

Low incidence of cardiovascular disease among the Inuit—what is the evidence?

Peter Bjerregaard^{a,*}, T. Kue Young^b, Robert A. Hegele^c

^a Division for Research in Greenland, National Institute of Public Health, Svanemøllevej 25 Copenhagen Ø, Denmark

^b Department of Public Health Sciences, University of Toronto, Toronto, Canada

^c Robarts Research Institute, London, Canada

Received 8 May 2002; received in revised form 26 September 2002; accepted 3 October 2002

Abstract

Background: The notion that the incidence of ischemic heart disease (IHD) is low among the Inuit subsisting on a traditional marine diet has attained axiomatic status. The scientific evidence for this is weak and rests on early clinical evidence and uncertain mortality statistics. **Methods:** We reviewed the literature and performed new analyses of the mortality statistics from Greenland, Canada, and Alaska. **Findings:** The evidence for a low mortality from IHD among the Inuit is fragile and rests on unreliable mortality statistics. Mortality from stroke, however, is higher among the Inuit than among other western populations. Based on the examination of 15 candidate gene polymorphisms, the Inuit genetic architecture does not obviously explain putative differences in cardiovascular disease prevalence. **Interpretation:** The mortality from all cardiovascular diseases combined is not lower among the Inuit than in white comparison populations. If the mortality from IHD is low, it seems not to be associated with a low prevalence of general atherosclerosis. A decreasing trend in mortality from IHD in Inuit populations undergoing rapid westernization supports the need for a critical rethinking of cardiovascular epidemiology among the Inuit and the role of a marine diet in this population. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Inuit; Cardiovascular disease; Ischemic heart disease; Stroke; Atherosclerosis; Marine diet; Mortality

1. Introduction

Bertelsen in his classic 1940 description of the disease and mortality pattern among the Inuit of Greenland stated that ‘arteriosclerosis and degeneration of the myocardium are quite common conditions among the Inuit, in particular considering the low mean age of the population.’ [1]. Bertelsen, who is considered the father of epidemiology in Greenland, based his opinion both on many years of clinical practice in Greenland and on the reports of medical officers since 1838. Despite this historical background, the unreferenced 1975 statement ‘coronary atherosclerosis is almost unknown among these people [the Greenland Eskimos] when living in their own cultural environment’ [2] has attained axio-

matic status in the atherosclerosis literature [3]. The present article will explore whether this latter widely accepted opinion of the medical research community is valid in the light of current knowledge.

The Inuit are a numerically small people scattered along the coastline of Alaska, Northern Canada, and Greenland with a small contingent in eastern Siberia. They traditionally subsisted on marine mammals and fish but post World War 2 development has impelled their lifestyle and diet to that of the industrialized world. The consumption of marine species is, however, still much higher than in USA, Canada, and Denmark. Our own unpublished studies from Greenland show that in 1993, 62% of the Inuit in Greenland consumed seal meat and 64% fish at least once a week; by 1999 these proportions had decreased to 46 and 58%, respectively. In Denmark, the proportion of people who consumed fish at least once a week remained stable at 45% from 1995 to 2001 [4] and seal or other marine mammals are not consumed at all.

* Corresponding author. Tel.: +45-3927-12-22; fax: +45-3927-30-95

E-mail address: p.bjerregaard@dadlnet.dk (P. Bjerregaard).

2. Material and methods

Literature about cardiovascular disease among the Inuit was identified in MEDLINE and existing bibliographies on Inuit health. Additional information was obtained by tracing the primary references cited in these publications. We furthermore attempted to collect and analyze officially collected mortality data in three jurisdictions with large Inuit populations, i.e. Greenland, Northern Canada, and Alaska and compare these with mortality statistics from Denmark, Canada and the USA, respectively. Due to the use of different standard populations (1940 USA population for Alaska Natives; 1991 Canada population for Canadian Inuit; and the IARC World Population for Greenlanders), the three regions are not directly comparable. Without access to raw data from Alaska and Canada with which to compute age-standardization using a single standard, comparison is only valid between the regional Inuit population and the respective national populations of USA, Canada, and Denmark.

2.1. Greenland

Mortality analyses were based on the mortality register for Greenland at the Danish National Institute of Public Health. This computerized register covers all deaths in Greenland since 1968 and has information among other things on causes of death and place of birth as a proxy measure of ethnicity. For 1968–1993, causes of death were coded according to ICD-8; from 1994 ICD-10 was used. Ischemic heart disease (IHD) was defined as ICD-8 codes 410–414 or ICD-10 codes I20–I25.9; stroke as 430–438 and I60–I69.9, respectively. For the years 1965–1967, we used published mortality information from the annual reports of the Chief Medical Officer in Greenland [5]. Population figures were obtained from the censuses of 1965 and 1970 [6,7] and, since 1976, from an annually updated population register [8]. This register is based on the population register of Denmark, in which each individual is assigned a unique identification number that follows the individual from birth to death. It is very comprehensive and accurate. The analyses included only persons born in Greenland, as a proxy for Inuit ethnicity, with permanent residence in Greenland at the time of death. Greenlanders who were permanent residents in Denmark, and Danes living in Greenland were excluded. Mortality analyses for Denmark were based on the Danish mortality register at the Danish National Institute of Public Health and on population figures from the population register of Denmark [9]. In Table 2, mortality from IHD was adjusted as suggested by Murray and Lopez [10]. The adjustment is based on the finding that, in many countries, a high proportion of cardiovascular deaths are attributed to ill-defined causes

such as heart failure, general atherosclerosis, or undefined heart disease—so-called ‘garbage codes’—while in other countries with a supposedly high validity of mortality statistics this proportion is much lower. In order to correct for the likely undercoding of IHD in the former countries a standard algorithm was applied to increase the estimate of mortality from IHD. Rates were age-standardized by the direct method to the World Standard Population [11]. The calculation of confidence intervals was based on the Poisson distribution.

2.2. Canada

While Canadian Inuit (or any ethnic group) cannot be identified in death certificates in Canada, Inuit constitute over 85% of the population of the Nunavut Territory (formerly part of the Northwest Territories) and 90% of the Nunavik region in the province of Québec. Age-standardized mortality rates for cardiovascular diseases are available online for these two health regions in Statistics Canada’s Health Indicators 2001 (<http://www.statcan.ca>) [12]. Inuit-specific data require special data linkage of administrative databases and are not routinely reported by the various government agencies.

2.3. Alaska

Mortality statistics for Alaska are generally reported under the broad rubric of ‘American Indians and Alaska Natives’. Further breakdown of the Alaska Native category into specific Indian tribes, Eskimos (Yupik and Inupiat) and Aleuts is not consistently available from either the State of Alaska or the US Indian Health Service. However, it is also possible, as in Canada, to obtain online age-standardized mortality rates for cardiovascular disease in specific census areas in Alaska, which have a predominantly Eskimo population (<http://www.hss.state.ak.us>) [13]. There are six such areas where Eskimos constitute over 90% of the Native population and more than 65% of the total all-race population: Bethel (83% of total all-race population), Dillingham (69%), Nome (78%), North Slope (72%), Northwest Arctic (84%), and Wade Hampton (88%) [14]. IHD was defined as ICD-9 codes 402, 410–414, and 429.2 and accordingly included some unspecific diagnoses contrary to the data from Greenland.

3. Results

In Alaska, early clinical evidence from before 1950 indicated an almost total absence of cardiovascular disease [15]. In contrast, early clinical evidence from Canada and Greenland indicated that the incidence of arteriosclerosis and cardiovascular diseases was similar

Table 1
Studies of ischaemic heart disease and arteriosclerosis among the Inuit

Author	Region	Data source	Conclusion
Rabinowitch, 1936 [16]	Eastern Canadian Arctic	Clinical examination and X-ray ($n = 389$)	Data definitively disprove the alleged absence of arteriosclerosis among the Eskimo
Bertelsen, 1940 [1]	Greenland	Clinical observations	Arteriosclerosis and degeneration of the myocardium are quite common conditions among the Greenlanders
Ehrström, 1951 [18]	Northwest Greenland	Clinical examination and X-ray ($n = 1073$)	The incidence of clinical manifestations of arteriosclerosis is lower than in Korpo, Finland
Rodahl, 1954 [17]	Alaska	X-ray examination ($n = 84$)	Same degree of arteriosclerosis among Eskimos and white people
Gottman, 1960 [19]	Alaska	Autopsy ($n = 57$)	Cardiovascular disease of an arteriosclerotic type is not uncommon
Lederman et al., 1962 [20]	Canada	Autopsy ($n = 90$)	Eskimos do have atherosclerosis
Maynard et al., 1967 [22]	Alaska	Death certificates	Mortality from heart diseases lower among Alaska Eskimos than among the general population of USA
Arthaud, 1970 [21]	Alaska	Autopsy ($n = 339$)	Notes cases of myocardial infarction and atherosclerosis. No comparisons with other populations
Clausen, 1974 [23]	Greenland	Mortality statistics	Coronary heart deaths more frequent in Greenland than in Denmark
Kroman and Green, 1980 [29]	Northwest Greenland	Hospital records	Very low incidence of acute myocardial infarction
Bjerregaard, 1988 [24], Bjerregaard and Dyerberg, 1988 [28]	Greenland	Mortality statistics	Relative risk for IHD compared with Denmark ~ 0.5
Middaugh, 1990 [25]	Alaska	Mortality statistics	Alaska Natives had lower mortality from cardiovascular disease and atherosclerosis than other Alaskans. Relative risk ~ 0.7
Hansen et al., 1990 [30]	Northwest Greenland	Ultrasound ($n = 61$)	Native Greenlanders had almost the same degree and extent of atherosclerosis in the carotid and femoral arteries as the Danes
Ingeman-Nielsen, 1990 [31]	Greenland	X-ray ($n = 268$)	Same prevalence of calcified lesions in the abdominal aorta as among Danes
Young et al., 1993 [27]	Northwest Territories, Canada	Mortality statistics	Mortality from IHD lower in NWT (all ethnic groups) than in all Canada
Davidson et al., 1993 [26]	Alaska	Mortality statistics	Relative risk for IHD ~ 0.5 compared with Alaska whites
Newman et al., 1993 [32]	Alaska	Autopsy ($n = 103$)	Fewer raised lesions in coronary arteries and aorta of Alaska Natives compared with whites

to that of western countries or higher [1,16,17], while one study from Greenland reported a lower incidence [18] (Table 1). A total of 486 autopsies taken from three studies from Alaska and Canada during the 1960s and 70s concluded that arteriosclerosis and myocardial infarction were present among the Eskimos, but the authors were reluctant to draw any conclusion about the relative incidence due to small numbers [19–21]. Mortality statistics and studies based on death certificates from 1955–1965 showed a low mortality from all cardiovascular diseases among the Alaska Eskimos compared with the general population of the USA [22], while mortality from IHD among those aged 65 and above was higher in Greenland than in Denmark [23].

More recent studies from Alaska, Canada, and Greenland based on routine reporting of causes of death concurred that age-adjusted IHD mortality was lower among the Inuit than among white comparison populations [24–27]. The relative risk for IHD mortality was ~ 0.5 in Alaska Eskimos compared with US whites [26]. Our own studies, which have been extensively cited in support of a low IHD mortality in Greenland,

compared mortality among the Greenland Inuit from 1968 to 1983 with the general population in Denmark in 1980 and found relative risks of ~ 0.5 for men and women [24,28]. Mortality from other heart diseases was higher than in the white comparison populations in both Alaska, Canada, and Greenland. Cerebrovascular disease mortality was similar among the Inuit in Alaska and Canada and the white populations with which they were compared, while it was significantly higher among Greenlanders than among Danes. Hospital records from Greenland and Canada likewise showed low incidences of IHD and high incidences of cerebrovascular disease [27,29].

X-ray and ultrasound studies showed that Inuit had almost the same degree and extent of atherosclerosis in the abdominal, femoral, and carotid arteries as the white comparison populations [16,17,30,31]. However, an autopsy study designed to specifically study coronary atherosclerosis showed significantly higher proportions of raised lesions in the coronary arteries of mostly forensic cases among Alaska non-natives than among Alaska Natives, while the differences were not significant for the abdominal aorta [32]. The study, however,

tells us little about the clinically important differences in the older age groups. Autopsy studies from Greenland led to the hypothesis that there is a U-shaped dose-response association between fat tissue *n*-3 polyunsaturated fatty acids (marine diet) and atherosclerosis and stroke [33].

3.1. An update of mortality analyses

Table 2 shows cardiovascular mortality rates in Greenland and Denmark age-adjusted to the World Standard Population. The population of Denmark is a homogeneous Caucasian population and the vital registration is comprehensive and reliable. The mortality from all non-stroke cardiovascular diseases was similar in Greenland and Denmark while mortality from stroke was higher in Greenland Inuit throughout. In the absence of autopsies, it is risky to analyze cause-specific mortality, but the table indicates that the reported mortality from IHD was consistently lower in Greenland than in Denmark. A decreasing secular trend was most obvious for IHD.

A substantial proportion of non-stroke cardiovascular deaths was attributed to unspecific 'garbage' codes: 32% compared with <15% in countries with good mortality statistics [10]. This suggests that there may be a rather large number of hidden deaths from IHD. After adjustment for this the IHD mortality in Greenland was

Table 2
Reported mortality from cardiovascular disease in Greenland and Denmark

	Greenland	Denmark	Ratio	CI (95%)
<i>Cerebrovascular disease</i>				
1965–1974	135	55	2.45	2.14–2.81
1975–1984	106	45	2.36	2.08–2.65
1985–1994	111	41	2.71	2.44–3.00
1995–1998	105	39	2.69	2.28–3.15
<i>Non-stroke cardiovascular disease (IHD and other)</i>				
1965–1974	270	253	1.07	0.97–1.18
1975–1984	195	201	0.97	0.89–1.06
1985–1994	179	170	1.05	0.97–1.14
1995–1998	159	137	1.16	1.01–1.32
<i>IHD^a</i>				
1965–1974	179	211	0.85	0.75–0.96
1975–1984	84	161	0.52	0.45–0.60
1985–1994	74	126	0.59	0.51–0.67
1995–1998	65	90	0.72	0.58–0.89
<i>IHD^b</i>				
1965–1974	206	211	0.98	0.87–1.09
1975–1984	120	161	0.75	0.66–0.84
1985–1994	112	126	0.89	0.80–0.99
1995–1998	98	90	1.09	0.91–1.29

Adjusted to the World Standard Population by direct standardization. Mortality rates per 100 000 person-years.

^a ICD-8 410–414; ICD-10 I20–I25.9.

^b Adjusted according to Murray 1996 [10].

not significantly lower than in Denmark in 1965–1974 and 1995–1998, and only slightly lower in 1975–1994.

In Canada's two regions with predominantly Inuit populations, Nunavik and Nunavut, the age-adjusted mortality rates in 1995–1997 for all cardiovascular diseases were 431 (95% CI: 223, 639) per 100 000 person-years and 216 (141, 290), respectively, which was not significantly different from the all-Canadian rate of 246 (245, 247) [12]. Because of the small population size and low number of events, further breakdown into IHD and stroke deaths in Nunavut and Nunavik results in very wide confidence intervals (Table 3). There is, however, some support based on vital statistics, that relative to all-Canadians, IHD mortality is lower among the Inuit whereas for stroke the mortality rate is higher.

Alaska Natives (50% of whom are Eskimos) had an age-adjusted mortality rate for IHD that was not different from that of all Alaskans, but a stroke rate that was higher (Table 3) [13]. Figures are not available for Inuit separately, but in 1990–1998 among the six predominantly Eskimo census areas the age-adjusted mortality rate for IHD was slightly lower than for all Alaskans.

3.2. Cardiovascular genetics

The genetic component of atherosclerosis is complex, with the contributions of numerous genes interacting with environmental determinants [34]. Alleles of many different candidate genes have been variably shown to be associated with atherosclerosis and its intermediate traits. Given the caveats of genetic association studies for complex diseases, and for atherosclerosis in particular, we nonetheless examined whether 'deleterious

Table 3
Mortality from cardiovascular diseases among the Inuit in Canada and Alaska in the 1990s

	Indigenous	All	Ratio	CI (95%)
<i>Cerebrovascular disease</i>				
Nunavik, Canada, 1995–1997 ^a	200	48	4.13	1.07–10.68
Nunavut, Canada	not available	–	–	–
Alaska Natives, 1993–1998 ^b	36	27	1.36	1.17–1.57
Alaska Inuit ^c	not available	–	–	–
<i>IHD</i>				
Nunavik, Canada	not available	–	–	–
Nunavut, Canada, 1995–1997 ^a	40	136	0.29	0.06–0.87
Alaska Natives, 1993–1998 ^b	79	79	0.99	0.88–1.11
Alaska Inuit, 1990–1998 ^{b,c}	70	82	0.85	0.74–0.96

Adjusted to different standard populations.

^a Adjusted to the Canadian population 1991.

^b Adjusted to the US population 1940.

^c Six census areas with predominantly Inuit population.

alleles' of candidate genes for atherosclerosis and related traits varied in frequency between Inuit and geographically matched Canadians of European descent as controls. Of 15 alleles examined, we found that in Inuit compared with Canadians of European descent, five were significantly less frequent, five were significantly more frequent, and five were not different in frequency, consistent with, respectively, decreased risk, increased risk, and no difference in risk [34–43] (Table 4). This suggested that differences in genetic architecture do not clarify possible differences in cardiovascular disease prevalence, although such an analysis is admittedly very preliminary and limited. The genetic variants tested may have had little biological association with disease in the Inuit, while unmeasured genomic variants could be playing a more important role. In addition, genetic associations can be 'context dependent' and it cannot be determined whether certain of the genetic variants studied might be relatively more important determinants of cardiovascular disease in the Inuit. Full understanding of the genetic component of cardiovascular disease in the Inuit will require more effort because of confounding factors such as context-dependency, small genetic effects, non-mendelian inheritance, gene–gene interactions and gene–environment interactions [34]. Even if there was more confidence in the Inuit 'genetic profile' as being consistent with either susceptibility or resistance to atherosclerosis, it is very possible that lifestyle factors could either attenuate or amplify the influence of the complex genetic component.

4. Discussion

The evidence in the 1970s for a low IHD incidence among the Inuit was based on scattered clinical observations and the routine mortality statistics from Alaska [15,22], while similar observations from Canada and Greenland indicated an incidence of IHD that was similar to white populations [1,16,17,23]. This weak evidence has been substantiated only to a certain degree in later studies. The current scientific evidence from clinical, X-ray and ultrasound studies seem to allow the cautious conclusion that atherosclerosis has been present among the Inuit at levels by and large similar to those of white populations of North America and Europe, at least in the Eastern Arctic. However, autopsy studies from Greenland showed a poor correlation between arteriosclerosis of the large arteries and the coronaries [33].

Our updated analyses of mortality indicate that the mortality from IHD was similar among the Inuit and the southern comparison populations or slightly lower. Mortality from stroke was higher among the Inuit in all three areas, in particular in Greenland. A serious argument against the validity of the results concerning mortality is the low autopsy rate and the assumed low general validity of the diagnoses at least in Greenland [44]. It is questionable to what extent the differentiation among the specific cardiovascular diagnoses is based on solid clinical evidence and to what extent it is mere conjecture—possibly influenced by the presupposition that IHD is rare among the Inuit. Adjustment for

Table 4
Allele frequencies of atherosclerosis candidate genes in Canadian Inuit and white controls

gene	Allele	Inuit (<i>N</i> = 175)	Europeans (<i>N</i> = 92)	
<i>Consistent with decreased risk in Inuit</i>				
<i>ACE</i>	angiotensin converting enzyme	intron 16 deletion	0.31*	0.46
<i>F5</i>	clotting factor V	Q506	0*	0.02
<i>MTHFR</i>	methylenetetra-hydrofolate reductase	677T	0.06*	0.24
<i>HFE</i>	hemochromatosis	Y282	0*	0.09
<i>MBL</i>	mannose binding lectin	non-A	0.09*	0.23
<i>Consistent with increased risk in Inuit</i>				
<i>AGT</i>	angiotensinogen	T235	0.82*	0.45
<i>APOE</i>	apolipoprotein E	E4	0.23*	0.13
<i>PON1</i>	paraoxonase-1	R192	0.70*	0.35
<i>FABP2</i>	intestinal fatty acid binding protein	T54	0.35*	0.25
<i>ADRB3</i>	beta-3 adrenergic receptor	R64	0.30*	0.08
<i>Consistent with no difference in risk among Inuit</i>				
<i>HL</i>	hepatic lipase	–480C	0.60	0.68
<i>APOC3</i>	apolipoprotein CIII	–455C	0.47	0.44
<i>PON2</i>	paraoxonase-2	G148	0.29	0.25
<i>PPP1R3</i>	protein phosphatase-1 (skeletal muscle)	deletion	0.33	0.29
<i>GNB3</i>	G-protein beta-3 subunit	825T	0.50	0.44

*, allele frequency is significantly different ($P < 0.05$).

'garbage codes' reduced the difference between IHD mortality in Greenland and Denmark considerably. Based on the above, we find the hypothesis that mortality from IHD is low among the Inuit compared with western populations insufficiently founded. Since mortality from stroke was higher among the Inuit and Alaska Natives than in the white comparison populations, a general statement that mortality from cardiovascular disease is high among the Inuit seems more warranted than the opposite.

In addition to our own genetic studies among the Canadian Inuit, studies in Greenland have shown a low prevalence of certain apolipoprotein (a) isoforms consistent with a low genetic disposition for IHD [45], but the genotype of the Inuit does not unequivocally indicate a population with a high or low predisposition for atherosclerosis.

The decrease in mortality from IHD in Greenland since 1965 is surprising in view of the rapid westernization of the country during the same period. A similar trend was present among Alaska Natives [13]. If this represents a real decrease in the incidence of IHD and not just a change in diagnostic habits or improved possibilities for treatment, it will be difficult to maintain the importance of the traditional marine diet for a low incidence of atherosclerosis and IHD in these populations. Studies from 1952 estimated that 54% of the daily energy intake in the villages of Northwest Greenland came from traditional food [46] compared with 25% in 1991 [47]. During the same period, according to the censuses, the proportion of the Greenlandic population living in the villages, where the consumption of traditional food is considerably higher than in towns, decreased from 51 to 21%. However, assuming that westernization reduces the proportion of individuals with a very high intake of traditional food, the findings are consistent with the hypothesis that the association between dietary intake of marine lipids and atherosclerosis is U-shaped. Although the genetic changes must be small over the time span considered, what little change that has been is likely to be towards greater European admixture and thus implicitly higher incidence of IHD.

Clinical trials in non-aboriginals indicate a cardiovascular survival benefit that is associated with dietary supplementation with fish or marine oils among patients surviving a recent myocardial infarction [48,49]. The pathophysiological basis is probably not through an anti-atherogenic but through an anti-arrhythmic effect [49]. In some studies of general populations fish consumption appears to be associated with reduced IHD mortality in high-risk populations only [50] while other studies show an effect also among those without evidence of prior cardiovascular disease [51]. It is obvious that the epidemiology of cardiovascular disease among the Inuit and the complicated interactions

among marine lipids, other environmental factors, and genetic factors are not yet fully understood.

5. Conclusion

Mortality from stroke is similar or probably higher among the Inuit than among other western populations. The evidence for a low mortality from IHD is fragile and rests on unreliable mortality statistics. If present, it seems not to be associated with a low prevalence of general atherosclerosis. The life style of the Inuit is rapidly changing towards an increased cardiovascular risk factor profile [52]. Physical activity declines, obesity is widespread, the reliance on imported food increases, and the smoking rates are alarmingly high. We may still obtain a picture of the determinants of the traditional Inuit cardiovascular disease and mortality pattern by studying the life style of the elders in an historical perspective and following their disease and mortality pattern over the coming years, but time is running out. In a few years from now we may not be able to find out why the Inuit were protected against IHD—if ever they were.

Acknowledgements

Kue Young is a Senior Investigator of the Canadian Institutes of Health Research. R.A. Hegele holds a Canada Research Chair in Human Genetics and a Career Investigator Award from the Heart and Stroke Foundation of Ontario. General support from the Canadian Institutes of Health Research and the Blackburn Group are acknowledged.

References

- [1] Bertelsen A. Grønlandsk medicinsk statistik og nosografi. Bd. III: Det sædvanlige grønlandske sygdomsbillede, [Medical statistics and nosography in Greenland: the usual disease pattern in Greenland], vol. 3. Meddelelser om Grønland 1940;117(3).
- [2] Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr* 1975;28:958–66.
- [3] Ulbricht TLV, Southgate DAT. Coronary heart disease: seven dietary factors. *Lancet* 1991;338:985–92.
- [4] Haraldsdóttir J, Astrup A, Dynesen AW, Holm L. Danskernes fødevarerforbrug i stadig ændring—klare tendenser i perioden 1995–2001 [Food consumption in Denmark shows clear trends during the period 1995–2001]. *Ugeskr Laeg* 2002;164:2028–33.
- [5] Chief Medical Officer. Landslægens årsberetning [annual report of the chief medical officer], Nuuk, Landslægen, 1951–1967.
- [6] Statistics Denmark. Greenland. Census and count of dwellings December 31st 1965. Copenhagen: Statistisk Tabelværk, 1969. ix.
- [7] Statistics Denmark. Greenland. Census and count of dwellings December 31st 1970. Copenhagen: Statistisk Tabelværk, 1974. vi.

- [8] Statistics Greenland. Kalaallit Nunaata inui [Population of Greenland], Nuuk, Statistics Greenland, 1976–2000.
- [9] Statistics Denmark. Statistical Yearbook. Copenhagen, Statistics Denmark, 1965–1998.
- [10] Murray CJL, Lopez AD. Estimating causes of death: New Methods and Global and Regional applications for 1990. In: Murray CJL, Lopez AD (editors). The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. World Health Organization, 1996.
- [11] Doll R, Payne P, Waterhouse J. Cancer incidence in five continents. IARC technical report. Berlin: Springer, 1966.
- [12] Statistics Canada. Health Indicators 2001. <http://www.statcan.ca/english/freepub/82-221-XIE/01201/tables/html>.
- [13] Health status in Alaska 2000. <http://www.hss.state.ak.us/dph/deu/publications/>.
- [14] Boedeker B. 2000 Census Counts for Alaska Natives. <http://www.ihs.gov/facilitieservices/areaoffices/alaska/dpehs/population%5Freports/2000CensusREPORT.pdf> and census.asp.
- [15] Wilber CG, Levine VE. Fat metabolism in Alaskan Eskimos. *Exp Med Surg* 1949;8:422–5.
- [16] Rabinowitch IM. Clinical and other observations on Canadian Eskimos in the eastern arctic. *Can Med Assoc J* 1936;34:487–501.
- [17] Rodahl K. Diet and cardiovascular disease in the Eskimos. *Trans Am Coll Cardiol* 1954;4:192–7.
- [18] Ehrström MC. Medical studies in north Greenland—1949. VI: blood pressure, hypertension and atherosclerosis in relation to food and mode of living. *Acta Med Scand* 1951;140:416–22.
- [19] Gottman AW. A report of one hundred three autopsies on Alaskan natives. *AMA Arch Pathol* 1960;70:117–24.
- [20] Lederman JM, Wallace AC, Hildes JA. Arteriosclerosis and neoplasms in Canadian Eskimos. In: Biological aspects of aging. Proceedings fifth international congress gerontology. New York: Columbia University Press, 1962:201–7.
- [21] Arthaud JB. Cause of death in 339 Alaskan natives as determined by autopsy. *Arch Pathol* 1970;90:433–8.
- [22] Maynard JE, Hammes LM, Kester FE. Mortality due to heart disease among Alaskan natives, 1955–1965. *Public Health Rep* 1967;82:714–20.
- [23] Clausen J. An epidemiological and demographic study of the coronary heart deaths in Denmark, the Faroes and Greenland. *Nordic Council Arctic Med Res Rep* 1974;11:13–28.
- [24] Bjerregaard P. Causes of death in Greenland 1968–1985. *Arctic Med Res* 1988;47:105–23.
- [25] Middaugh JP. Cardiovascular deaths among Alaskan natives, 1980–1986. *Am J Public Health* 1990;80:282–5.
- [26] Davidson M, Bulkow LR, Gellin BG. Cardiac mortality in Alaska's indigenous and non-native residents. *Int J Epidemiol* 1993;22:62–71.
- [27] Young TK, Moffatt MEK, O'Neil JD. Cardiovascular diseases in a Canadian arctic population. *Am J Public Health* 1993;83:881–7.
- [28] Bjerregaard P, Dyerberg J. Mortality from ischaemic heart disease and cerebrovascular disease in Greenland. *Int J Epidemiol* 1988;17:514–9.
- [29] Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. *Acta Med Scand* 1980;208:401–6.
- [30] Hansen JP, Hancke S, Møller-Petersen J. Atherosclerosis in native Greenlanders. An ultrasonographic investigation. *Arctic Med Res* 1990;49:151–6.
- [31] Ingeman-Nielsen MW. Arteriosklerose hos grønlandere [Arteriosclerosis among Greenlanders]. *Ugeskr Læg* 1990;152:2641–3.
- [32] Newman WP, Middaugh JP, Propst MT, Rogers DR. Atherosclerosis in Alaskan natives and non-natives. *Lancet* 1993;341:1056–7.
- [33] Pedersen HS. Det grønlandske obduktionsprojekt. Atherosclerose og intracerebral hægorrhagi i relation til fedtsyresammensætningen i fedtvæv og validering af dødsårsagsmønsteret [Autopsies in Greenland. Atherosclerosis and hemorrhagic stroke in relation to the fatty acid composition of lipid tissue and a validation of the causes of death]. Thesis. Aarhus, Center for Arctic Epidemiology, University of Aarhus, 2000.
- [34] Hegele RA. Genetic prediction of atherosclerosis: lessons from studies in native Canadian populations. *Clin Chim Acta* 1999;286:47–61.
- [35] Hegele RA, Tully C, Young TK, Connelly PW. V677 mutation of methylenetetrahydrofolate reductase and cardiovascular disease in Canadian Inuit. *Lancet* 1997;349:1221–2.
- [36] Hegele RA, Young TK, Connelly PW. Are Canadian Inuit at increased genetic risk for coronary heart disease. *J Mol Med* 1997;75:364–70.
- [37] Mandelcorn R, Connelly PW, Boright A, Young TK, Hegele RA. F5 Q506 mutation and the low prevalence of cardiovascular disease in Canadian Inuit. *J Invest Med* 1998;46:232–5.
- [38] Hegele RA, Busch CP, Young TK, Connelly PW, Cao H. Mannose-binding lectin gene variation and cardiovascular disease in Canadian Inuit. *Clin Chem* 1999;45:1283–5.
- [39] Hegele RA, Harris SB, Brunt JH, Young TK, Hanley AJ, Zinman B, Connelly PW. Absence of association between genetic variation in the LIPC gene promoter and plasma lipoproteins in three Canadian populations. *Atherosclerosis* 1999;146:153–60.
- [40] Hegele RA, Anderson C, Young TK, Connelly PW. G-protein beta3 subunit gene splice variant and body fat distribution in Nunavut Inuit. *Genome Res* 1999;9:972–7.
- [41] Fanella S, Harris SB, Young TK, Hanley AJ, Zinman B, Connelly PW, Hegele RA. Association between PON1 L/M55 polymorphism and plasma lipoproteins in two Canadian aboriginal populations. *Clin Chem Lab Med* 2000;38:413–20.
- [42] Hegele RA, Huff MW, Young TK. Common genomic variation in LMNA modulates indexes of obesity in Inuit. *J Clin Endocrinol Metab* 2001;86:2747–51.
- [43] Hegele RA, Wang J, Harris SB, et al. Variable association between genetic variation in the CYP7 gene promoter and plasma lipoproteins in three Canadian populations. *Atherosclerosis* 2001;154:579–87.
- [44] Bjerregaard P. Validity of Greenlandic mortality statistics. *Arctic Med Res* 1986;42:18–24.
- [45] Klausen IC, Gerdes LU, Schmidt EB, Dyerberg J, Faergeman O. Differences in apolipoprotein (a) polymorphism in West Greenland Eskimos and Caucasian Danes. *Hum Genet* 1992;89:384–8.
- [46] Uhl E. Nogle undersøgelser af grønlandske levnedsmidler og kostforhold [Some investigations of Greenlandic foodstuffs and dietary conditions. In Danish with a summary in English], vol. 3. Copenhagen: Beretninger om Grønland, 1955:I–II.
- [47] Pars T. En kostundersøgelse—foretaget i to nordvestgrønlandske bygder: Saqqaq & Oqaatsut i 1991 [a dietary survey in two villages in northwest Greenland: Saqqaq and Oqaatsut, in 1991]. Odense: Odense University, 1992.
- [48] Burr ML, Gilbert JF, Holliday RM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;ii:757–61.
- [49] GISSI-Prevenzione Investigators. Dietary supplementation with *n*–3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. *Lancet* 1999;354:447–55.
- [50] Marckmann P, Grønbæk M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *Eur J Clin Nutr* 1999;53:585–90.
- [51] Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain *n*–3 fatty acids and the risk of sudden death. *New Engl J Med* 2002;346:1113–8.
- [52] Bjerregaard P, Young TK. The circumpolar Inuit. Health of a population in transition. Copenhagen: Munksgaard, 1998.