Public Health Nutrition: 19(2), 318–325 doi:10.1017/S1368980015001020

Fish and fish-liver oil consumption in adolescence and midlife and risk of CHD in older women

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Submitted 1 November 2013: Final revision received 26 January 2015: Accepted 20 February 2015: First published online 17 April 2015

Abstract

Objective: To study the association of fish and fish-liver oil consumption across the lifespan with CHD later in life among Icelandic women, with special emphasis on the effects of consumption in adolescence.

Design: Prevalence association study. Logistic regression was used to estimate odds ratios and 95 % confidence intervals of CHD according to fish or fish-liver oil exposure. Models were adjusted for age, education, concurrent diet and other known risk factors.

Setting: The study was nested within the AGES-Reykjavik Study, conducted in Reykjavik, Iceland.

Subjects: Participants were 3326 women aged 66–96 years, with available information on CHD status at entry to the study and information on fish and fish-liver oil consumption during midlife and adolescence. Dietary habits were assessed retrospectively using a validated FFQ.

Results: CHD was identified in 234 (7·9 %) women. Compared with women with no intake of fish-liver oil in adolescence or midlife, women who consumed fish-liver oil at least three times weekly in adolescence or in midlife had a decreased risk of CHD (OR = 0·62; 95 % CI 0·45, 0·85 and OR = 0·68; 95 % CI 0·50, 0·94, respectively). No associations were observed between fish intake (>2 portions/week *v.* ≤2 portions/week) in adolescence or midlife and CHD in this population with high fish intake.

Conclusions: Fish-liver oil consumption, from early life, may reduce the risk of CHD in older women. Lifelong nutrition may be of importance in the prevention of CHD in older women.

Keywords
Fish
Fish oil
CHD
Early-life diet
Women

Consumption of fish, particularly fatty fish and fish-liver oil, has been associated with reduced risk of fatal and non-fatal CHD in numerous studies[1–5]. The cardio-protective effects of fish have largely been attributed to the actions of *n*-3 long-chain PUFA (LC-PUFA), both EPA and DHA, mainly found in fatty fish. Consequently, numerous national health agencies and organizations have published recommendations of one or two meals of fish per week in order to lower CHD risk[2,4].

Less is known of the importance of early-life fish and *n*-3 LC-PUFA intake for prevention of CHD later in life. A study on children's diet from 1939 did not observe an association between fish consumption in early life and CHD risk later in life[6]. Yet, a Danish study on young women (mean age at baseline was 29·9 years) with median follow-up of 8 years showed that almost no fish and *n*-3 LC-PUFA intake was associated with increased risk of CHD[7].

Some risk factors for CHD may develop in young age, implying that early-life exposures may have an impact on CHD risk in later life. For example, studies of fatty streaks in children and young adults have demonstrated that atherosclerosis begins early in life and there is a correlation between the number of CHD risk factors and severity

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of asymptomatic coronary and aortic atherosclerosis later in life[8]. Moreover, little is known about the importance of lean fish consumption for cardiovascular risk.

Nested in an Icelandic population, known for its high intake of lean fish and common use of fish-liver oil[9], the present study aimed to assess the impact of high lean fish consumption and cod-liver oil intake in adolescence and midlife on the risk of CHD in older women.

Methods

Study design and population

The present study is a prevalence association study nested within the Age, Gene/Environment Susceptibility (AGES)-Reykjavik cohort study of the Icelandic Heart Association[10]. The AGES-Reykjavik Study is a follow-up of the Reykjavik Study, initiated in 1967, with a response rate of 71 %. All men and women born in 1907–1935 and residing in Reykjavik and nearby communities in 1967 were selected; from the 27 281 invited to participate, 19 381 attended[11]. Of the 11 549 cohort members still alive in 2002 when AGES-Reykjavik Study examinations began, 8030 individuals were randomly chosen and invited to the study. From these, 5764 (58 % women) individuals had participated in the AGES-Reykjavik Study by 2006 (71·8 %). The women were 66–96 years old at the time of examinations, average age 76 years. Extensive data were collected in the AGES-Reykjavik Study during clinical examinations, including data on food intake in adolescence, midlife and at present old age[10]. For our analysis we used data from the first clinical examination of the 3326 women who participated, aged 66–96 years (see Fig. 1).

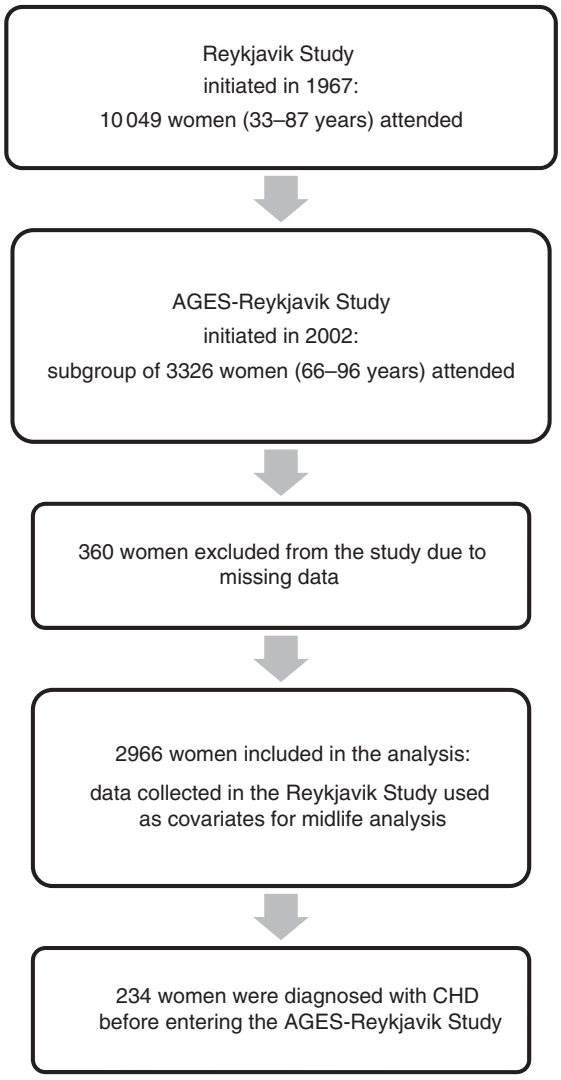

Fig. 1 Selection of participants, originally from the Reykjavik Study and later, the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 1967–2006

Assessment of fish and fish-liver oil consumption

Using a validated FFQ designed for the present project[12,13], the participants answered questions on current diet, midlife diet (between the ages of 40 and 50 years) and adolescent diet (between the ages of 14 and 19 years). Two questions on fish consumption in the FFQ were used for the analysis. One concerned frequency of fish as a main meal and the other frequency of fish as a topping on bread and in salad. Possible response categories were: (i) 'never'; (ii) 'less than once a week'; (iii) '1–2 times a week'; (iv) '3–4 times a week'; (v) '5–6 times a week'; (vi) 'daily'; and (vii) 'more than once a day'. Total fish consumption was estimated by combining the two questions on fish consumption into one variable, giving the amount of fish for bread topping a relative value of 40/150 of that for fish as main meal. The relative value was obtained from average portion sizes from Icelandic national nutrition surveys, 40 g of fish for bread toppings and 150 g for fish as main meal. Numerical values for portions of fish were thus calculated, adding the frequency of fish as bread toppings and as main meals. Total fish consumption was divided into three groups: high (>4 portions/week), moderate (2–4 portions/week) and low (<2 portions/week). The FFQ did not include questions on fish type, but cod and haddock were the predominant fish species in the early 20th century and also today, accounting for 80–85 % of total fish consumption in Iceland[14–17]. Intake of salted and smoked fish was evaluated in the FFQ, using a separate question. Salted and smoked fish was included in the total fish consumption. Information on salted and smoked fish intake for each time period was used in adjustment analysis.

Frequency of intake of fish-liver oil (cod liver) supplements (liquid or capsules), hereafter referred to as fish-liver oil, was assessed for each period of life, using the same response categories as for fish, omitting the last option of 'more than once a day'. Responses were further categorized as seen in Table 1. Cod-liver oil is traditionally a common supplement in Iceland[16] and the common dose is 10 ml/d. According to the Icelandic food

Table 1 Characteristics of women aged 66–96 years with and without CHD*, Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 2006 (*n* 2966)

	With CHD (*n* 234)		Without CHD (*n* 2732)		
	n	%	*n*	%	*P* value†
Age (years)‡, mean and SD	77·59	5·04	76·37	5·71	0·001
Education‡					
Primary school	84	36	789	29	0·049
Secondary	104	45	1294	48	
College–university	44	19	641	23	
Smoking status‡					
Never	99	42	1470	54	0·002
Past smoker	103	44	916	33	
Current smoker	32	14	346	13	
Family history of heart disease‡					
No	87	37	1691	62	0·001
Yes	146	63	1039	38	
Physical activity-adolescence and midlife‡					
Never–rarely	118	54	1218	48	0·14
Occasionally	48	22	543	21	
Moderate–high	54	24	780	31	
Alcohol consumption‡					
Never	102	44	1087	41	0·087
Less than once monthly	70	31	710	26	
1–3 times monthly	45	20	691	26	
Weekly	12	5	197	7	
Diabetes in midlife§					
No diabetes	226	97	2693	99	0·01
Diabetes (type 1 and 2)	8	3	39	1	
Hypertension in midlife§					
No hypertension (SBP < 120 mmHg and DBP < 80 mmHg)	51	22	726	27	0·02
Pre-hypertension (120 ≤ SBP mmHg <140 or 80 ≤ DBP mmHg < 90)	99	42	1264	46	
Hypertension present (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)	84	36	742	27	
Total blood cholesterol in midlife§					
Low (<6 mmol/l)	59	25	1070	39	0·001
High (≥6 mmol/l)	175	75	1660	61	
BMI in midlife§					
<30 kg/m^2	213	93	2446	90	0·22
≥30 kg/m^2	17	7	269	10	
Food consumption: midlife‖					
Fish					
<2 portions/week	24	11	316	11	0·83
2–4 portions/week	146	62	1683	62	
>4 portions/week	64	27	733	27	
Fish-liver oil					
Never	100	43	878	32	0·004
≤2 times/week	24	10	304	11	
≥3 times/week	110	47	1550	57	
Vegetables					
≤2 times/week	153	66	1680	62	0·239
≥3 times/week	80	34	1040	38	
Fruit					
≤2 times/week	163	70	1741	64	0·066
≥3 times/week	70	30	981	36	
Spread quantity					
Never or little	57	24	577	21	0·257
Medium or much	177	76	2146	79	
Food consumption: adolescence‖					
Fish					
<2 portions/week	112	48	1349	49	0·446
2–4 portions/week	21	9	301	11	
>4 portions/week	101	43	1082	40	
Fish-liver oil					
Never	124	53	1140	42	0·02
≤2 times/week	26	11	303	11	
≥3 times/week	84	36	1289	47	
Fruits					
Never	102	44	939	35	0·013
<1 time/week	86	37	1235	45	
≥1 time/week	45	19	543	20	

Table 1 *Continued*

	With CHD (*n* 234)		Without CHD (*n* 2732)		
	n	%	*n*	%	*P* value†
Vegetables					
Never	57	24	538	20	0·233
<1 time/week	94	40	1184	43	
≥1 time/week	83	36	1001	37	
Spread quantity					
Never or little	46	20	405	15	0·049
Medium or much	187	80	2312	85	

SBP, systolic blood pressure; DBP. diastolic blood pressure.
*Due to missing cases, the number of women included in the table varies from 2761 to 2966.
†*P* values are based on the χ^2 test, except for age, where the independent-sample *t* test was used.
‡Status at entry to the AGES-Reykjavik Study.
§Status at entry to the Reykjavik Study.
‖Data from FFQ on midlife and adolescent diet from the AGES-Reykjavik Study.

composition database, the amount of EPA is 0·75 g in 10 ml of cod-liver oil and the amount of DHA is 1·0 g/10 ml[18].

Validation of the FFQ

For midlife dietary habits, retrospective food consumption of 56–72-year-old participants (107 women) was estimated by comparing the results in the AGES-FFQ with detailed dietary data (an hour-long interview on dietary habits in the past 3 months) gathered from the same individuals 18–19 years previously in a 1990 national nutrition survey. The strongest correlation was found for fish-liver oil ($r = 0{\cdot}56$, $P < 0{\cdot}001$) while the correlation coefficient for fish consumption was 0·28 ($P = 0{\cdot}004$)[12]. Validity of the early-life dietary assessment has not been, and cannot be, investigated. Yet, the participants provided information on early-life residency and the dietary data importantly show similar residency-dependent variation in dietary habits as documented in contemporary studies by Sigurjonsson[17]. For example, in our data we can see that those who reported early-life residency in coastal villages also reported higher fish and fish-liver oil intakes compared with those raised in rural areas or Reykjavik in the early-life period, corresponding to the results from the 1939 dietary survey.

CHD – outcome assessment

An end point for CHD was obtained from hospital records. The records were systematically reviewed according to the MONICA (Monitoring of trends and determinants in cardiovascular disease) protocol based on the incidence of myocardial infarction (MI), coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI). Participants were defined as having a CHD event if MI, CABG or PCI had occurred at entry to AGES-Reykjavik. The quality of the registration in Iceland according to MONICA methods has previously been described elsewhere[19].

Covariate assessment

Information on midlife diabetes, total blood cholesterol, hypertension and BMI was obtained from the Reykjavik Study, as the concurrent information on these risk factors might be biased due to ageing. Diabetes was either self-reported or based on glucose value (≥126 mg/l) after overnight fasting. Total blood cholesterol was categorized into high (≥6 mmol/l) and low (<6 mmol/l). All blood chemistry was measured after overnight fasting. Blood pressure was measured with a mercury sphygmomanometer and the mean value of two blood pressure measurements from separate occasions used. Blood pressure measurements were divided into no hypertension, pre-hypertension and hypertension. BMI was categorized by obesity status (see Table 1).

From the AGES-Reykjavik Study we retrieved information on age at entry, educational level, smoking status, family history of heart disease, physical activity in adolescence and midlife, alcohol consumption in midlife and dietary habits in youth and midlife. Family history of coronary disease was recorded if father, mother, siblings or children had coronary thrombosis. Information on self-reported frequency of moderate or vigorous physical activity in three time periods (20–34 years, 35–49 years and 50–65 years of age) was pooled and categorized into never, rarely, occasionally, moderately and often. Dietary covariates were consumption of fruit, vegetables and amount of spread used on bread. For fruit and vegetables there were seven responses possible; the same as described earlier for fish. There were four response options for usual amount of spread used on bread, with pictures showing buttered bread with the respective amounts. In Iceland, butter was the predominant spread used on bread during the study period.

Statistical analyses

We excluded 360 women from the analysis due to missing data regarding heart disease, fish and/or fish-liver oil consumption, leaving 2966 women in our analysis.

We used χ^2 tests to estimate different characteristics of women with and without CHD, of fish and fish-liver oil consumers in midlife, and of fish and fish-liver oil consumers in adolescence. *P* values ≤0·05 were considered statistically significant. We used logistic regression to calculate odds ratios and 95 % confidence intervals of

CHD by differential fish and fish-liver oil consumption, for midlife and adolescent consumption separately.

The first multivariable model was adjusted for age (as a continuous variable) at entry to AGES-Reykjavik. The second model was adjusted for age, education, smoking status, physical activity, alcohol consumption, fish consumption (for the outcome of the fish-liver oil analysis) and fish-liver oil consumption (for the fish analysis). The third model was adjusted for the same variables as in the second model, adding vegetable and fruit consumption, as well as the amount of spread used on bread (see categories in Table 1). The categories for fruit and vegetables in adolescence are different from the midlife categories due to different consumption pattern and availability of foods. In the fourth model additional adjustments were made for diabetes, blood pressure, total blood cholesterol and BMI in midlife. This was done only for midlife consumption since these covariates were not available for adolescence.

The statistical software package PASW version 18, release version 18·00 (2009) was used for all statistical analyses.

Results

Out of 2966 women, 234 (7·9 %) had previously known CHD at entry into the AGES-Reykjavik Study, while 2732 did not have CHD according to MONICA registration. Major characteristics of women with and without CHD are presented in Table 1.

Table 2 presents multivariable analysis results for the association between CHD and fish and fish-liver oil consumption in adolescence. No statistically significant association was observed between fish consumption and CHD (>2 portions/week *v.* ≤2 portions/week), while all three models showed a significant protective association between adolescent fish-liver oil intake and CHD. Compared with women with no intake of fish liver oil, those who consumed fish-liver oil at least three times weekly had an OR of 0·61 (95 % CI 0·45, 0·81) for CHD in model 1, 0·62 (95 % CI 0·45, 0·84) in model 2 and 0·62 (95 % CI 0·45, 0·85) in model 3.

Table 3 presents multivariable analysis results for fish and fish-liver oil consumption in midlife. No statistically significant association was observed between fish consumption (>2 portions/week *v.* ≤2 portions/week) and CHD, while midlife fish-liver oil consumption was associated with decreased risk of CHD. Using women with no intake of fish-liver oil as a reference group, those with fish-liver oil consumption of at least three times weekly had an OR of 0·63 (95 % CI 0·48, 0·84) to develop CHD in model 1, 0·67 (95 % CI 0·49, 0·91) in model 2, 0·68 (95 % CI 0·50, 0·92) in model 3 and 0·68 (95 % CI 0·50, 0·94) in model 4. Additional adjustment for salted and smoked fish consumption did not alter our results (data not shown). Testing for interaction between fish and salted and smoked fish yielded a *P* value of 0·11 for the adolescent period and 0·87 for the midlife period. No significant association was found between fish intake and CHD when stratified by high and low intake of salted and smoked fish (see online supplementary material, Supplemental Table 1).

Pooling fish-liver oil consumption in both midlife and adolescence showed that frequent (three times weekly or more) intake of fish-liver oil in both adolescence and midlife was associated with lower risk of CHD compared with two times weekly or less in both life periods (OR = 0·60; 95 % CI 0·43, 0·84). No significant association was found in the group with infrequent intake in adolescence but high frequency in midlife or vice versa (Table 4). Adjustments were made for age, education smoking status and alcohol consumption in midlife, physical activity in midlife and early adulthood, and family history of heart disease. Sixty-seven per cent of the participants had high intake of fish-liver oil in both adolescence and midlife.

Discussion

In the present study in a female population with high consumption of lean fish and consistent use of fish-liver

Table 2 Odds ratio estimates (and 95 % confidence intervals) for CHD in women aged 66–96 years by fish and fish-liver oil consumption in adolescence, Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 2006 (*n* 2966)

	Age-adjusted OR (non-CHD, *n* 2732; CHD, *n* 234)		Model 2* (non-CHD, *n* 2495; CHD, *n* 213)		Model 3† (non-CHD, *n* 2470; CHD, *n* 211)	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
Fish						
<2 portions/week (*n* 1461)	1·00	Ref.	1·00	Ref.	1·00	Ref.
2–4 portions/week (*n* 322)	0·81	0·50, 1·31	0·88	0·53, 1·47	0·88	0·52, 1·47
>4 portions/week (*n* 1183)	1·12	0·84, 1·48	1·12	0·83, 1·52	1·13	0·83, 1·54
Fish-liver oil						
Never (*n* 1264)	1·00	Ref.	1·00	Ref.	1·00	Ref.
≤2 times/week (*n* 329)	0·81	0·52, 1·25	0·80	0·49, 1·30	0·82	0·50, 1·34
≥3 times/week (*n* 1373)	0·61	0·45, 0·81	0·62	0·45, 0·84	0·62	0·45, 0·85

Ref., reference category.
*Adjustments were made for age, education, smoking status, physical activity, alcohol consumption, family history of heart disease, fish consumption (for fish-liver oil) and fish-liver oil consumption (for fish).
†Additional adjustments were made for consumption of fruit and vegetables and amount of spread used in adolescence.

Table 3 Odds ratio estimates (and 95 % confidence intervals) for CHD in women aged 66–96 years by fish and fish-liver oil consumption in midlife, Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 2006 (*n* 2966)

	Age-adjusted OR (non-CHD, *n* 2732; CHD, *n* 234)		Model 2* (non-CHD, *n* 2495; CHD, *n* 213)		Model 3† (non-CHD, *n* 2471; CHD, *n* 212)		Model 4‡ (non-CHD, *n* 2451; CHD, *n* 209)	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Fish								
<2 portions/week (*n* 340)	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
2–4 portions/week (*n* 1829)	1·09	0·69, 1·70	1·26	0·76, 2·08	1·25	0·75, 2·06	1·20	0·73, 1·99
>4 portions/week (*n* 797)	1·03	0·63, 1·69	1·27	0·73, 2·20	1·29	0·74, 2·23	1·25	0·72, 2·18
Fish-liver oil								
Never (*n* 978)	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
≤2 times/week (*n* 328)	0·72	0·45, 1·14	0·79	0·48, 1·29	0·80	0·49, 1·30	0·87	0·53, 1·42
≥3 times/week (*n* 1660)	0·63	0·48, 0·84	0·67	0·49, 0·91	0·68	0·50, 0·92	0·68	0·50, 0·94

Ref., reference category.
*Adjustments were made for age, education, smoking status, physical activity, alcohol consumption, family history of heart disease, fish consumption (for fish-liver oil) and fish-liver oil consumption (for fish).
†Additional adjustments made for consumption of fruit and vegetables and the amount of spread used in midlife.
‡Additional adjustments were made for cholesterol level, diabetes, hypertension and BMI, all measured in midlife.

Table 4 Odds ratio estimates (and 95 % confidence intervals) for CHD in women aged 66–96 years by longitudinal fish-liver oil consumption, Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 2006 (*n* 2966)

		Age-adjusted OR (non-CHD, *n* 2732; CHD, *n* 234)		Adjusted OR* (non-CHD, *n* 2675; CHD, *n* 226)	
Adolescence	Midlife	OR	95 % CI	OR	95 % CI
Low	Low	1·00	Ref.	1·00	Ref.
Low	High	0·90	0·63, 1·29	0·99	0·68, 1·44
High	Low	0·86	0·53, 1·40	0·93	0·57, 1·53
High	High	0·55	0·40, 0·76	0·60	0·43, 0·84

Ref., reference category.
Low, fish-liver oil consumption two times weekly or less; high, fish-liver oil consumption three times weekly or more.
*Adjustments made for age, smoking, education, family history of heart disease and alcohol consumption.

oil, we found clear support for the hypothesis that fish-liver oil consumption reduces the risk of CHD in women aged 66–96 years. Our data did not show any protection by fish consumption against CHD, neither during the adolescent period nor in midlife.

Our findings of a reduced risk of CHD in women reporting prolonged consumption of fish-liver oil starting in early life may be explained by several factors. Studies have shown that risk factors for CHD such as dyslipidaemia, hypertension, obesity and insulin resistance can develop early and affect formation of atherosclerosis, and therefore increase CHD risk[8,20,21]. Fish-liver oil is rich in *n*-3 LC-PUFA, the physiological effects of which can be both long term and short term. *n*-3 LC-PUFA's lowering effect on plasma TAG concentration, blood pressure and platelet aggregation might require months or years before clinical outcomes are evident[22]. Our estimates appear to be independent of major risk factors for CHD and stratifying the data by cholesterol (high/low), diabetes (yes/no) and hypertension (yes/no/pre-hypertension) did not reveal any differential association (data not shown). However, fish-liver oil is not only rich in *n*-3 LC-PUFA but also vitamin D. Although the effect of vitamin D on CHD is not clear, its effect, or the effects of other nutrients found in fish-liver oil, cannot be excluded as confounding factors in our analysis[23,24].

Not finding the putative protective effect of fish consumption on CHD risk in our study population may be explained by several factors. In this population with high fish consumption, there is a lack of a reference group of women consuming fish seldom or never. In our study, the lowest fish intake category that could be used for reference is defined as those who consumed fish twice or less per week and within that category only ten participants never consumed fish in adolescence and four participants never consumed fish in midlife. Studies have shown 20–36 % reduced risk of CHD death when two fish meals are consumed per week compared with no fish or less than once weekly consumption[3,5], while no benefit has been reported by further increase in fish consumption[3]. Similarly a Danish study on young women only found increased risk for CVD among women who consumed between 0 and 3 g fish/d[7]. A beneficial threshold level for fish consumption might thus already have been reached by our reference group. On the other hand, haddock and cod, the most common fish consumed in Iceland during the 20th century[14–17], are lean species containing only

small amounts of *n*-3 LC-PUFA[25]. Lean fish has not consistently been associated with protection against CHD[26–29], suggesting that *n*-3 LC-PUFA or other fat-soluble substances in fish may be the important factor for this effect. Interestingly, cod-liver oil contributes 42 % of total intake of *n*-3 LC-PUFA in the present diet of Icelanders, compared with 40 % from fish and seafood[9]. Also, information on cooking methods and condiment use are not available. Stick margarine, high in both saturated and *trans*-fatty acids, was commonly used with fish in the years 1980–2000 approximately[15], possibly masking any putative benefit of fish consumption in midlife. Alternatively, the presence of environmental pollutants such as mercury or polychlorinated biphenyls in fish cannot be excluded, counteracting a possible benefit of fish intake. This, however, remains an unlikely explanation since insignificant levels of these pollutants have been measured in the Atlantic cod fish, including haddock[3], the most common fish type consumed in Iceland during the exposure windows of our study. Also, salted fish was a significant proportion of fish intake in Iceland in former times, which could possibly affect our results. Adjustment for intake of salted fish in the present study did not change our results. Further, doing a stratified analysis for salted fish consumption revealed no significant outcome. However, women with high consumption of salted fish who also reported to consume more than four portions of fish weekly (with at least one portion being salted fish) showed an insignificant positive association with CHD, seen both for midlife and the adolescence period. Interestingly, women with low consumption of salted fish who reported to consume more than two portions fish weekly showed an insignificant inverse association in adolescence. This suggests that the proportion of salted fish in the total fish consumption might be of great importance in the present study and could be one of the reasons why no association was found between high total fish consumption and CHD in our analysis. Another possible reason for not finding an association with fish intake is the low validity of the retrospective question of fish intake in midlife (0·28, $P=0·004$)[12]. In spite of being considered acceptable, the validity may not be sufficient to detect a putative beneficial association.

To our knowledge, few studies are available on early-life dietary factors and CHD risk in later life. The Boyd Orr cohort study, a prospective study of English children's diet from 1939, did not find any beneficial relationship between diet in childhood, including fish, and CHD later in life[6]. The reference group in that study also had a relatively low percentage of people consuming low amounts of fish and the participants could therefore, as in our study, have reached a potential beneficial threshold of fish intake. A more likely explanation, however, may be that the estimated consumption in childhood was based on household, rather than individual consumption.

The strength of our study includes the detailed and valid assessment of outcome as well as access to a wide selection of covariates. The fact that our results on fish-liver oil are robust through multiple adjustments suggests that our findings may indeed be valid, especially considering that Icelandic women are a low-risk population for CVD[30]. Few studies have been able to provide data on early-life diet combined with detailed ascertainment of CHD outcomes later in life and we believe our study is unique in that aspect. Also long-term use of cod-liver oil has not been studied previously to our knowledge.

Our study is likely to suffer somewhat from recall bias since the women were asked to recall their diet many decades earlier. However, a previous US-based study showed that food-related memory from childhood over four decades later can be as accurate as from current diet, especially for food items eaten rarely or daily[31]. Our own data show that the validity of the questions on fish-liver oil and fish consumption was similar for midlife consumption and recent consumption, $r=0·56$ ($P<0·001$) and 0·28 ($P=0·004$), respectively[12]. Additionally, despite the rich covariate selection and multiple adjustments, the influence of unmeasured confounders cannot be excluded.

The Icelandic Heart Association has a long reputation of valid end-point assessment of CHD. Nevertheless, we cannot exclude that the non-case group might include women with unrecognized non-fatal MI. However, additional analysis where the end point was based on electrocardiogram, responses to Rose Angina questionnaire and questions concerning previous heart procedures at entry revealed similar results (data not shown).

Conclusion

With few existing studies on early-life dietary factors and CHD, our study provides important evidence for the potential preventive role of fish-liver oil consumption throughout life on the development of CHD in women. Our results suggest that moderate prolonged fish-liver oil consumption initiated in early life may be protective against the development of CHD in women. If confirmed in future studies, preferably with prospective ascertainment of fish-liver oil consumption, these findings may have significant public health implications.

Acknowledgements

Financial support: This present analysis received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The AGES-Reykjavik Study was funded by the National Institutes of Health (contract number N01-AG-12100); the Intramural Research Program of the National Institute on Aging; the Icelandic Heart Association; and the Icelandic Parliament. The funding agencies (National Institute on Aging, Icelandic Heart Association and Icelandic Parlament) for the

AGES-Reykjavik Study had no role in the design, analysis or writing of this article. *Conflict of interest:* None. *Authorship:* A.H., J.E.T., U.A.V. and L.S. were responsible for formulating the research questions and the design of the study. A.H. and J.E.T. were responsible for analysing the data. All authors were responsible for writing the article. *Ethics of human subject participation:* This study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the Institutional Review Board covering research for the National Institute on Aging, USA.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1368980015001020

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