Use of Mathematical Optimization Models to Derive Healthy and Safe Fish Intake

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Title: Use of mathematical optimization models to derive healthy and safe fish intake 1, 2, 3, 4

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Supplemental Tables 1–4 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

Abbreviations used: DANSDA, Danish national survey of diet and physical activity; DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid; LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; QP, quadratic programming model allowing all species of fish in modeled intake; QPr, quadratic programming model only allowing reported fish in modeled intake; UB, upper bound; 2D, two-dimensional; 8D, eight-dimensional.

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Abstract

Background. Recommended fish intake differs substantially from observed fish intake. In Denmark, around 15% of the population meets the Danish recommendation on fish intake. How much fish individuals eat varies greatly. There are so many different patterns of fish intake that the fish intake of the average population cannot reflect this.

Objective. We developed a method that may provide realistic and achievable personalized dietary recommendations based on an individual's body weight and current fish intake. The objective of the study was to propose specific fish intake levels for individuals that meet the recommendations for eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and vitamin D without violating the tolerable intake recommendations for methyl mercury, dioxins, and polychlorinated biphenyls (dl-PCBs).

Methods. Two mathematical optimization models were developed that apply quadratic programming to model personalized recommended fish intake, fulfilling criteria on nutrients and contaminants, while simultaneously deviating as little as possible from observed individual intake. A recommended intake for eight fish species was generated for each individual in a group of 3,016 Danes (1,552 women and 1,464 men, ages 18-75), whose fish intakes and body weights were known from a national dietary survey.

Results. Individual, personal dietary recommendations were successfully modeled. Modeled fish intake levels were compared with observed fish intakes. For women, the average proposed increase in fish intake was 14 g/wk for lean fish and 63 g/wk for fatty fish; and for men these numbers were 12 g/wk and 55 g/wk, respectively.

Conclusions. Using fish intake as an example, we show how quadratic programming models may be used to advise individual consumers on the optimization of their diet, taking both benefits and risks
into account. This approach has the potential to increase compliance with dietary guidelines by targeting the individual consumers and minimizing the need for large and eventually unrealistic behavior changes.

**Key words:** dietary habits, diet optimization model, quadratic programming, risk-benefit assessment, Denmark, adults, nutrients, contaminants

**Introduction**

The research area **risk-benefit assessment of foods** focuses on comparing food-related health risks and benefits (1–3). Today, about 70% of all risk-benefit assessments of foods have analyzed fish (1,4–8). Fish is associated with health benefits, mainly due to its content of essential long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but also vitamins and minerals. However, being the one significant source of methyl mercury, and containing organic pollutants, the health risks from fish consumption need to be critically considered. According to a risk-benefit assessment of fish in the Norwegian diet (6), positive health effects from fish consumption are especially due to its content of the nutrients EPA, DHA, and vitamin D, whereas methyl mercury, dioxins, and dioxin-like polychlorinated biphenyls (dl-PCBs) are contaminants in fish, posing a relevant risk to human health. These nutrients and contaminants are representing the benefits and risks included in this study, based on the assumption that the Danish diet is comparable to the Norwegian diet. Hence, a fish intake that meets constraints on these nutrients is defined as healthy, and similarly, a fish intake that meets constraints on these contaminants is defined as safe.

Risk-benefit assessments have shown that health benefits of fish consumption outweigh the potential risks in a population (4,6). Based on this, the recommended intake of fish in the Danish official dietary guidelines is 350 g/wk of which 200 g should be fatty fish (9). However, most Danes do not meet these guidelines. According to the Danish National Survey of Diet and Physical Activity (DANSDA)
the observed average fish intake in Denmark (n = 3,016, ages 18-75) was 222 g/wk of which 120 g was fatty fish. Species with fat content higher than 5% are classified as fatty fish (6). The standard deviation of total fish intake was 228 g/wk. This large variation is partly due to 329 individuals (11%) in the study population who did not report consumption of fish during one week. Furthermore, only 445 (15%) of the individuals met the Danish official dietary guideline recommendation on fish.

Mathematical optimization has previously been used to analyze if and how diets could be changed to fulfill several health-related criteria, both on population level (11,12) and for individuals (13,14). Many of the previous diet optimization studies have constructed food intake meeting several criteria, while simultaneously deviating as little as possible from the observed intake. The arguments were that new intakes that differ least from current intakes were the most realistic and achievable for consumers.

Previous fish intake optimizations and risk-benefit assessments of fish have studied average population fish intake (5,6) and random fish intake scenarios (4). In this study, self-reported fish intakes for 3,016 individuals were considered, and thereby, a personalized recommended fish intake was obtained for each individual in the study population. Since personal recommendations were of interest, the intake for each individual in the study population was optimized separately and no inference to the rest of the population was made. Quadratic programming techniques were used as compared with linear programming that has been used in several previous diet optimization studies (5,11–14).

We developed a method that may provide realistic and achievable personalized dietary recommendations based on an individual's body weight and current reported intake. The objective of the study was to propose specific fish intake levels for individuals that meet the recommendations for EPA, DHA, and vitamin D without violating the tolerable intake recommendations for methyl mercury, dioxins, and dl-PCBs. By minimizing the need for large and eventually unrealistic behavior changes, a new intake was generated for each individual in the study population, that is the selected DANSDA
study participants (n=3,016, ages 18-75). Since fish may not be the only source of the nutrients and contaminants considered, different background exposure scenarios were compared.

**Methods**

A mathematical optimization model minimizes (or maximizes) an objective function subject to constraints. The optimization variable that minimizes (or maximizes) the objective function with respect to the given constraints is the solution to the problem. A quadratic programming problem has a quadratic objective function and linear constraints, and is a special case of the general convex optimization problem: optimization of a convex function over a convex set. This convexity property guarantees that a minimum (or maximum) found is a global minimum (or maximum) (15). Furthermore, the objective function of a quadratic problem is strictly convex, which guarantees that a minimum found is a unique global minimum.

Two mathematical quadratic programming models were developed: QP and QPr, which differ by one constraint only. The optimization variable of the models denotes weekly intake amounts of different types of fish for one individual. The objective function minimizes the sum of the square of the deviations between the observed intake (from individual intake data) and the optimized (by the model) intake. The constraints ensure that the optimized intake meet weekly lower limits on the nutrients EPA + DHA and vitamin D, without violating weekly upper limits on the contaminants methyl mercury and dioxins + dl-PCBs (See 2.3). The QP model allows non-reported fish to be added in the modeled intake, whereas the QPr model only allows reported fish in the modeled intake. For each individual, a non-reported fish is a species of which she/he reported a zero intake. Hence, for an individual who does not consume fish, all species of fish are non-reported. The QP model was considered most relevant because the observed intakes were 7-day estimated records and other species of fish may well have been consumed by an individual during another week.
The models were run both as two-dimensional and eight-dimensional (2D and 8D). The 2D models optimize the sub-groups lean and fatty fish, whereas the 8D models optimize the four most consumed fish species per sub-group. The intakes of the study population, obtained from DANSDA, are reported on specie-level. Species with fat content higher than 5% are classified as fatty fish (6). For the 2D models, the reported intake of one individual is translated to amounts of lean and fatty fish by this classification.

**Quadratic programming models**

The QP models are expressed as

$$\begin{align*}
\text{minimize} & \quad f(x, x_{\text{obs}}) \\
\text{subject to} & \quad Bx \geq b \quad (a) \\
& \quad Rx \leq r \quad (b) \\
& \quad x \geq 0 \quad (c)
\end{align*}$$

where the vector $x$ ($d\times1$) is the optimization variable representing weekly intake amounts of $d$ different fish species or subgroups of fish species; the vector $x_{\text{obs}}$ ($d\times1$) is a constant vector describing the corresponding observed intake amounts of an individual; and equations (a), (b) and (c) are the constraints of the problem. Besides (possible) additional equality constraints in (c), QPr is identical to QP. The function $f(x, x_{\text{obs}})$ is the objective function of the problem. The variable $d$ determines the dimension of the problem. In this study, the models were run with both $d=2$ and $d=8$. For $d=2$, the two elements of the vector $x$ denote the subgroups lean and fatty fish. For $d=8$, the eight elements of the vector denote the eight species of fish included in the study: cod, plaice, tuna, 'other lean'; and salmon, herring, mackerel and 'other fatty'.

**Linear constraints.** The vector \( b \) (m×1) in constraint (a) defines the weekly lower limits for m different nutrient intake amounts contributed by fish. These are weekly recommendations for the nutrients scaled for background exposure, as fish probably are not the only source of the nutrients. In this study, \( m = 2 \) (EPA + DHA and vitamin D). The vector \( r \) (k×1) in constraint (b) defines the weekly upper limits for k different contaminant intake amounts from fish. These are tolerable weekly intakes of the contaminants, also scaled for background exposure. In this study, \( k = 2 \) (methyl mercury and dioxins + dl PCBs), and each individual gets a specific \( r \) vector, defined by her/his body weight. The matrix \( B \) (m×d) in constraint (a) describes the mean concentrations of m nutrients for the n different (subgroups of) fish species. Similarly, the matrix \( R \) (k×d) in constraint (b) describes the mean concentrations of k contaminants. Consequently, the matrix product \( Bx \) (m×1) represents the weekly intake amounts of nutrients from fish and the matrix product \( Rx \) (k×1) represents the weekly intake amounts of contaminants from fish. The constraint (c) ensures that no negative intakes occur. For the QPr model, elements of constraint (c) corresponding to non-reported (subgroups of) fish species are set equal to zero, instead of greater than or equal to zero. All feasible vectors \( x \) (i.e., vectors that satisfy the constraints) make up the feasible region of the problem. Among the feasible vectors, the vector that optimizes the objective functions is the solution to the problem.

**Quadratic objective function.** The objective function is defined as the \( L_2 \)-norm of \( x - x_{obs} \) (the Euclidean distance between \( x \) and \( x_{obs} \)).

\[
 f(x, x_{obs}) = ||x - x_{obs}||_2 = \sqrt{|x_1 - x_{obs,1}|^2 + |x_2 - x_{obs,2}|^2 + \cdots + |x_n - x_{obs,d}|^2}
\]

The objective function is minimized. Minimizing \( \sqrt{x} \) gives the same optimal solution as minimizing \( x \), and when \( x \) is real-valued \( |x|^2 = x^2 \). Hence, for this problem, the objective function can be rewritten to a quadratic function:

\[
 f(x, x_{obs}) = (x_1 - x_{obs,1})^2 + (x_2 - x_{obs,2})^2 + \cdots + (x_n - x_{obs,d})^2
\]
Each individual gets a specific objective function, defined by her/his observed intake amounts \( x_{\text{obs},1}, x_{\text{obs},2}, \ldots, x_{\text{obs},d} \). Observe that the objective function is strictly convex and minimized over a convex set, hence a unique global minimum exists.

**Observed intake data**

Current fish intakes on species-level (7-day estimated records) and self-reported body weights were obtained from DANSDA (10). Individuals younger than 18 years of age were excluded, which resulted in a dataset of 3,016 individuals (1,552 women and 1,464 men) of age 18-75. There were 47 missing values in body weight among the 3,016 individuals in the study population. For those 47 individuals (16 men and 31 women) the gender-specific mean for body weight was used: 69.7 kg for women and 84.4 kg for men. Mean daily intakes were converted to mean weekly intakes by multiplying the mean daily intake by seven.

For each subgroup (lean and fatty fish), the three most consumed species were selected and the remaining species were classified as 'other'. As eel is considered critically endangered, marketing and consumption of European eel is debated, and therefore it was excluded from this study. The individual observed weekly fish intakes along with the recommendation in the Danish official dietary guidelines are shown in Figure 1, and the statistics of the intakes are shown in Table 1.

**Constraint data**

**Concentrations.** Nutrient concentration data were obtained from the Danish food composition database (16). Mean nutrient concentrations were available for different species or subcategories of fish species. Contaminant concentration data were obtained from the EFSA Circle of Trust initiative (17). For mercury, concentrations for several samples per fish species, along with limit of detection (LOD) and limit of quantification (LOQ) values were available. For dioxins + dl-PCBS, lower bound (LB) and upper bound (UB) values were available for several samples per fish species. In this study,
conservative estimates for the contaminants were used: total mercury was regarded as methyl mercury, and for dioxins + dl-PCBs, the UB values were used for each sample. It is generally found that about 80% - 100% of total mercury in fish is methyl mercury (18), and UBs most likely represent an overestimate of the true values (6). For mercury samples with low concentrations, and hence no data values, the mean of LOD and LOQ were used. The means of the sample concentrations were used as mean contaminant concentrations in this study.

For some species of fish, intake data on subcategories were available. For example, intake data for both raw and smoked salmon were available. In those cases, the weighted arithmetic mean, with mean observed intake for the different categories serving as weights, was calculated as mean concentration for the species. For the subgroups lean and fatty fish, mean nutrient and contaminant concentrations were also calculated as weighted arithmetic means, for women and men. For the subgroup 'other lean' fish, concentration data for scrub, representing 86% of that group, was used. Similarity, for 'other fatty' fish, concentration data for trout, representing 87% of that group, was used. See the mean concentrations used in this study in Table 2.

**Nutrition-based recommendations.** Recommended daily intakes for EPA + DHA (19) and vitamin D (20) are shown in Table 3 and converted to weekly values. For vitamin D, there is an upper level of 100 µg/day (21). In this study, this upper level was neglected after establishing that the contaminant constraints were limiting the fish intake amount long before.

**Contamination-based tolerable intakes.** Tolerable weekly intakes per body weight of methyl mercury (18) and dioxins + dl-PCBs (22) are shown in Table 3. The per-body-weight values were converted to individual values by multiplication with the self-reported body weights, or with mean body weight when no body weight was reported.
Background exposures. Since other sources than fish may provide nutrients and contaminants, the recommended daily intakes and tolerable weekly intakes were multiplied by the scaling factor: ‘100 - background exposure (%)’. The background exposure is not easily quantified because it is dependent on the whole individual diet and on potential environmental exposure. Therefore, the impact of background exposure was analyzed by scenario analysis.

A baseline scenario was defined, indicating the most likely background exposure. The background exposures of EPA + DHA, methyl mercury, and dioxins + dl-PCBs were used from a French study (5). For vitamin D, the value 39% was not considered representative for Denmark, and it gave no feasible solutions. Therefore, a higher background exposure was used. The mean intake of vitamin D in Denmark is 4.8 µg/day (23), and this intake is considered to provide sufficiently high levels of vitamin D in the population. Fish is assumed to contribute 50% of the vitamin D intake in Denmark (24), and therefore it was assumed that Danes acquire 2.4 µg/day from other sources than fish. Hence, the limit value in the baseline was set as 2.4 µg/day. This corresponds to 76% background exposure with a recommended intake of 10 µg/day.

Furthermore, to study the importance of the assumptions on the background exposures, eight alternative background exposure scenarios were defined and studied, by visual comparison of feasible region for different scenarios. The scaling factor values for background exposures for the baseline and the alternatives are given in Table 4. For vitamin D, three alternatives were chosen because the background exposure of vitamin D is partly dependent on the contribution from sunlight, and therefore highly uncertain. EPA and DHA are well known to come mainly from fish, and therefore only one alternative was chosen. The background exposure from dioxins and dl-PCBs is more uncertain, and hence two alternatives were chosen. Fish is known to be the one significant source of methyl mercury, hence only the baseline was considered.

Software
The models were implemented in Matlab R2015b (version 8.6). To solve the problems CVX was used, a package for specifying and solving convex programs (25). The statistical analyses were also performed in Matlab R2015b (version 8.6).

**Statistical analysis**

The Lilliefors test for normality was run for observed and modeled fish intakes. The equality between the medians of the modeled and observed intakes was tested using Wilcoxon matched-pairs signed-rank test. All tests were run with a significance level of $\alpha = 5\%$.

**Results**

This section is divided between the 2D and 8D models. The modeled intakes represent a proposed fish intake for each individual in the study population. The baseline scenario (Table 4) is the background exposure used for all modeled intakes.

**2D models: subgroups lean and fatty fish (d=2)**

**Feasible regions.** The feasible regions with baseline background exposure for the average-weight woman (69.7 kg) and average-weight man (84.4 kg) (Figure 2) are created by the lower nutrient constraints and the upper contaminant constraints. The recommended fish intake in Denmark meets all constraints of the model for both women and men. For men, the feasible region is larger than for women because the upper contaminant constraints are body weight dependent. The feasible regions for the eight alternative background exposure scenarios (Table 3) for the average-weight woman (Figure 3) show the variation due to background exposure (the variation is similar for women and men). The feasible region for scenario D is identical with the baseline feasible region (Figure 2a) since the vitamin D constraint is the lower limit and a lower background exposure of EPA + DHA does not affect the region. Recommended fish intake in Denmark lies within the feasible region for scenarios B
through G. Typically, scenarios A and H have a lower background exposure to vitamin D. The increased demand for vitamin D requires a high intake of fish that may lead to exceeding the tolerable weekly intake of dioxins + dl-PCBs.

**Modeled intakes.** With the 2D QP model, all 3,016 individuals had feasible solutions. The mean (with standard deviation) suggested an increase in fish intake (delta intake) for women of 25(30) g of lean fish/wk and 80(90) g of fatty fish/wk; and for men these numbers were 21(41) g/wk and 73(116) g/wk, respectively (Figure 4, Supplemental Table 1). The vitamin D constraint often determines the proposed increase in fish intake for those who presently consume too little fish. This results in a line of points in figures, as the lower vitamin D constraint is not body weight dependent. Some consumers with a high intake of fish are proposed to reduce their fish consumption due to the upper constraints of the contaminants. This does not occur as a line of points as it occurs less frequently and the individual constraints differ due to the variation in body weight.

With the 2D QPr model, an optimized intake was found for 1,397 women and 1,279 men. Hence, there was no combination of the reported intake of lean and fatty fish meeting all constraints for 340 individuals. These individuals need to expand their fish intake repertoire to get feasible solutions. The results are available in Supplemental Table 2.

The cumulative distributions for the difference between modeled and observed intake (delta intake) with the 2D QP and QPr models for women are shown in Figure 5. For men, the figures are similar, hence they are not shown. For example, looking at the QP model, 20% of the women should increase their lean fish intake with more than 53 g/wk (this number is found by reading the delta intake corresponding to the y-value 0.8 for the lean fish curve). Both the QP and QPr models suggest a larger change in intake of fatty fish than lean. For the QPr model, note that there is a sharp edge in the lean fish curve for individuals proposed to increase their intake with more than 50 g of lean fish/wk. These individuals receive a zero delta intake of fatty fish from the models, so they are suggested to
increase their lean fish intake more. Also, note that the maximum delta intake of lean fish for the QPr model is 615 g/wk, as compared with 179 g/wk for the QP model. As shown in the feasible region for the average weight woman (Figure 2a), the minimum feasible intake of lean fish, when not consuming fatty fish, is 622 g/wk. Hence, a woman who did not report any fatty fish intake is suggested to increase her lean fish intake with 615 g/wk, while her reported intake was 7 g/wk of lean fish.

**8D models: eight species of fish (d=8)**

**Modeled intakes.** With the 8D QP model, all 3,016 individuals had feasible solutions. The mean (with standard deviation) suggested an increase in fish intake (delta intake) for women of 14(24) g of lean fish/wk and 63(75) g of fatty fish/wk; and for men these numbers were 12(35) g/wk and 55(103) g/wk respectively (Supplemental Table 3). The 3,016 modeled intakes of the 8D QP model are plotted in two-dimensions by summing the species of lean and fatty fish respectively (as compared with the 2D models where lean and fatty fish were the optimization variables), see Figure 6. Lower intakes do not create as clear a line as for the 2D models (Figure 4): a result of the eight-dimensionality that implies higher flexibility.

With the 8D QPr model, only allowing reported species in the modeled intake, an optimized intake was found for 1,262 women and 1,124 men. The results are given in Supplemental Table 4.

The cumulative distributions for delta intake for the 8D QP model are shown in Figure 7. As the cumulative distributions look similar for women and men, only those for women are shown. For fatty fish species, the model suggests the largest change in intake for the category ‘other fatty’, which represents trout. For lean fish species, cod is suggested to be increased the most.

**Discussion**
This study shows how mathematical optimization, specifically quadratic programming, can be used to derive individual food intake that ensure a healthy and safe consumption pattern. This is illustrated for fish, using fish consumption data of 3,016 Danes. For each individual, a proposed fish intake that differs the least from her/his current intake, while meeting several criteria on nutrients and contaminants was modeled. The eight most consumed fish species in Denmark were considered. Allowing non-reported species in the modeled intake, an optimized intake was found for all 3,016 individuals. When only reported species were allowed, an optimized intake was found for 2,386 individuals (79%). Furthermore, several scenarios for background exposure of nutrients and contaminants were compared for a 2D model (where the subgroups lean and fatty fish were optimized) by showing feasible regions for eight background exposure scenarios as alternatives to the baseline that included the most likely background exposures.

Our results show that to follow the current Danish official dietary guidelines regarding intake of fish, most Danes should increase their fish intake, and a smaller fraction should either eat less fish or not change their fish intake at all. We show that when the requirement is to meet the recommendations for EPA + DHA and vitamin D without violating tolerable intake recommendations for methyl mercury and dioxins + dl-PCBs, an intake of 350 g fish/wk of which 200 g should be fatty fish (recommendation in the Danish official dietary guidelines), is not necessary. According to the criteria used in this study, eating this amount is healthy and not harmful, but it requires larger behavior changes than necessary, which may lead to lack of compliance.

In general, our results suggest that women need to increase their fish intake more than men, and fatty fish should be prioritized over lean fish for both genders. Within the subgroups, cod and 'other fatty', which is mainly trout, are the species proposed to be increased the most, whereas plaice and mackerel are the species suggested to be increased the least.
In general, mathematical optimization methods are suitable for addressing the complexity of data on food intake and dietary requirements, thanks to their ability to deal with several factors simultaneously. The models presented in this paper can be expanded to address additional and/or other nutrients, contaminants, foods, or food (sub)groups. Whole diets can also be optimized (11,13,14). Furthermore, mathematical optimization methods can be expanded to include other food related issues, such as sustainability and economy (26–30).

In previous studies on diet optimization, the $L_1$-norm was typically used as an objective function, and the optimization problems were transformed into a linear problem (11–14) to ensure unique global minima (12). In this study, quadratic programming with an objective function using the $L_2$-norm was preferred for two reasons. First, quadratic programming punishes large deviations and typically makes small changes to almost all elements of the optimization variable. Linear programming, on the other hand, typically makes large changes in a limited number of elements and leaves the others unchanged. Since we are dealing with a change in behavior, our argument is that many smaller changes, as obtained from quadratic programming, are more realistic and achievable than fewer larger changes. The researchers that developed the Dutch food-based dietary guidelines (31) have compared the linear and quadratic programming and their conclusion was that the later gave more achievable results. This was also concluded in the WWF report ‘Eating for 2 degrees’ (32–34).

Second, our method guarantees a unique global minimum without transformation and therefore, as compared to using the $L_1$-norm, enables direct interpretation of the constraints (12).

In previous diet optimizations, the objective functions were typically standardized across foods by dividing with observed intake of the specific food items (5,11,13,14). This was considered not necessary in this study, as only the consumption of fish was modeled.

At present, lack of appropriate data and uncertainty on the recommended and tolerable intakes as well as the background exposures are important limiting factors for intake optimization. Recommended
daily intakes and tolerable weekly intakes are based on available scientific evidence, but may change if new data become available. Furthermore, these limits are average values, and thus do not take into account variability in the population, e.g., in terms of food consumption, age, gender or weight (only nutrient limits). As this inter-individual variation is unknown, it cannot be included in our model. If these data were available, our approach could be individualized further to propose more precise individual results. For example, common genetic variations in genes have been shown to determine vitamin D status in Danes (35), and incorporation of such individual information would reduce the uncertainty of the results.

Nutrients and contaminant concentrations for fish may vary depending on region of capture, season, whether the fish is farmed or wild, etc. (6). Average values, as used in this study, allow a realistic estimate of long-term consumption and exposure. Furthermore, if data on individual selection of, e.g., wild/farmed fish and region of capture, were available, the approach could be individualized further. Finally, the intake data (7-day estimated records) are also uncertain due to memory bias of the participants, limited time of reporting, and a potential selection bias of participants.

To our knowledge, this is the first intake optimization paper showing the variation in feasible regions due to uncertainty in background exposure. The feasible regions are sensitive to this uncertainty. The vitamin D background exposure appears to be especially important, and also the one most difficult to establish because vitamin D can be obtained from many food products and is thus highly dependent on individuals’ diet and sun exposure. For this reason, vitamin D is commonly excluded in intake optimization studies. When a substantial amount of vitamin D is required to come from fish, there is a conflict between vitamin D and contaminants (5,11). In a French fish optimization study (5), the authors removed the vitamin D constraint, and instead maximized the Vitamin D intake. In a French whole diet optimization study (11), the vitamin D constraint was removed, and with the argument that vitamin D can be provided by supplements and sunlight, ignored it in the model. In our study, the
vitamin D constraint was not removed. Our argument was that fish is an important source of vitamin D, and people in Scandinavian countries rely more on vitamin D intake from food, especially in winter. Also, we chose to include vitamin D because our analysis shows that it is an important constraint that cannot be ignored. However, we had to accept a lower limit value in the baseline scenario to obtain feasible results, and therefore considered it to be sufficient that each individual at least reach the mean vitamin D intake from fish in the Danish population.

Options to deal with individual background exposure from food in future research are [1] a whole diet optimization approach (11,13,14) and [2] inclusion of individual intake data of the nutrients and contaminants to calculate individual background exposure from foods other than fish. In both cases, environmental or other specific, individual background exposures still require consideration. The first option would be more data demanding and is less focused on optimizing fish intake, but it would give dietary advice that was more complete. Also, substitution with other foods is a relevant issue, as, when fish intake is increased, the intake of other food(s) is probably decreased. In this paper, no substitution was accounted for. For whole diet optimization, the substitution is dealt with naturally. However, for optimization of a single food item such as fish, a future challenge for diet modeling is to include substitution. With data on individual preferences of substituting foods, the models could be individualized further, and hence give more precise individual recommendations.

Conclusions

It was shown that mathematical optimization, specifically quadratic programming, can be used to derive recommended individual fish intake based on current fish consumption and body weight, that ensure a safe and healthy fish consumption pattern. The model can be extended to other nutrients, contaminants and foods, and utilized to provide recommendations that are adapted to individuals. By minimizing the need for large and eventually unrealistic behavior changes, our hypothesis is that this
approach may have the potential to increase compliance with guidelines. A further development and expansion of this approach may therefore have an impact on the promotion of health and prevention of disease in populations.

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The authors' responsibilities were as follows - M. Pe. and M. J. N. designed research; M. Pe. conducted research and analyzed data; and M. Pe. and M. J. N. wrote the paper. F. S. provided essential material; and S. M. P., M. Po., and F. V. provided essential input during the research and writing the paper. M. Pe. and M. J. N. had primary responsibility for final content. All authors read and approved the final manuscript.
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Achtergrondgegevens van referentievoedingen voor de Richtlijnen Schijf van Vijf 2016


Table 1: Observed fish intakes from 3,016 participants (1,552 women and 1,464 men) aged 18-75 from the DANSDA study

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means±SDs, g/wk</td>
<td>Medians(IQRs), g/wk</td>
<td>nr</td>
<td>Means±SDs, g/wk</td>
</tr>
<tr>
<td>Total</td>
<td>200±193</td>
<td>149(241)</td>
<td>1,408</td>
<td>245±258</td>
</tr>
<tr>
<td>Lean fish (≤5% fat)</td>
<td>92±118</td>
<td>50(138)</td>
<td>1,158</td>
<td>111±155</td>
</tr>
<tr>
<td>Cod</td>
<td>37±72</td>
<td>0(46)</td>
<td>703</td>
<td>40±81</td>
</tr>
<tr>
<td>Plaice</td>
<td>25±66</td>
<td>0(9.7)</td>
<td>408</td>
<td>34±101</td>
</tr>
<tr>
<td>Tuna</td>
<td>21±49</td>
<td>0(15)</td>
<td>753</td>
<td>25±64</td>
</tr>
<tr>
<td>Other lean</td>
<td>8.9±28</td>
<td>0(0)</td>
<td>246</td>
<td>13±41</td>
</tr>
<tr>
<td>Fatty fish (&gt;5% fat)</td>
<td>108±138</td>
<td>58(161)</td>
<td>1,231</td>
<td>134±191</td>
</tr>
<tr>
<td>Salmon</td>
<td>41±68</td>
<td>8.6(54)</td>
<td>924</td>
<td>42±77</td>
</tr>
<tr>
<td>Herring</td>
<td>31±63</td>
<td>1.4(38)</td>
<td>860</td>
<td>49±103</td>
</tr>
<tr>
<td>Mackerel</td>
<td>23±40</td>
<td>9.2(33)</td>
<td>947</td>
<td>31±57</td>
</tr>
<tr>
<td>Other</td>
<td>12±25</td>
<td>0(8.0)</td>
<td>697</td>
<td>13±31</td>
</tr>
</tbody>
</table>

n =3,016. The observed fish intakes are not normally distributed, according to the Lilliefors test at significance level 5%. DANSDA, Danish national survey of diet and physical activity; nr, number of individuals with reported intake.
Table 2: Nutrient and contaminant concentrations for fish used in this study

<table>
<thead>
<tr>
<th></th>
<th>EPA+DHA, mg/g</th>
<th>Vitamin D, µg/g</th>
<th>Methyl mercury, µg/g</th>
<th>Dioxins dl-PCBs, pg TEQ/g</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lean fish (≤5% fat)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod</td>
<td>3.1</td>
<td>0.043</td>
<td>0.091±0.085</td>
<td>0.27±0.48</td>
</tr>
<tr>
<td>Plaice</td>
<td>6.0</td>
<td>0.011</td>
<td>0.061±0.071</td>
<td>0.75±0.96</td>
</tr>
<tr>
<td>Tuna</td>
<td>2.0</td>
<td>0.027</td>
<td>0.22±0.27</td>
<td>1.2±4.0</td>
</tr>
<tr>
<td>Other lean</td>
<td>4.2</td>
<td>0.0080</td>
<td>0.082±0.055</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Fatty fish (&gt;5% fat)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon</td>
<td>16</td>
<td>0.079</td>
<td>0.034±0.034</td>
<td>1.1±2.2</td>
</tr>
<tr>
<td>Herring</td>
<td>18</td>
<td>0.095</td>
<td>0.029±0.024</td>
<td>1.4±0.89</td>
</tr>
<tr>
<td>Mackerel</td>
<td>26</td>
<td>0.044</td>
<td>0.081±0.11</td>
<td>2.6±1.9</td>
</tr>
<tr>
<td>Other fatty</td>
<td>14</td>
<td>0.16</td>
<td>0.034±0.034</td>
<td>1.1±2.2</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs or only means (when SDs were not available). DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid.
Table 3: Recommendations on nutrients and contaminants used in this study

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended daily intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA+DHA, mg/day</td>
<td>250</td>
<td>(19)</td>
</tr>
<tr>
<td>Vitamin D, µg/day</td>
<td>10</td>
<td>(20)</td>
</tr>
<tr>
<td><strong>Tolerable weekly intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl mercury, µg/kg BW/wk</td>
<td>1.3</td>
<td>(18)</td>
</tr>
<tr>
<td>Dioxins + dl-PCB, pg TEQ/kg BW/wk</td>
<td>14</td>
<td>(22)</td>
</tr>
</tbody>
</table>

1 DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid.
Table 4: Background exposure scenarios for visual comparison of feasible regions for average weight Danish woman $^{1,2}$

<table>
<thead>
<tr>
<th></th>
<th>Baseline, %</th>
<th>A, %</th>
<th>B, %</th>
<th>C, %</th>
<th>D, %</th>
<th>E, %</th>
<th>F, %</th>
<th>G, %</th>
<th>H, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA+DHA</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>76</td>
<td>39</td>
<td>70</td>
<td>95</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>95</td>
<td>39</td>
</tr>
<tr>
<td>Methyl mercury</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dioxins+dl-PCBs</td>
<td>34</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>20</td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

$^1$ Values are percentage values of total exposure. The background exposure is defined as the exposure from other sources than fish. Baseline background exposure scenario and eight alternative background exposure scenarios, A through H, are shown. Cell marked ‘-’ refers to corresponding baseline value.

$^2$ The baseline background exposure scenario was used in the models for generating fish intake levels for all individuals.
Figure legends

Figure 1 Observed fish intakes from 3,016 participants; 1,552 women (A) and 1,464 men (B), aged 18-75 from the DANSDA study. DANSDA, Danish national survey of diet and physical activity.

Figure 2 Feasible region for 69.7 kg Danish woman (A) and 84.4 kg Danish man (B) modelled with two-dimensional QP model. The baseline background exposure is used. The feasible regions are created by the lower constraint on vitamin D, and the upper constraints on methyl mercury and dioxins + dl-PCBs. The lower EPA + DHA constraint does not affect the regions. DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid; QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 3 Alternative feasible regions for 69.7 kg Danish woman (A-H) modeled with two-dimensional QP model. The alternative background exposures are used. Scenario A has no feasible solutions. QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 4 Modeled fish intake for 1,552 Danish women (A) and 1,464 Danish men (B) generated with two-dimensional QP model. The figures illustrate how individuals with an observed intake within her/his feasible region get a modeled intake identical with the observed, whereas individuals with an observed intake outside her/his feasible region get a modeled intake on the region border; the point on the feasible region closest to the observed intake. The modeled intakes were significantly different from observed intakes, P<0.05, according to the Wilcoxon matched-pairs signed-rank test. QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 5 Cumulative distributions for delta fish intake (modeled minus observed intake) for 1,552 Danish women modeled with two-dimensional QP model (A) and QPr model (B). The figures give information on how many individuals that are recommended to change their fish intake and how. The fraction of individuals that are suggested to not change (delta intake = 0), decrease (delta intake < 0),
or increase (delta intake > 0) their intake can be read from the graphs. QP, quadratic programming model allowing all species of fish in modeled intake; QPr, quadratic programming model only allowing reported fish in modeled intake.

**Figure 6** Modeled fish intake for 1,552 Danish women (A) and 1,464 Danish men (B) generated with eight-dimensional QP model. The figures illustrate how individuals with an observed intake within her/his feasible region get a modeled intake identical with the observed, whereas individuals with an observed intake outside her/his feasible region get a modeled intake on the region border; the point on the feasible region closest to the observed intake. The modeled intakes were significantly different from observed intakes, P<0.05, according to the Wilcoxon matched-pairs signed-rank test. QP, quadratic programming model allowing all species of fish in modeled intake.

**Figure 7** Cumulative distributions for delta fish intake (modeled minus observed intake) for 1,552 Danish women modeled with eight-dimensional QP model. The figures give information on how many individuals that are recommended to change their fish intake and how. The fraction of individuals that are suggested to not change (delta intake = 0), decrease (delta intake < 0), or increase (delta intake > 0) their intake can be read from the graphs. QP, quadratic programming model allowing all species of fish in modeled intake.