n*-3 Fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* **84**, 5–17.
16. Nesheim MC & Yaktine AL (2007) Seafood Choices: Balancing Benefits and Risks. Seafood Choices Balanc Benefits and Risks. https://doi.org/10.17226/11762 (accessed March 2021).
17. USDA (2009) Report of Quantitative Risk and Benefit Assessment of Consumption of Commercial Fish, Focusing on Fetal Neurodevelopment Effects (Measured by Verbal Development in Children) and on Coronary Heart Disease and Stroke in the General Population. Draft report. https://www.federalregister.gov/documents/2009/01/21/E9-1081/report-of-quantitative-risk-and-benefit-assessment-of-commercial-fish-consumption-focusing-on-fetal (accessed March 2021).
18. Cohen JT, Bellinger DC, Connor WE, *et al.* (2005) A quantitative risk-benefit analysis of changes in population fish consumption. *Am J Prev Med* **29**, 325–334.e6.
19. Lopes C, Torres D, Oliveira A, *et al.* (2017) National Food, Nutrition and Physical Activity Survey of the Portuguese general population. *EFSA Support Publ* **14**, 1341E.
20. Lopes C, Torres D, Oliveira A, *et al.* (2018) National Food, Nutrition, and Physical Activity Survey of the Portuguese General Population (2015–2016): protocol for design and development. *JMIR Res Protoc* **7**, e42.
21. EFSA (2014) Guidance on the EU Menu methodology. *EFSA J* **12**, 3944.
22. Goios AC, Severo M, Lloyd AJ, *et al.* (2020) Validation of a new software eAT24 used to assess dietary intake in the adult Portuguese population. *Public Health Nutr* **23**, 3093–3103.
23. ASAE (2020) Plano Nacional de Colheita de Amostras (PNCA) (National Sampling Plan (PNCA)). https://www.asae.gov.pt/cientifico-laboratorial/area-tecnico-cientifica/pnca-plano-nacional-de-colheita-de-amostras.aspx (accessed July 2020).
24. FAO (2016) *FAO/INFOODS Global Food Composition Database for Fish and Shellfish Version 1.0- uFiSh1.0*. Rome: FAO.
25. Haytowitz DB, Ahuja JKC, Wu X, *et al.* (2018) *USDA National Nutrient Database for Standard Reference, Legacy Release. Nutrient Data Laboratory*. Washington, DC: Beltsville Human Nutrition Research Center, ARS, USDA.
26. Jackson CH (2011) Multi-state models for panel data: the MSM package for R. *J Stat Softw* **38**, 1–28.
27. R Core Team (2018) *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing.
28. Lumley T (2020) Survey: Analysis of Complex Survey Samples. R Package Version 4.0. https://cran.r-project.org/web/packages/survey/index.html (accessed July 2020).
29. Rubin DB (1996) Multiple imputation after 18+ years. *J Am Stat Assoc* **91**, 473.
30. IARC (2018) Red Meat and Processed Meat. IARC Monographs vol 114. https://publications.iarc.fr/564 (accessed July 2020).
31. Zeilmaker MJ, Hoekstra J, van Eijkeren JCH, *et al.* (2013) Fish consumption during child bearing age: a quantitative risk-benefit analysis on neurodevelopment. *Food Chem Toxicol* **54**, 30–34.
32. Bouvard V, Loomis D, Guyton KZ, *et al.* (2015) Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* **2045**, 1599–1600.
33. Chan DSM, Lau R, Aune D, *et al.* (2011) Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One* **6**, e20456.
34. IHME (2018) *Global Burden of Disease Study 2017 (GBD 2017) Disability Weights*. Seattle: IHME.
35. American Psychiatric Association (APA) (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV-TR). *Am J Psychiatry* **152**.
36. WHO (2019) *International Statistical Classification of Diseases and Related Health Problems ICD-10*, 6th ed. Geneva: WHO.
37. Instituto Nacional de Estatística (2019) Esperança média de vida à idade x, 2016–2018 (Average life expectancy at age x, 2016–2018). https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0001746&contexto=bd&selTab=tab2&xlang=pt (accessed July 2020).
38. Instituto Nacional de Estatística (2019) Taxa de fecundidade geral (‰) por Grupo etário; Annual, 2018 (General fertility rate (‰) by age group; anual, 2018). https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0001540&contexto=bd&selTab=tab2 (accessed July 2020).
39. Instituto Nacional de Estatística (2019) População residente (N.o) por Local de residência (NUTS - 2013), Sexo e Grupo etário; Anual, 2018 (Resident population (Number) by Place of residence (NUTS - 2013), Sex and Age group; Annual, 2018). https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&contecto=pi&indOcorrCod=0008273&selTab=tab0 (accessed July 2020).
40. Berlin JA, Longnecker MP, Epidemiology S, *et al.* (1993) Meta-analysis of epidemiologic dose-response data. *Epidemiology* **4**, 218–228.

41. Barendregt JJ & Veerman JL (2010) Categorical versus continuous risk factors and the calculation of potential impact fractions. *J Epidemiol Community Heal* **64**, 209–212.
42. Instituto Nacional de Estatística (2019) Taxa de mortalidade por doenças isquémicas do coração por 100 000 habitantes (N.o) por Local de residência (NUTS - 2013), Sexo e Grupo etário; Anual, 2017 (Mortality rate due to ischemic heart diseases per 100 000 inhabitants (No.) by Place of residence (NUTS - 2013), Sex and Age group; Annual, 2017). https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0003725&contexto=bd&selTab=tab2 (accessed July 2020).
43. Soerjomataram I, Lortet-Tieulent J, Ferlay J, *et al.* (2012) Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. *BMC Med Res Methodol* **12**, 1.
44. Ferlay J, Ervik M, Lam F, *et al.* (2018) Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer. https://gco.iarc.fr/today (accessed July 2020).
45. Bray F, Ferlay J, Soerjomataram I, *et al.* (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**, 394–424.
46. Ferlay J, Colombet M, Soerjomataram I, *et al.* (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* **144**, 1941–1953.
47. Jacobs S, Sioen I, Jacxsens L, *et al.* (2017) Risk assessment of methylmercury in five European countries considering the national seafood consumption patterns. *Food Chem Toxicol* **104**, 26–34.
48. Rittenschober D, Stadlmayr B, Nowak V, *et al.* (2016) Report on the development of the FAO/INFOODS user database for fish and shellfish (uFiSh) – challenges and possible solutions. *Food Chem* **193**, 112–120.
49. Khalili Tilami S & Sampels S (2018) Nutritional value of fish: lipids, proteins, vitamins, and minerals. *Rev Fish Sci Aquac* **26**, 243–253.
50. Caetano T, Branco V, Cavaco A, *et al.* (2019) Risk assessment of methylmercury in pregnant women and newborns in the island of Madeira (Portugal) using exposure biomarkers and food-frequency questionnaires. *J Toxicol Environ Heal – Part A Curr Issues* **82**, 833–844.
51. Hibbeln JR, Davis JM, Steer C, *et al.* (2007) Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Obstet Gynecol Surv* **62**, 437–439.
52. Fox TE, Van den Heuvel EGHM, Atherton CA, *et al.* (2004) Bioavailability of selenium from fish, yeast and selenate: a comparative study in humans using stable isotopes. *Eur J Clin Nutr* **58**, 343–349.
53. Watanabe C (2002) Modification of mercury toxicity by selenium: practical importance? *Tohoku J Exp Med* **196**, 71–77.
54. Santos APM, Mateus ML, Carvalho CML, *et al.* (2007) Biomarkers of exposure and effect as indicators of the interference of selenomethionine on methylmercury toxicity. *Toxicol Lett* **169**, 121–128.
55. Ralston NVC, Ralston CR & Raymond LJ (2016) Selenium health benefit values: updated criteria for mercury risk assessments. *Biol Trace Elem Res* **171**, 262–269.
56. Ralston NVC, Blackwell JL & Raymond LJ (2007) Importance of molar ratios in selenium-dependent protection against methylmercury toxicity. *Biol Trace Elem Res* **119**, 255–268.
57. Bjørklund G, Aaseth J, Ajsuvakova OP, *et al.* (2017) Molecular interaction between mercury and selenium in neurotoxicity. *Coord Chem Rev* **332**, 30–37.
58. Kosta L, Byrne AR & Zelenko V (1975) Correlation between selenium and mercury in man following exposure to inorganic mercury. *Nature* **254**, 238–239.
59. Falnoga I, Tušek-Žnidarič M & Stegnar P (2006) The influence of long-term mercury exposure on selenium availability in tissues: an evaluation of data. *BioMetals* **19**, 283–294.
60. Steuerwald U, Weihe P, Jørgensen PJ, *et al.* (2000) Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *J Pediatr* **136**, 599–605.
61. Choi AL, Budtz-Jørgensen E, Jørgensen PJ, *et al.* (2008) Selenium as a potential protective factor against mercury developmental neurotoxicity. *Environ Res* **107**, 45–52.
62. Llop S, Guxens M, Murcia M, *et al.* (2012) Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in spain: study of potential modifiers. *Am J Epidemiol* **175**, 451–465.
63. Lemire M, Fillion M, Frenette B, *et al.* (2011) Selenium from dietary sources and motor functions in the Brazilian Amazon. *Neurotoxicol* **32**, 944–953.
64. Türkkan AU, Cakli S & Kilinc B (2008) Effects of cooking methods on the proximate composition and fatty acid composition of seabass (Dicentrarchus labrax, Linnaeus, 1758). *Food Bioprod Process* **86**, 163–166.
65. Candela M, Astiasarán I & Bello J (1998) Deep-fat frying modifies high-fat fish lipid fraction. *J Agric Food Chem* **46**, 2793–2796.
66. Weber J, Bochi VC, Ribeiro CP, *et al.* (2008) Effect of different cooking methods on the oxidation, proximate and fatty acid composition of silver catfish (Rhamdia quelen) fillets. *Food Chem* **106**, 140–146.
67. Gladyshev M, Sushchik N, Gubanenko G, *et al.* (2006) Effect of way of cooking on content of essential polyunsaturated fatty acids in muscle tissue of humpback salmon. *Food Chem* **96**, 446–451.
68. Larsen D, Quek SY & Eyres L (2010) Effect of cooking method on the fatty acid profile of New Zealand King Salmon (Oncorhynchus tshawytscha). *Food Chem* **119**, 785–790.
69. Castro-González I, Maafs-Rodríguez AG & Pérez-Gil Romo F (2015) Effect of six different cooking techniques in the nutritional composition of two fish species previously selected as optimal for renal patient's diet. *J Food Sci Technol* **52**, 4196–4205.
70. Gladyshev M, Sushchik N, Gubanenko G, *et al.* (2007) Effect of boiling and frying on the content of essential polyunsaturated fatty acids in muscle tissue of four fish species. *Food Chem* **101**, 1694–1700.
71. Bastías JM, Balladares P, Acuña S, *et al.* (2017) Determining the effect of different cooking methods on the nutritional composition of salmon (Salmo salar) and chilean jack mackerel (Trachurus murphyi) fillets. *PLOS ONE* **12**, e0180993.
72. de Castro FAF, Pinheiro Sant'Ana HM, Campos FM, *et al.* (2007) Fatty acid composition of three freshwater fishes under different storage and cooking processes. *Food Chem* **103**, 1080–1090.
73. Thomsen ST, de Boer W, Pires SM, *et al.* (2019) A probabilistic approach for risk-benefit assessment of food substitutions: a case study on substituting meat by fish. *Food Chem Toxicol* **126**, 79–96.
74. Anual ZF, Maher W, Krikowa F, *et al.* (2018) Mercury and risk assessment from consumption of crustaceans, cephalopods and fish from West Peninsular Malaysia. *Microchem J* **140**, 214–221.

75. Groth E (2017) Scientific foundations of fish-consumption advice for pregnant women: epidemiological evidence, benefit-risk modeling, and an integrated approach. *Environ Res* **152**, 386–406.
76. FDA & EPA (2019) Advice about Eating Fish For Women who are or might become Pregnant, Breastfeeding Mothers, and Young Children. https://www.fda.gov/food/consumers/advice-about-eating-fish (accessed March 2021).
77. AESAN (2019) Recomendaciones de consumo de pescado (Recommendations on fish and seafood consumption). Agencia Española Segur. Aliment. y Nutr. https://www.aesan.gob.es/AECOSAN/docs/documentos/publicaciones/seguridad_alimentaria/RECOMENDACIONES_consumo_pescado_MERCURIO_AESAN_WEB.PDF (accessed March 2021).
78. Willett W, Rockström J, Loken B, *et al.* (2019) Food in the anthropocene: the EAT–Lancet commission on healthy diets from sustainable food systems. *Lancet* **393**, 447–492.
79. Poore J & Nemecek T (2018) Reducing food's environmental impacts through producers and consumers. *Science* **360**, 987–992.
80. Springmann M, Wiebe K, Mason-D'Croz D, *et al.* (2018) Health and nutritional aspects of sustainable diet strategies and their association with environmental impacts: a global modelling analysis with country-level detail. *Lancet Planet Heal* **2**, e451–e461.
81. Scarborough P, Appleby PN, Mizdrak A, *et al.* (2014) Dietary greenhouse gas emissions of meat-eaters, fish-eaters, vegetarians and vegans in the UK. *Clim Change* **125**, 179–192.

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