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Brief summary:

The notion that coronary artery disease (CAD) is rare among Greenland Eskimos due to high fish intake, gained acceptance in the 1970s. Since then, thousands of reports on the cardioprotective effects of the “Eskimo diet” have been published. We conducted a literature review to assess whether there was sufficient evidence to support the “Eskimo diet and low CAD” hypothesis. Our conclusion is that this hypothesis lacked a solid foundation.

Abstract:

During the 1970s, two Danish investigators, Bang and Dyerberg, upon being informed that the Greenland Eskimos had a low prevalence of coronary artery disease (CAD) set out to study the diet of this population. Bang and Dyerberg described the "Eskimo diet" as consisting of large amounts of seal and whale blubber (i.e. fats of animal origin) and suggested that this diet was a key factor in the alleged low incidence of CAD. This was the beginning of a proliferation of studies that focused on the cardioprotective effects of the "Eskimo diet". In view of data, which accumulated on this topic during the past 40 years, we conducted a review of published literature to examine whether mortality and morbidity due to CAD are indeed lower in Eskimo/Inuit populations compared to their Caucasian counterparts. Most studies found that the Greenland Eskimos as well as the Canadian and Alaskan Inuit have CAD as often as the non-Eskimo populations. Notably, Bang and Dyerberg's studies from the 1970sdid not investigate the prevalence of CAD in this population; however, their reports are still routinely cited as evidence for the cardioprotective effect of the "Eskimo diet". We discuss the possible motives leading to the misinterpretation of these seminal studies.

Introduction:

The notion that fish oil has health-promoting and healing properties has captured the attention of the scientific community for the past 50 years. Currently, nutritional guidelines in Canada, the United States and Europe recommend at least two meals a week containing fish (preferably oily) as part of a healthy diet and, particularly, for the prevention of cardiovascular disease (CVD).[1-4]According to the American Heart Association guidelines, patients with documented coronary artery disease (CAD) should be advised to consume 900–1000 mg of omega-3 fatty acids (EPA–DHA combined) per day from oily fish or fish oil supplements.[2] While these recommendations remain in effect, recent randomized trials and systematic reviews report ambiguous or negative results regarding the cardioprotective effects of fish oil and omega-3 fatty acids.[5-7]On the other hand, another component of fish that has not been sufficiently explored, is the amino acid taurine, which has been shown by Yamori et al to have an inverse relation to ischemic heart disease mortality.[8]

The contemporary "fish story" started in the 1970s, when two Danish physicians, Hans Olaf Bang and Jorn Dyerberg, visited Greenland to investigate why Eskimos, as they were informed, have a very low incidence of CAD despite eating large amounts of seal and whale blubber i.e. fats of animal origin.[9-12]Food specimens were collected by means of the double-portion technique from seven persons, on seven consecutive days. The researchers found that the food of this population "*contained more protein and fewer carbohydrates compared to the average Danish food and an almost equal amount of fat. In addition, compared to Danish food, the fatty acid pattern of the consumed lipids-essentially of mammalian marine origin-showed a higher content of long chain polyunsaturated fatty acids (especially C20:5) and lower contents of linoleic and linolenic acid".*[12]

Bang and Dyerberg's studies were conducted in the area around the town of UmanaK, located 500km north of the Arctic Circle. The town has approximately 1300 inhabitants, representing approximately 2.3% of Greenland's population, and some settlements are more than 100 miles away from the nearest hospital or health station.

Although the studies of these two Danish investigators are routinely quoted in connection with the alleged low occurrence of CAD in Greenland Eskimos, [13-19] the fact is that Bang and Dyerberg did not examine the cardiovascular status of Greenland Eskimos or those living in and around the small community of UmanaK. Instead, they relied mainly on Annual Reports produced by the Chief Medical Officer (CMO) in Greenland for the years 1963-1967 and 1973-1976.[9-10]As we will discuss later in this paper, these reports have limited validity.

Thus, the first question is whether the incidence and/or prevalence of CAD among Greenland Eskimos is indeed low? Notably, in 1940, A. Bertelsen, a Danish doctor that practiced for many years in Greenland, described frequent occurrence of CAD in this Inuit population. Bertelsen's report, which was written in Danish and published in a book with limited circulation, was largely ignored. [20]

More recently, a number of studies have confirmed what Bertelsen ascertained more than 70 years ago, i.e. that the prevalence of CAD among Eskimos in Greenland and other Inuit populations in Canada and the US is similar or higher compared to that of non-Eskimo/Caucasian populations.[21-23]Nevertheless,it seems that most researchers and clinicians have accepted the notion of low prevalence of CAD at face value and continue to refer to the studies of Bang and Dyerberg.

The objective of this paper was to re-visit the origin of the "fish oil and CAD" story and assess whether there was ever reliable evidence to support the hypothesis that the Eskimo diet provides CAD protection.

Methods:

We reviewed the original series of publications by Bang and Dyerberg (1970-1980), [9-12; 24-26] and we verified that the objective of these studies was to analyze the composition of the Eskimo food. A search for the CMO reports and all other relevant literature in relation to the alleged low incidence and prevalence of CAD in Greenland Eskimos, as quoted in the original series of publications by Bang et al, was also performed.

Furthermore, an online search was conducted in peer-review journals listed in PubMed to retrieve clinical and experimental studies, case reports, and review articles in English by using combinations of the key words: "*Eskimos, cardiovascular disease, coronary heart disease, stroke and mortality"*. No date limits were applied (latest search performed on January 30, 2014).

Selection criteria included: 1. **Language**: English and/or Danish; 2. **Study population:** Eskimos and/or Inuit; 3. **Method:** Direct measurement i.e. clinical investigation of presence of CAD and/or CVD risk factors OR assessment of morbidity and mortality outcomes using mortality statistics, hospital records or death certificates; 4. **Outcomes:** Morbidity or mortality due to CAD.

The search yielded 734 articles. The titles and abstracts of these articles were screened for duplicates and relevancy (Figure S1 in Supplementary Materials). Full text of the remaining

48articles were obtained (abstracts described CVD/CAD /stroke mortality and/or morbidity) and were reviewed independently for inclusion by two reviewers. A hand search through reference lists of included articles was also performed.

The type of evidence reported by each of the studies was assessed and categorized as Evidence I (study reported outcomes based on direct measurements), Evidence II (study reported findings based on, hospital records or mortality data (death certificates) or Evidence III (other).

An additional search with the keywords "*Eskimos, Inuit, cardiovascular disease and fish oil"* focused on retrieving articles from 2003 onwards that refer to the Bang and Dyerberg reports as evidence for low level of CAD morbidity and mortality in Greenland Eskimos.

Results:

Table S1 (in Supplementary Materials) summarizes information from the original Bang and Dyerberg publications, as related to CAD in the Greenlandic population, along with a list of the sources that the authors cite to document the low incidence/prevalence of CAD among Greenland Eskimos.

We were able to retrieve the CMO annual reports for the years 1963-1967[27] (Table S2 in Supplementary Materials). The reported deaths due to CAD in these years in Greenland varied between 8.5 %-11.8percent of total number of deaths.

Our search for studies that have performed direct measurements on the Greenland Eskimo population for assessing the presence of CAD or CAD risk factors yielded only one study by

Jørgensen et al, 2008.[28]This study ascertained that CAD morbidity was as high among Inuit as in American and European populations (Table S3 in Supplementary Materials).

Nine studies were identified in relation to CVD status in Eskimo/Inuit populations in Canada and the US (Table S4 in Supplementary Materials).[22-23; 29-35] Young et al (1993), [29] reported that the age-standardized mortality rate for ischemic heart disease among the Northwest Territories population was lower than among the Canadian population (1950-1989). On the other hand, the majority of studies reported that the prevalence of CAD among Alaska Eskimos was high.[23;30-31; 34-35]According to McLaughlin et al (2004),[34] while Alaska Inuits were previously at lower risk for death from CAD compared to Caucasians (death certificate data for 1979-1990), this discrepancy disappeared during 1990-2002.

Table S5(in Supplementary Materials) presents a sample of studies published in the past 10 years (2003-2013). These recent studies refer to papers authored or co-authored by Dyerberg and Bang to support the notion of low prevalence of CAD among Eskimos and its inverse relation to the high consumption of marine fat and omega 3 fatty acids.

Discussion:

The alleged absence of CAD in Greenland Eskimos is a paradoxical finding, given that this is a population mainly sustained on a diet high in animal fat, absence of fruits and vegetables and other important nutrients;[36] in other words, a diet which violates all principles of balanced and heart-healthy nutrition.

The totality of reviewed evidence leads us to the conclusion that Eskimos have a similar prevalence of CAD as non-Eskimo populations, [20-23; 31-32;34-35] they have excessive mortality due

to cerebrovascular strokes,[37-38] their overall mortality is twice as high as that of non-Eskimo populations[38]and their life expectancy is approximately 10 years shorter than the Danish population.[39-40]

We also reviewed studies that have assessed the prevalence of CAD or other CVD in the Eskimo/Inuit populations in areas such as the Northwest Territories and Nunavik, in Canada or in Alaska, USA. The results of these investigations confirm that the prevalence of CAD in Inuits is as high or higher compared to non-Eskimo populations.[22-23;31-32;34-35]In 2003, a thorough analysis of the incidence and available mortality statistics among Inuit populations in Greenland, Canada and Alaska by Bjerregaard et al, also concluded that the totality of evidence from various Northern areas makes a strong argument for high presence of CVD in Eskimos (Appendix A in Supplementary Materials).[21]

Considering the dismal health status of Eskimos, it is remarkable that instead of labeling their diet as dangerous to health, a hypothesis has been construed that dietary intake of marine fats prevents CAD and reduces atherosclerotic burden. Bang and Dyerberg's seminal studies from the 1970s are routinely invoked as "proof" of low prevalence of CAD in Greenland Eskimos ignoring the fact that these two Danish investigators did not study the prevalence of CAD.[9-12] Instead, their research focused on the dietary habits of Eskimos and offered only speculation that the high intake of marine fats exerted a protective effect on coronary arteries.[9-12]

As mentioned earlier, Bang and Dyerberg's acceptance of the low incidence of myocardial infarction (MI) relied on the reports of the CMO in Greenland for 1963-1967 and 1973-1976.[27,41]These reports are based on death certificates and hospital admissions. Concerns over the validity and accuracy of death certificates and mortality statistics in Greenland have been raised

in a number of reports.[38,42-43]According to the Deputy CMO in Greenland, Flemming Mikkelsen (1974), [44]30% of the total population lived in outposts and small settlements where no medical officer was stationed. If a person died in one of these areas, the certificate would be completed by the nearest medical officer, based on information provided by a medical auxiliary or some other "competent" person. Thus, 20% of death certificates were completed without a doctor having examined the patient or the body. Kroman and Green (1980) [45], also pointed out that there was a specific concern with mortality data and hospital admission statistics in Greenland, as doctors had limited diagnostic facilities and the study population was widely scattered with few possibilities of communication during certain seasons. Therefore, the reported data are likely an underestimation of the true magnitude of the disease in this area.

In addition to the CMO reports, Bang and Dyerberg also refer to a report by Bent Harvald (1974). [46] In his contribution, Harvald stated: "*MI does not occur in the Eskimo population. On the other hand, ECG records in those older than 50 years of age show numerous abnormalities compatible with history of MI at least as frequent as in many Western populations. The same is true for frequent deaths caused by heart failure as a consequence of arteriosclerotic degenerative heart disease. It is therefore a mystery that there are no MIs*" (translated from Danish by JGF). We suggest that the likely explanation for this "mystery" lies in the fact that patients suffering MI in remote Greenland settlements have limited possibilities for reaching health centres in the acute phase of the disease where proper diagnostic work-up is possible.

In the US as well as in Europe, at least one fourth of MIs remain unrecognized .[47]Regarding hospital admissions, according to O'Donnell et al (1996), [48] in the United States during the 1990s, only 40% of those who suffered from a MI reached a hospital alive. In 20% of MI cases,

the first manifestation was sudden death. In Europe, 25% of acute heart attack cases die within two hours.[49] To assume that the proportion of those who suffer from an MI in remote arctic areas would have a better chance to reach a hospital alive is unlikely. This is confirmed by Peter Bjerregaard (1986)[43]who reported that "*in Greenland, only one in seven deaths occurs in a hospital with specialized departments and paraclinical facilities allowing thorough investigation of cases*".

The theory concerning the beneficial effects of marine fats on Greenland CAD should have been put to rest after Bjerregaard's et al analysis of the Greenland mortality (2003).[21]Although the notion that Eskimos are protected against CAD cannot be supported by scientific evidence, a large number of recent publications reporting on the effects of fish oil consumption still perpetuate this belief. Our search for such publications yielded at least nine articles published within the last ten years (i.e. after Bjerregaard's et al 2003 report).[13-19, 50-51] A recent example is a paper published in the New England Journal of Medicine (2011)[51], stating that *"Bang and Dyerberg undertook six expeditions to Greenland… in response to anecdotal reports of low prevalence of coronary heart disease… they confirmed a very low incidence of myocardial infarction…"*.In the "Fish oil and marine omega-3 fatty acids" chapter of the UptoDate database (written by Mozaffarian D et al)a Bang and Dyerberg reference (1980)[26] is cited to support the statement: "*ecologic studies found low rates of coronary heart disease death among Greenland Eskimos consuming large amounts of seafood*".[52]

Why do so many researchers seem to uncritically quote these reports? Publications still referring to Bang and Dyerberg's nutritional studies as proof that Eskimos have low prevalence of CAD represent either misinterpretation of the original findings or an example of confirmation bias.

Perhaps, they may also represent a trend of applying less rigorous standards of scientific evidence when reporting about non-pharmacological, i.e. lifestyle interventions.

Recently, two meta-analyses[5, 53] and a well-conducted randomized controlled trial[7] reported ambiguous or negative results regarding the cardioprotective benefits of omega-3 fatty acids. At the same time, nutritional guidelines in Canada, US and Europe encourage the dietary intake of fish and omega-3 as part of a preventive approach toward CAD and overall heart-health. The American Heart Association recommends eating fish (particularly fatty fish) at least two times (two servings) a week.[54]Similarly, the ESC-ESH 2013 Guidelines advise patients with hypertension to eat fish at least twice a week.[55]Although the evidence for these recommendations is unclear, it is estimated that in the US approximately 11 million adults and close to half a million children consume fish oil capsules.[56]To date, more than 5000 papers have been published studying the alleged beneficial properties of omega-3 fatty acids not to mention the billion dollar industry producing and selling fish oil capsules based on a hypothesis that was questionable from the beginning.

"Man prefers to believe what he prefers to be true." Francis Bacon

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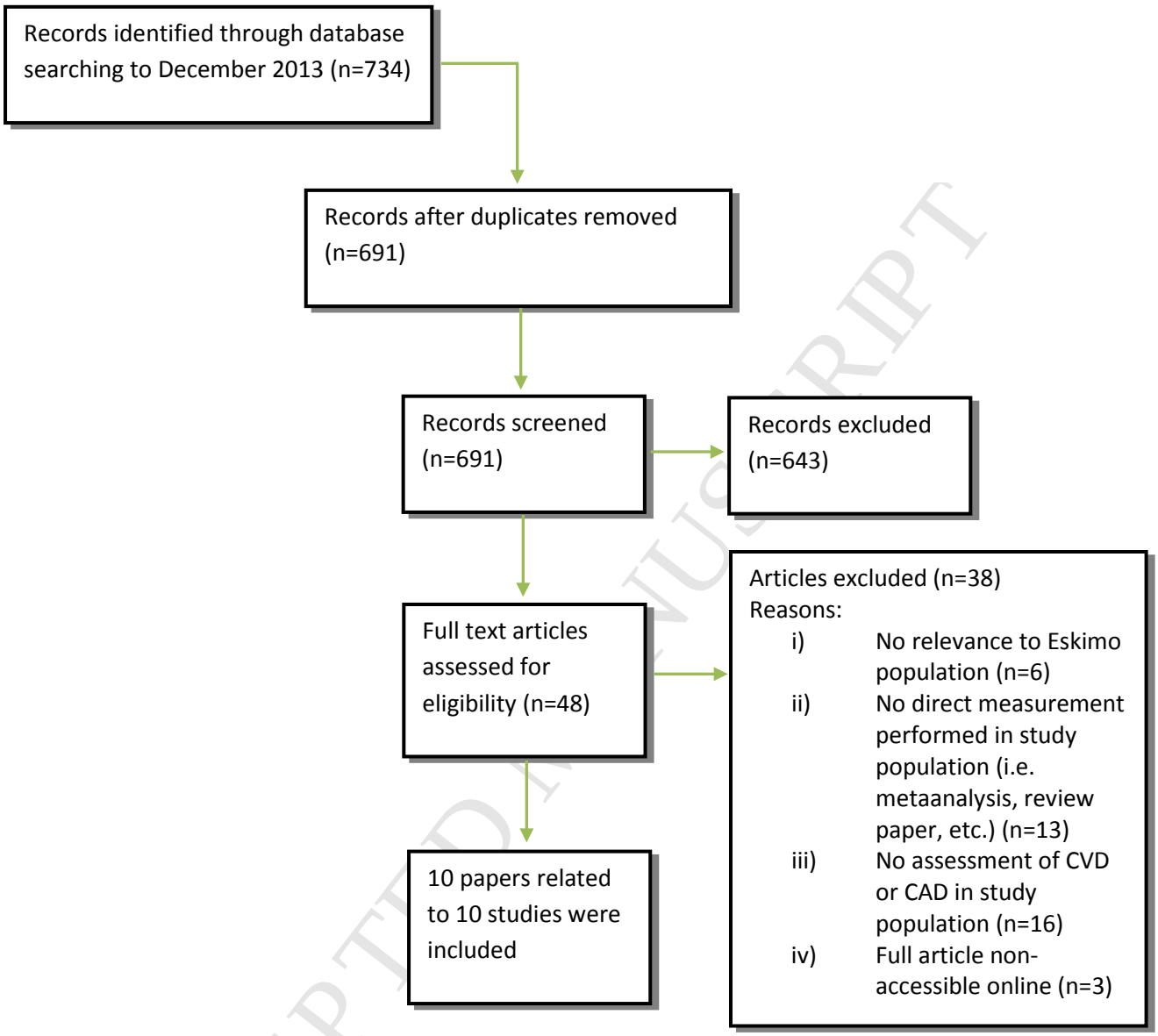

Table S1. Evidence regarding low incidence of CAD in Greenland as cited in Bang, Dyerberg et al publications 1971-1980

Publication	**Objective**	**Statement regarding CAD incidence**	**Reference(s) cited**	**Authors' conclusions in relation to CAD**
Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-Coast Eskimos. Lancet 1971; 1143-1145[9]	*"In an attempt to describe in details the serum-lipids in Eskimos and perhaps explain the low incidence of ischemic heart disease in these people, we undertook an expedition to the north-west coast of Greenland in August and September, 1970, in order to examine the serum-lipid pattern in Eskimos, hoping that the*	*"From an investigation by Sagild it appears that the serum-cholesterol level in Eskimos is lower than that of the population of Western Europe, but no thorough examination of the serum-lipid pattern of Greenlandic Eskimos has been carried out until now".* *"…the incidence of ischemic heart disease is very low in Eskimos in the northern part of Greenland even*	Sagild, U. Personal communication No reference provided	*"In the Eskimos the association of low level of most types of lipid (except a-lipoproteins) with very low incidence of ischemic heart disease is striking, but not necessarily causal"*

	findings would throw some light on the pathogenetic role of the serum-lipids in atherosclerotic diseases, especially ischemic heart disease, in the Western world".	*though the Eskimo food in this part of Greenland is extremely rich in animal fat"* "*The incidence of "atherosclerotic heart disease including coronary arterial disease" (Annual Health Report from Greenland) in the years 1963-1967 has been evaluated by the Danish medical officers of the UmanaK district. Only 3 cases of these diseases were reported*".	Annual Report from the Chief Medical Officer in Greenland, 1963-1967	
Bang HO and Dyerberg J. Plasma lipids and	"*In the present paper the plasma lipid and lipoprotein*	"*Ischemic heart disease is, on the contrary, rare in Greenlandic*	No reference provided	"*The generally accepted fact that*

lipoproteins in Greenlandic West Coast Eskimos. Acta Med Scand 1972; 192: 85-94[10]	*concentrations in 130 Greenlandic west coast Eskimos will be compared with the levels of the same components in a Danish population consisting of 316 persons, including 25 female Greenlandic Eskimos living in Denmark*"	*Eskimos in spite of the extraordinarily high intake of protein and fat of animal origin in these people*" *"The very low incidence of ischemic heart disease and diabetes mellitus in the UmanaK district of Greenland is very remarkable. During the 5-year period 1963-1967 only three cases of atherosclerotic heart disease were registered, and not a single case of diabetes mellitus".*	Annual Report from the Chief Medical Officer in Greenland, 1963-1967	*high levels of plasma cholesterol and probably also of triglycerides are correlated with high incidence of coronary atherosclerosis, and vice versa, is confirmed by our study, as coronary atherosclerosis is a very uncommon disease among Greenlandic Eskimos (Annual*

				Report from the Chief Medical Officer in Greenland, 1963-1967)"
Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J ClinNutr 1975; 28: 958-966[11]	*"… to investigate the composition of esterified fatty acids in the plasma lipids in 130 Greenland Eskimos, compared with those of 32 Greenland Eskimos living in Denmark and of 31 Caucasian Danes in Denmark"*	*"Coronary atherosclerosis is almost unknown among these people (Greenland Eskimos) when living in their original cultural environment"*	No reference provided	*"… it is very tempting to the documented observations to the low plasma lipid and lipoprotein concentrations in Eskimos and to the low incidence of atherosclerotic heart disease*

				among these peoples. Coming to this point, it is very difficult to combine the generally accepted concept of the advantage of a high intake of polyunsaturated fatty acids in prevention of ischemic heart disease with the present results"
Bang HO, Dyerberg J, Hjorne N. The	*"To investigate the composition of the Eskimo*	*" Coronary occlusion is uncommon in Greenland Eskimos"*	No reference provided	*"At this point it may be important*

composition of food consumed by Greenland Eskimos. Acta Med Scand 1976; 200: 69-73[12]	*diet, in order to elucidate any accord between the serum fatty acid pattern and the fatty acid composition of the dietary fats consumed by Eskimos"*	*"…a different fatty acid composition of the Eskimo diet could be one of the main reasons for the low plasma lipid concentration, and hypothetically for the low incidence of coronary occlusions"*	Hypothetical statement	*not to focus too strongly on the relationship between the low incidence of coronary occlusions among Eskimos and their low serum cholesterol level"* "*Although no epidemiological data so far have shown that high serum triglyceride (and pre-b-*

				lipoprotein) levels contribute information on the risk of coronary heart disease, independently of the associated serum cholesterol level, the very low levels of serum triglycerides and pre-b-lipoprotein in Eskimos may also be essential for their low incidence of coronary

				occlusions and of diabetes mellitus"
Dyerberg J, Bang HO, Stoffersen E. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978; 117-119[24]				
Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. Am J ClinNutr 1980; 33: 2657-2661[25]	*".. an examination of the composition of the Eskimo food was carried out during late winter of 1976 in the settlement of Idglorssuit in the UmanaK district of north western Greenland at latitude 71N"*	*"Death from ischemic heart diseases constitutes only 3.5% of all deaths in Greenland Eskimos despite a life span of more than 60 years"*	The State of Health in Greenland. Annual report from the Chief Medical Officer in Greenland for the years 1973, 1974,1975 and 1976. Ministry of Greenland, 1978.	"*Even if the cause of ischemic heart diseases is not to be found exclusively in the composition of the dietary and consequently the plasma lipids, our*

				examinations of Greenland Eskimos have helped substantially to clarify the reason for the rarity of IHD in these people"
Bang HO and Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. H.H. Draper (ed), Advances in Nutritional Research. Springer Science and Business Media New		*"Ischemic heart disease is very uncommon in Greenland Eskimos"* "*In the annual report of the state of health in Greenland covering the years 1973-1976, death from*	Harvald B, 1974, Third international symposium on circumpolar health, Ugeskr. Laeg. 136: 2461 Boggild J, Halberg O, Jorgensen FS, 1978, Sundhedstilstanden I	

York 1980[26]		*ischemic heart diseases constitutes an average of 3.5% of all causes of death"* *"The same statistical source reports an annual average of 9 ½ cases of myocardial infarction among hospitalized patients in Greenland. The majority of these, as well as of the deaths reportedly caused by ischemic heart diseases, is from the southern and most "Westernized" part of Greenland, whereas from 1968 to 1978, not a single death from ischemic heart disease or case of myocardial infarction was reported from the UmanaK district*	Grønland. Landslaegensarsbetetningfor Irene 1973, 1974, 1975 og 1976, Godthab, Greenland, 1978	

		(population of about 2600, where the present investigations were carried out"		

Table S2. Chief Medical Officer Report for Number of Total Deaths and Coronary Artery Disease (CAD) Deaths in Greenland for 1963-1967[27]

Year	**Total number of deaths**	**Number of CAD deaths (% of all deaths)**
1963	269	27 (10.0%)
1964	308	29 (9.4%)
1965	327	35 (10.7%)
1966	329	28 (8.5%)
1967	305	36 (11.8%)
Total	**1538**	**155 (10.0%)**

Table S3. Studies on prevalence of cardiovascular disease in Greenland Eskimos

Study	**Study Objective**	**Comparison Population**	**Conclusion**	**Type of Evidence**
Jørgensen ME, Bjerregaard P, Kjaergaard J et al , 2008[28]	To assess the prevalence of coronary heart disease among Greenland Inuit	Western populations (Belgian study) Danish population (Danish Copenhagen City Heart Study) General US population (NHANES study)	*"Coronary heart disease morbidity seems to be at least as high among Inuit as in American and European populations".*	Survey questionnaires, Rose questionnaire for angina pectoris, blood tests, ECG, structured interviews, anthropometry, measurements of blood pressure and oral glucose tolerance test. Evidence I

Level of evidence: I = based on actual investigation, clinical, autopsies imaging techniques

Table S4.Studies comparing CVD among Canadian and US Inuits vs non-Inuit populations.

Study	Study Objective	Comparison population	Conclusion	Type of Evidence
Chateau-Degat et al, 2010[22]	To update information on the global health status and cardiovascular diesease of the Inuit population.	Canadian population (published data)	*"The prevalence of some cardiovascular diseases among the Nunavik Inuit reached values recorded among other Canadians".* *"Hospitalization separation rates after ischemic heart disease and coronary disease were higher in Nunavik compared to Canada and Quebec".*	Antropometric, biological (lipid, glucose and insulin) and blood pressure measurements. Information from medical files was also used. Evidence I
Davidson M, Bulkow LR& Gellin BG,	Provides detailed mortality data on cardiac disease	Alaskan Whites and US Whites	*"Both Eskimo men and women had ischemic heart disease rates that were markedly lower than*	Death certificate data of all Alaskan residents during 1979-1988. Evidence II

1993[33]	for Alaska's indigenous residents by major ethnic group		*those for Alaskan Whites and less than half the rates for US whites".*	
Day GE & Lanier AP, 2003[32]	To compare mortality patterns for the Alaska Native population and the U.S. white population for 1989-1998 and examine trends for the 20-year period 1979-1998.	U.S. white population (National Center for Health Statistics)	*"The Alaska Native and U.S. white populations did not differ in heart disease mortality rates for men and women combined, men, or women".* *"There was no significant change in heart disease death rates for Alaska Natives in the 20-year period 1979-1998. Heart disease death rates for U.S. whites decreased 32% during the same*	Death certificate data Evidence II

			general time period”.	
Ebbesson SO, Risica PM, Ebbesson LO et al, 2005[30]	To relate omega-3 fatty acid consumption and plasma concentration with the presence, or absence, of coronary heart disease in Eskimos.	American population (published omega-3 fatty acid consumption data)	*“No differences were found in the consumption of omega-3 fatty acids between those with and without coronary heart disease”.* *“The coronary heart disease prevalence data obtained in this study confirmed the high prevalence noted in an earlier screening study of one Eskimo village, in which 15% of those ≥ 45 years old were diagnosed with coronary heart disease using the Strong Heart Study protocol”.*	Screening for coronary heart disease using a protocol that included ECG, medical history, Rose questionnaire, blood chemistries, including plasma fatty acid concentrations, and a 24-hour recall and a food frequency questionnaire assessment of omega-3 fatty acid consumption. Evidence I
Ebbesson SO,	To determine the	Earlier published data for	*“There is a high prevalence of*	Study designed based on the Strong

Adler AI, Risica PM et al, 2005[31]	prevalence of cardiovascular disease and to identify and characterize associated risk factors in three distinct Eskimo populations	US Whites, Danish and Canadian populations is discussed. This study's data is compared with the Strong Heart Study data for American Indians.	*cardiovascular disease in Alaskan Eskimos. This preliminary analysis, coupled with the high prevalence of coronary heart disease shown here, suggests that a high consumption of w-3 fatty acids does not necessarily protect against cardiovascular disease if other risk factors are present".*	Heart Study. Personal interview and physical examination. Fasting blood samples, anthropometric measurements, blood pressure measurements, personal interviews and Rose questionnaire for assessing angina pectoris.ECG results and chart reviews were read by staff cardiologists. Evidence I
Howard BV, Comuzzie A, Devereux RB, et	To explore cardiovascular diseaseprevalence	American Indians (Strong Heart Study) Whites and Blacks (ARIC	*"High coronary heart disease and stroke prevalence in Alaska Eskimos, despite low average*	Physical examination, personal interviews, collection of biological specimens, diagnostic tests

al, 2010[23]	and its relation to risk factors in Alaska Eskimos	study) Other U.S. populations (American Heart Association stroke data)	*LDL-C and high HDL-C".* *"Similar MI rates with American Indians (Strong Heart Study)".* *"Lower myocardial infarction rates than whites and blacks (ARIC study)".*	including ECG according to standard procedures and medical records. Medical records for cardiovascular disease were adjudicated by an adjudication committee. Evidence I
McLaughlin JB, Middaugh JP, Utermohle CJ et al, 2004[34]	To compare trends in CHD mortality and differences in prevalence of CHD risk factors between Alaska natives and non-	Non-native Alaskans	*"Alaska Natives were previously at lower risk for death from CHD than were non-native Alaskans; however, this discrepancy has disappeared. Alaska Natives currently have a higher prevalence of numerous risk factors for CHD compared with non-native*	Death certificate data (1979-2002) and CHD risk factors from Alaska's Behavioural Risk Factor Surveillance System (BRFSS) Evidence II

	native Alaskans		*Alaskans”*.	
Middaugh JP, 1990[35]	To present data based on death certificates on the causes of death among Alaska Natives	Other Alaskans	*“Alaskan Natives have less cardiovascular disease than other Alaskans”*. *“Female Natives had a slightly higher average annual, age-adjusted death rate than other females for death due to acute myocardial infarction”*.	All Alaskan death certificates for 1980 through 1986. Evidence II
Young TK, Moffatt ME&O'Neil JD, 1993[29]	To review cardiovascular mortality, morbidity, and risk factors in the	National population of Canada	*“The age-standardized mortality rate for ischemic heart disease (but not for other heart diseases or stroke) among the Northwest Territories population was lower*	Death certificates, hospital records, and a community health and examination survey data on electrocardiographic abnormalities and behavioural, biochemical, and

	multiethnic population of the Northwest Territories, Canada.		*than among the Canadian population (1950-1989)"*. *"Among the indigenous Inuit/Eskimos and Indians, the age-standardized mortality rate for all circulatory diseases was lower than Canadians"*.	anthropometric risk factors. Evidence II

Table S5. Articles published between 2003-2013 referring to the original Bang and Dyerbergstudy for support of the "low CAD prevalence" in Eskimo/Inuit populations

Article Title	Objective	Statement	Cited Sources	Conclusion	Reference
Omega-3 fatty acids. Their beneficial role in cardiovascular health(2006)[13]	To examine evidence for the role of omega-3 fatty acids in cardiovascular disease.	*"Bang and Dyerberg (3) and Dyerberg et al (4) did epidemiologic studies (level II evidence) to establish the cardioprotective effects of omega-3 fatty acids from marine sources in the Inuit people of Greenland in the 1970s. Despite a high-fat diet, the incidence of cardiovascular disease was exceptionally low among these*	3. Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Acta Med Scand 1972;192(1-2):85-94. 4.Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J ClinNutr 1975;28(9):958-66.	*"There is good evidence in the literature that increasing intake of omega-3 fatty acids improves cardiac outcomes. Physicians need to integrate dietary recommendations for consumption of omega-3 fatty acids into their usual cardiovascular care."*	Schwalfenberg G, Omega-3 fatty acids. Their beneficial role in cardiovascular health. Can Fam Physician, 2006;10; 52(6): 734–740.

		people".			
Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality: A Meta-Analysis of Cohort Studies(2004)[14]	To examine the association between fish intake and coronary heart disease mortality	*"Two decades ago, epidemiologists observed a low coronary heart disease mortality rate among native Alaskan and Greenland Eskimos who consumed a large amount of fish (1,2)."*	1. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. *Am J ClinNutr*. 1980;33:2657–2661. 2.Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland: incidence of some chronic diseases 1950–1974. *Acta Med Scand*. 1980;208:401–406.	*"Fish consumption is inversely associated with fatal coronary heart disease. Mortality from coronary heart disease may be reduced by eating fish once per week or more".*	He K, Song Y, Daviglus ML et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 109: 2705–11, 2004

The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease(2003)[15]	REVIEW ARTICLE	*"Interestingly, Greenland Eskimos have a low mortality rate from coronary heart disease, 5-7 despite a high intake of fat (about 40% of their total caloric intake) in their diet."*	5.Bjerregaard P, Mulvad G, Pedersen HS. Cardiovascular risk factors in Inuit of Greenland. Int J Epidemiol 1997; 26:1182–90. 6.Bjerregaard P, Dyerberg J. Mortality from ischaemic heart disease and cerebrovascular disease in Greenland. Int J Epidemiol 1988; 17:514–19. 7.Dyerberg J. The epidemiology of omega 3 fatty acids. World Rev Nutr Diet 1994; 76:133–6.		Lee KW& Lip GY. The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease. QJM. 2003; 96(7):465-80.
Dietary Patterns are Linked to Cardiovascular Risk	To evaluate dietary patterns of Alaska Eskimos and investigated	*"Eskimos and Inuit peoples were thought to be protected from cardiovascular*	1.Dyerberg J, Schmidt EB. n-3 Fatty acids and cardiovascular disease: observations	*"The identification of distinct dietary patterns reflecting the changing*	Cutchins A, Roman M J. Devereux R B, et

Factors but Not to Inflammatory Markers in Alaska Eskimos(2009)[50]	the relations between these dietary patterns and known cardiovascular risk factors, including inflammatory markers.	*diseasebecause of their high intakes of marine mammals that contain (n-3) fatty acids (1).Despite the tradition of a diet high in fish oils and abundant physical activity, coronary artery disease is increasing among Alaska Eskimos. Explanations for this observation include lifestyle changes"*	generated by studies in Greenland Eskimos. Wien KlinWochenschr. 1989;101:277–82.	*lifestyle of Alaska Eskimos afforded a tool to elucidate dietary changes. This analysis has shown beneficial associations of the traditional diet with CVD risk factors".*	al. Dietary patterns are linked to cardiovascular risk factors but not to inflammatory markers in Alaska Eskimos. J Nutr. 2009;139(12):2322-8.
Omega-3 fatty acid supplementation and cardiovascular disease(2012) [16]	A key question examined in this review is whether nonfish sources of omega 3 PUFA are as effective as fatty fish-derived $C_{20–22}$ omega 3 PUFA at managing risk factors	*"Considerable interest in the health benefits of very long chain C20–22 □omega 3 PUFA arose in the 1970s when epidemiological studies on Greenland Inuits established that this*	2.Bang,H.O.,J.Dyerberg,andA.B.Nielsen.1971.Plasmalipidand lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet. 1: 1143–1145.	*"Nonfish sources of ω 3 PUFA vary in their capacity to regulate blood levels of C(20-22) ω 3 PUFA and CVD risk factors".*	Jump DB, Depner CM, Tripathy S. Omega-3 fatty acid supplementation and cardiovascular disease. J Lipid

	linked to CVD.	*population had reduced rates of myocardial infarction compared with individuals in Western countries (2–7)"*	3. Bang, H. O., and J. Dyerberg. 1972. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Acta Med. Scand. 192: 85–94. 4.Dyerberg,J.,H.O.Bang,andN .Hjorne.1975.Fattyacidcompos i- tion of the plasma lipids in Greenland Eskimos. Am. J. Clin. Nutr. 28: 958–966. 5. Bang, H. O., J. Dyerberg, and N. Hjorne. 1976. The composition of food consumed by Greenland Eskimos. Acta Med. Scand. 200: 69–73. 6. O'Keefe, J. H., Jr., and W. S. Harris. 2000. From Inuit to		Res. 2012; 53(12):2525-45.

			imple- mentation: omega-3 fatty acids come of age. Mayo Clin. Proc. 75: 607–614. 7. Harris, W. S., D. Mozaffarian, M. Lefevre, C. D. Toner, J. Colombo, S. C. Cunnane, J. M. Holden, D. M. Klurfeld, M. C. Morris, and J. Whelan. 2009. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. J. Nutr. 139: 804S–819S.		
Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death		*"Landmark ecologic studies demonstrated low rates of coronary heart disease death among Greenland Eskimos, which appeared related to high consumption of marine n*	2. Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper H, ed. Advances in	*"The concordance of findings from different studies also suggests that effects of fish or fish oil on coronary heart disease death and sudden cardiac*	Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart

(2008)[17]		*3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from whales and seals (2)*".	nutrition research. New York, NY: Plenum Press, 1980:1–22.	*death do not vary depending on presence or absence of established coronary heart disease. The strength and consistency of the evidence, and the magnitude of this effect are each notable. Because more than one-half of all coronary heart disease deaths and two- thirds of sudden cardiac death occur among individuals without recognized heart disease, modest consumption of fish or fish oil, together with smoking cessation and regular moderate physical activity, should be among the first-line treatments for*	disease and sudden cardiac death. Am J ClinNutr. 2008;87(6):1991S-6S.

				prevention of CHD death and sudden cardiac death".	
Antiatherogenic effects of n-3 fatty acids - evidence and mechanisms (2006)[18]	This article summarizes the evidence for such a claim that high consumption of fish, and therefore, of fish oil-derived n-3 fatty acids has cardioprotective effects and to understand underlying mechanisms. Decreased atherogenesis is currently thought to be a part of the cardiovascular protection by n-3 fatty acids.	*"The epidemiologic association between dietary consumption of n-3 fatty acids and cardiovascular protection was first suggested by Bang and Dyerberg(2, 3). The authors identified the high consumption of fish, and therefore, of fish oil-derived n-3 fatty acids, as the likely explanation for the strikingly low rate of coronary heart disease events reported in the Inuit population (2, 3)."*	2. Bang HO, Dyerberg J, Hjoome N. The composition of food consumed by Greenlandic Eskimos. Acta Med Scand 1976; 200: 69-73. 3.Dyerberg J, Bang HO. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet 1979; 2: 433-5.		DeCaterina R, Zampolli A. Antiatherogenic effects of n-3 fatty acids - evidence and mechanisms. Heart Int. 2006;2(3-4):141.

Role of n–3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease(2008)[19]		*"One of the earliest observations made by Bang and Dyerberg in the 1970s (1–3) was that Greenland Inuits had lower rates of heart disease than Danes despite a diet high in fats and cholesterol. It was also noted that Inuits consumed high amounts of long chain n-3 fatty acids (i.e.- 5–10 g) and had lower intakes of n–6 fatty acids".*	1. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapen- taenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978;2:117–9. 2. Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. AdvNutr Res 1980;3:1–22. 3.Dyerberg J. Linolenate-derived polyunsaturated fatty acids and preven- tion of atherosclerosis. Nutr Rev 1986;44:125–34.	*"Existing large-scale clinical trials such as the GISSI-Prevenzione Study and JELIS with low doses of n□3 FAs (1–2 g) show clinical benefit in reducing coronary heart disease without substantial changes in concentrations of TGs or other lipids".*	Jacobson TA. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. Am J ClinNutr. 2008; 87(6):1981S-90S.

n-3 fatty acids in cardiovascular disease (2011)[51]	To review and discuss advances on the topic of increased dietary intake of n–3 (polyunsaturated) fatty acids in relation to preventing cardiovascular disease and highlight current gaps in knowledge.	*"In response to anecdotal reports of a low prevalence of coronary heart disease among Greenland Eskimos (Inuits), Bang and Dyerberg undertook six expeditions to Greenland starting in the late 1960s. They confirmed a very low incidence of myocardial infarction and reported an antiatherogenic blood lipid pattern, as well as markedly reduced platelet reactivity, in this population as compared with Danish controls (2,3) These findings were attributed to the Inuit diet, which was composed mainly of seal*	2. Bang HO, Dyerberg J, NielsenAB.Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet 1971;1:1143-5. **3.**Dyerberg J, Bang HO, Aagaard O. Alpha- linolenic acid and eicosapentaenoic acid. Lancet 1980;1:199. **5.**Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978;2:117-9.	*"The n–3 fatty acids continue to attract interestas a possible addition to available lifestyle measures and medications for the prevention of cardiovascular disease, but important gaps in knowledge remain. Data are lacking from clinical and mechanistic studies of the putative benefits of n–3 fatty acids for both primary and secondary prevention".*	De Caterina R. N-3 fatty acids in cardiovascular disease. NEJM 2011; 364: 2439-2450

		and whale and was extremely rich in marine n–3 fatty acids. In a seminal article in 1978, Dyerberg and colleagues presented the hypothesis that marine n–3 fatty acids might provide protection against atherosclerosis and thrombosis (5) and they began research on the potential effects of n–3 fatty acids in the prevention and treatment of vascular disease".			

APPENDIX A

Studies cited by Bjerregaardet al[21] that refer to CHD and atherosclerosis among Greenland Eskimos.

Eskimos have less CHD/atherosclerosis thannon-Eskimos

Level of evidence: I

Ehrström, 1951[57]

Level of evidence: II

Bjerregaard,1988;[58]Bjerregaard&Dyerberg, 1988[38]

Level of evidence: III

Kroman and Green, 1980[45]

Eskimos have the same or more CHD/atherosclerosis than non-Eksimos

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Level of evidence: I

Bertelsen, 1940;[20] Hansen et al. 1990;[59]Ingeman- Nielsen, 1990[60]

Level of evidence: I = based on actual investigation, clinical, autopsies imaging techniques

Level of evidence: II= Mortality statistics

Level of evidence: III= Hospital admission statistics and other reports